



Drisapersen Safety



(b) (4)

1

25 pages have been withheld as b(4) (CCI/TS) immediately following this page

Philips, Howard

From: Bastings, Eric
Sent: Friday, November 20, 2015 8:29 AM
To: Farkas, Ronald; Tandon, Veneeta; Rao, Ashutosh; Jin, Kun; Yan, Sharon
Cc: Unger, Ellis; Temple, Robert; Dunn, Billy; Choy, Fannie (Yuet)
Subject: RE: CONFIRMED: AC Practice NDA 206031 / drisapersen-- EMS ID: 392455

I compiled edits from the various teams, and made a few editorial changes. Please have a look at this before we meet this afternoon. Thanks.



Drisapersen 2015
20151120.pptx

Eric

-----Original Appointment-----

From: Choy, Fannie (Yuet)
Sent: Monday, August 31, 2015 7:41 PM
To: Choy, Fannie (Yuet); Unger, Ellis; Temple, Robert; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Rao, Ashutosh; Yasuda, Sally; Mentari, Evelyn; Jin, Kun; Yan, Sharon
Cc: Kozauer, Nicholas; Bautista, Philip; Ngo, Diem-Kieu (CDR,USPHS); CDER 120 Calendar; Bhattaram, Atul; Hung, Hsien Ming J; LaVange, Lisa
Subject: CONFIRMED: AC Practice NDA 206031 / drisapersen-- EMS ID: 392455
When: Friday, November 20, 2015 1:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Building 22 - Room 4201

11/18/15 Update: Eric has requested to extend the session to 2 hours.

Purpose: AC Prep for November 24, 2015 PCNS Meeting on drisapersen

AC PRACTICE / AC Prep

Agenda:

1. Review of latest version of efficacy slides.
2. Review of safety slides (safety team does not need to be present before 2 PM)

~scheduled by Fannie Choy on 8/31/15 301-796-2899~

Fannie Choy invites you to an online meeting using WebEx.

Meeting ID: 746 541 639

Meeting Password: (b) (4)

To join this meeting

1. Go to <https://fda.webex.com/fda/j.php?MTID=m3e1f40257921dcb3c471d116325784fb>
2. If requested, enter your name and email address.
3. If a password is required, enter the meeting password: (b) (4)
4. Click "Join".
5. Follow the instructions that appear on your screen.

Teleconference information

1. Provide your number when you join the meeting to receive a call back. Alternatively, you can call one of the following numbers:
Local: 1-301-796-7777
toll free: 1-855-828-1770
2. Follow the instructions that you hear on the phone.
Your Cisco Unified MeetingPlace meeting ID: 746 541 639

FDARichMedia@fda.hhs.gov

Technical support:

Contact FDA Rich Media at 301-796-3333.

IMPORTANT NOTICE: This WebEx service includes a feature that allows audio and any documents and other materials exchanged or viewed during the session to be recorded. By joining this session, you automatically consent to such recordings. If you do not consent to the recording, discuss your concerns with the meeting host prior to the start of the recording or do not join the session. Please note that any such recordings may be subject to discovery in the event of litigation.



Drisapersen

Duchenne Muscular Dystrophy
In patients with mutations amenable to skipping of exon 51

FDA Efficacy Review

(b) (5)

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67 pages of draft language have been withheld as b(5) immediately following this page

explor

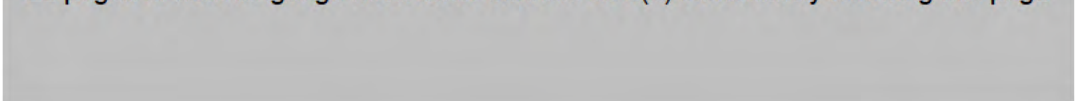
The concerns of the primary review team are described briefly below.



(b) (5)



22 pages of draft language have been withheld as b(5) immediately following this page



Philips, Howard

From: Temple, Robert
Sent: Wednesday, November 25, 2015 1:10 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farchione, Tiffany; Mentari, Evelyn; Choy, Fannie (Yuet); Yan, Sharon; Tandon, Veneeta; Rao, Ashutosh; Yasuda, Sally; Jin, Kun
Cc: Jenkins, John K
Subject: RE: drisapersen AC mtg

I agree that finding the testimonial people would be of great interest if that were possible. Also agree that it was a great job at the AC.

From: Unger, Ellis
Sent: Wednesday, November 25, 2015 11:57 AM
To: Dunn, Billy; Bastings, Eric; Farchione, Tiffany; Mentari, Evelyn; Choy, Fannie (Yuet); Yan, Sharon; Tandon, Veneeta; Rao, Ashutosh; Yasuda, Sally; Jin, Kun
Cc: Temple, Robert; Jenkins, John K
Subject: drisapersen AC mtg

Thanks to everyone for the great job yesterday at the AC! It was clear you were all well-prepared.

If you have a half-hour, you might find the live blog interesting (and humorous – at least I thought it was funny): <http://www.thestreet.com/story/13374430/1/biomarin-fda-panel-live-blog.html>

One thought I had last night - - would it be possible to identify (in the 6MW datasets) the patients who gave the positive testimonies at the ACM and see how they did? When you treat a couple hundred patients with a drug, you know that a few dozen will do a lot better. Maybe they were the ones who were paid to testify.

But I'm interested to see if these patients appeared to do as well as they said they did. If not, it suggests that the 6MWT is really not a good endpoint, that these testimonies were "embellished," or both.

Have a great holiday,

Ellis

Philips, Howard

From: Temple, Robert
Sent: Wednesday, November 25, 2015 12:01 PM
To: Eby, Michelle; Dunn, Billy; Bastings, Eric
Cc: Unger, Ellis
Subject: RE: Response to DMD letter for your review by COB on Friday, Nov 27

Well, it does not really address their questions but it does explain why we really can't do that. So it seems OK to me. Others??

From: Eby, Michelle
Sent: Wednesday, November 25, 2015 11:09 AM
To: Dunn, Billy; Bastings, Eric
Cc: Unger, Ellis; Temple, Robert
Subject: Response to DMD letter for your review by COB on Friday, Nov 27

Dear Dr. Dunn or Dr. Bastings,

Please see attached letter (png file) to Dr. Woodcock from the DMD community regarding the scheduling of the AC meetings for eteplersen and drisapersen.

It is my understanding that you may have already seen this when it was sent to DDI. However, since the letter was addressed to Dr. Woodcock, DEO was asked to respond.

Please see attached response memo for your review and clearance by COB this Friday, Nov 27.

Thanks, Michelle

Michelle Eby, Pharm.D, CCRP.
Consumer Safety Officer
Division of Executive Operations
Office of Executive Programs
FDA-Center for Drug Evaluation and Research
White Oak Complex
Building #51, Room 6184
Office: 301-796-4714
Email: Michelle.Eby@fda.hhs.gov

Philips, Howard

From: Temple, Robert
Sent: Monday, November 30, 2015 2:00 PM
To: Blount, Aprile
Subject: FW: Quick Minutes of the November 24, 2015 PCNS Meeting

[For my comments](#)

From: Choy, Fannie (Yuet)
Sent: Friday, November 27, 2015 3:02 PM
To: Farkas, Ronald; Mentari, Evelyn; Rao, Ashutosh; Yan, Sharon; Tandon, Veneeta
Cc: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Choy, Fannie (Yuet)
Subject: RE: Quick Minutes of the November 24, 2015 PCNS Meeting

Hello,

I uploaded the document to SharePoint for the team to edit.

Link to Quick Minutes: [Click Here](#)

Thank you,
Fannie

From: Bautista, Philip
Sent: Wednesday, November 25, 2015 2:45 PM
To: Choy, Fannie (Yuet)
Cc: Ngo, Diem-Kieu (CDR,USPHS); Dunn, Billy; Bastings, Eric; Farkas, Ronald; Mentari, Evelyn; Rao, Ashutosh; Yan, Sharon; Tandon, Veneeta; Unger, Ellis; Temple, Robert
Subject: Quick Minutes of the November 24, 2015 PCNS Meeting

Hi Fannie,

I've attached the Confidential Quick Minutes for the November 24, 2015 PCNS meeting. Please have the team review and revise the document (**please track all changes**), and e-mail me the revised version with tracked changes no later than **December 7, 2015** so that they can be incorporated into the Final Summary Minutes, which will be reviewed/signed by the Chairperson.

Once I will receive the transcript from the transcribing company, I will forward it to you for the team to review and comment as well.

Regards,

Phil

Phil Bautista, PharmD
Designated Federal Officer

Division of Advisory Committee and Consultant Management
Office of Executive Programs, CDER
(301) 796-9006

Philips, Howard

From: Temple, Robert
Sent: Wednesday, December 02, 2015 12:59 PM
To: Choy, Fannie (Yuet); Dunn, Billy; Unger, Ellis; Farkas, Ronald; Bastings, Eric
Subject: RE: Drisapersen - BioMarin follow up

Looks fine.

From: Choy, Fannie (Yuet)
Sent: Wednesday, December 02, 2015 12:47 PM
To: Dunn, Billy; Temple, Robert; Unger, Ellis; Farkas, Ronald; Bastings, Eric
Cc: Choy, Fannie (Yuet)
Subject: RE: Drisapersen - BioMarin follow up

Please see draft email. Thanks Fannie

Dear Dr. Fuchs,

Reference is made to your pending NDA 206031 for drisapersen. On behalf of Dr. Temple, I would like to acknowledge and thank you for your November 30, 2015, electronic communication. Dr. Temple would like to convey the following in response to your communication.

(b) (4)

From: Dunn, Billy
Sent: Tuesday, December 01, 2015 7:15 PM
To: Temple, Robert; Unger, Ellis; Farkas, Ronald; Bastings, Eric
Cc: Choy, Fannie (Yuet)
Subject: RE: Drisapersen - BioMarin follow up

Fannie,

Please prepare a reply to the email below from Hank Fuchs, to be sent by you on Dr. Temple's behalf, that thanks him for his communication,

(b) (4)

If we could take a quick peek at that email before you actually send it, it would be great.

Thanks,
Billy

From: Temple, Robert
Sent: Tuesday, December 01, 2015 6:52 PM
To: Dunn, Billy; Unger, Ellis; Farkas, Ronald; Bastings, Eric
Cc: Choy, Fannie (Yuet)
Subject: RE: Drisapersen - BioMarin follow up

Sounds good. Let's work on specific language with Fannie.

From: Dunn, Billy
Sent: Tuesday, December 01, 2015 5:14 PM
To: Temple, Robert; Unger, Ellis; Farkas, Ronald; Bastings, Eric
Subject: RE: Drisapersen - BioMarin follow up

No. (b) (4) (by email, from Fannie on your behalf) (b) (4)
[Redacted]

From: Temple, Robert
Sent: Tuesday, December 01, 2015 4:57 PM
To: Unger, Ellis; Dunn, Billy; Farkas, Ronald
Subject: FW: Drisapersen - BioMarin follow up

Obviously, I will not discuss this solo with him. (b) (4)

From: Hank Fuchs [<mailto:HFuchs@bmrn.com>]
Sent: Monday, November 30, 2015 10:31 AM
To: Temple, Robert
Subject: Drisapersen - BioMarin follow up

Dear Dr. Temple,

[Redacted] (b) (4)
[Redacted] (b) (4)

[Redacted] (b) (4)
Based on the comments at the Advisory Committee. (b) (4)

[Redacted] (b) (4)

Best regards and thanks,

Hank Fuchs
Chief Medical Officer
BioMarin Pharmaceutical, Inc.

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Philips, Howard

From: Hank Fuchs <HFuchs@bmrn.com>
Sent: Thursday, December 03, 2015 4:02 PM
To: Choy, Fannie (Yuet); Temple, Robert
Subject: Re: Drisapersen - BioMarin follow up

Dear Fannie (and Dr. Temple),

Thank you for your email and your interest in keeping engaged with us in this process.

[Redacted content] (b) (4)

[Redacted content] (b) (4)

[Redacted content] (b) (4)

While the most conclusive substantial evidence of benefit comes from our 3 randomized placebo controlled studies, the benefits described during the OPH provide further qualitative evidence that drisapersen is making a positive difference in these patients' lives. The testimonies were provided from a broad range of patients,

across different studies and different trial sites, and while the individual testimonies described a range of benefits experienced by the patient and his family, the collective takeaway is that these families were strongly in favor of making drisapersen available now.

We request that the Agency carefully consider the totality of data, particularly the consistent clinical benefit demonstrated across three adequate and well-controlled, randomized, placebo-controlled studies in this ultra-rare, fatal disease with an urgent unmet medical need. This dataset, the largest compiled in an application for Duchenne to date, provides clearly positive results in Study 1, strongly supportive results in Study 2, and supportive results in Study 3 in a similar population as studied in Studies 1 and 2, providing evidence that the overall result seen in Study 3 does not negate the findings of Studies 1 and 2. Approval of drisapersen based on this extensive dataset would be consistent with previous approvals in rare diseases in which the Agency has approved new orphan drugs under circumstances in which evidence to support approval was something other than "conventional or traditional showing of effectiveness".

(b) (4)

I look forward to further discussions on how we can advance drisapersen as an approved treatment option for patients and their families living with Duchenne.

Best regards,

Hank

From: "Choy, Fannie (Yuet)"

Date: Wednesday, December 2, 2015 at 2:58 PM

To: Hank Fuchs

Cc: "Choy, Fannie (Yuet)"

Subject: RE: Drisapersen - BioMarin follow up

Dear Dr. Fuchs,

Reference is made to your pending NDA 206031 for drisapersen. On behalf of Dr. Temple, I would like to acknowledge and thank you for your November 30, 2015, electronic communication. Dr. Temple would like to convey the following in response to your communication.

(b) (4)

Best Regards,
Fannie

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

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From: Hank Fuchs [<mailto:HFuchs@bmrn.com>]
Sent: Monday, November 30, 2015 10:31 AM
To: Temple, Robert
Subject: Drisapersen - BioMarin follow up

Dear Dr. Temple,

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)
Based on the comments at the Advisory Committee,
[Redacted] (b) (4)

[Redacted] (b) (4)

Best regards and thanks,

Hank Fuchs

Chief Medical Officer

BioMarin Pharmaceutical, Inc.

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MEMORANDUM

DATE: December 8, 2015

FROM: Ronald Farkas, M.D., Ph.D.
Clinical Team Leader
Division of Neurology Products, CDER, FDA

TO: Center Director and Briefing Attendees

SUBJECT: Briefing Memo for New Drug Application (NDA) 206488, for the use of Exondys 51 (eteplirsen) for the treatment of Duchenne muscular dystrophy in patients with mutations amenable to exon 51 skipping

(b) (5)

35 pages of draft language have been withheld as b(5) immediately following this page

Philips, Howard

From: Farkas, Ronald
Sent: Wednesday, December 09, 2015 10:33 AM
To: Unger, Ellis; Temple, Robert
Subject: FW: memo for tomorrow's eteplirsen briefing
Attachments: RF CD briefing memo.docx

The new appendix to this document is designed to replace the slides that explained the bias in the image selection for the first 3 biopsies. This is the version that will be presented today

Thanks

Ron

From: Farkas, Ronald
Sent: Tuesday, December 08, 2015 5:28 PM
To: Diggs, Felicia
Cc: Choy, Fannie (Yuet)
Subject: memo for tomorrow's eteplirsen briefing

Felicia,

This document is an update of the previous Word document. We can project this from the start of the meeting, and can just scroll down to see the various figures.

Thanks

Ron

Philips, Howard

From: Unger, Ellis
Sent: Friday, December 11, 2015 5:11 PM
To: Jenkins, John K
Cc: Temple, Robert; Locicero, Colleen L
Subject: quick update on some issues

John,

I might have to miss the SMT meeting Monday, and so I want to give you some quick updates.

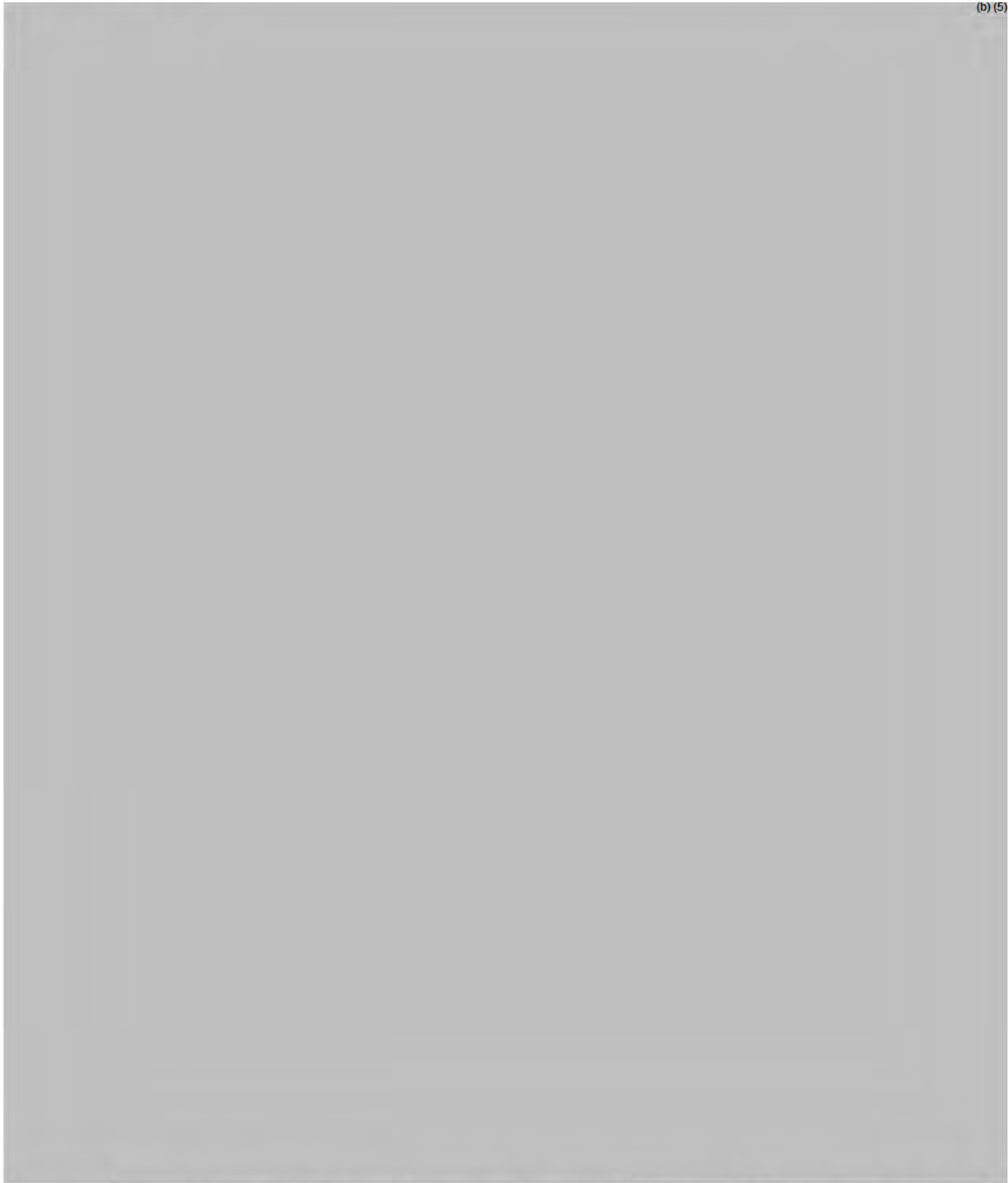
1. Selexipag – the drug for pulmonary HTN with goal date = 12/22: We were hoping to approve this a bit early, but my own review has turned up some uncertainty about deaths in the P3 trial. We are trying to sort out the issue with the applicant. If we are able to reach some certainty and feel reassured by early next week, we'll plan for an approval late next week or Monday the 21st. (b) (4)
2. Drisapersen – you've seen the letter. I'm not sure if it will move the needle; at this point the plan is still a CR.
3. Eteplirsen – The Division and ODE are still working on the backgrounder for the AC. I had thought that Ron would not present in January, but apparently Billy was thinking that he would present – Billy says he does fine when he's rehearsed. We'll see. There is still time to sort that out.

Ellis

et al.

MEMORANDUM

(b) (5)



14 pages of draft language have been withheld as b(5) immediately following this page

Philips, Howard

From: Unger, Ellis
Sent: Tuesday, December 15, 2015 8:30 AM
To: Farkas, Ronald; Bastings, Eric; Dunn, Billy
Cc: Temple, Robert
Subject: Re: Eleteplirsen AC package

Can u steer me to the specific passage in the specific document that u can't live with?
Ellis

Sent from my BlackBerry.

From: Farkas, Ronald
Sent: Tuesday, December 15, 2015 8:14 AM
To: Unger, Ellis; Bastings, Eric; Dunn, Billy
Cc: Temple, Robert
Subject: RE: Eleteplirsen AC package

Ellis,

I do not agree with the “usual line” here. You have to understand – everyone in the public thinks the FDA screwed up by not approving this drug years ago, and management has to take responsibility. You have to understand – **you already made decisions, senior management already made decisions – not approving the drug years ago is a management decision.** I will not continue with this unless that is communicated to the public.

Thanks
Ron

From: Unger, Ellis
Sent: Tuesday, December 15, 2015 1:03 AM
To: Farkas, Ronald; Bastings, Eric; Dunn, Billy
Cc: Temple, Robert; Choy, Fannie (Yuet)
Subject: RE: Eleteplirsen AC package

Hi Ron et al,

It is true that ODE-I and other higher-ups have been unusually involved with this development program and have concurred with the concerns expressed by the review team. But speaking for myself, I won't know what I really think until I draft my own memo. And just to be clear, I haven't seen a primary review memo yet.

So I would stick to the usual “line” here: management has been closely involved with this development program, but no conclusions have been reached. This is the truth. Moreover, if we were to tell the public that everyone in the management chain had made up their minds in advance of the ACM, the meeting would be declared a sham and a lie – all just so that the AC will agree with the FDA position and make FDA's job easier.

I read all of Eric's covering memo, but now that I see Ron's new comments to Eric/Billy, I'll wait to opine until the Division reaches an internal consensus.

I read Xiang Ling's review, and have only a few comments. There are some typos and the need for rounding the data in tables. When we write that the percent positive fibers is “23.345%” or the 6MWD is “234.43” meters, we are implying that there is precision that goes FAR beyond reality.

I've read through the first 5 pages of your (Ron's) review, and it's excellent so far.

Not having read beyond that, I would say the following:

There are 3 lines of evidence that could support efficacy – presence on mRNA, protein production, and clinical evidence.

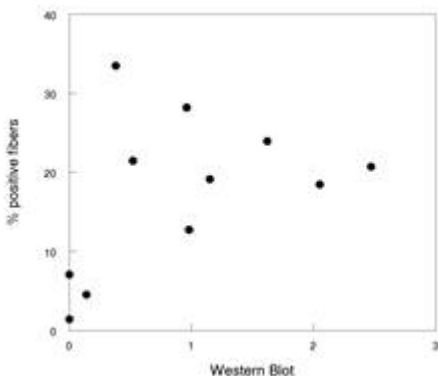
Based on PCR, they have evidence that messenger RNA is produced, but (if nothing has fundamentally changed since the 1990s) PCR is an incredibly sensitive technique that can detect just a few copies of a message. Thus, a positive finding (with negative controls) provides only proof-of-concept. Positive PCR carries no weight of being “reasonably likely to predict...” because it is too sensitive. If I am correct here, someone should write this in the backgrounder.

The “positive” findings on % positive fibers are based on a comparison of two groups of 4 patients to 4 controls. I agree that there was no correction for multiplicity, but the p-value would survive correction for multiplicity. Thus, lack of correction for multiplicity is irrelevant here. But no one has said explicitly that with two comparisons of etep to placebo, there was a positive finding for only one dose (the lower dose) and for just one of the two time points. It's not a matter of the p-value or correction for multiplicity. The lack of an effect in the higher dose group refutes the finding in the lower dose group. The lack of even a trend at the earlier time point (with a higher dose) sheds doubt on the finding at a later time point. And irrespective of the p-value, this was a comparison of 4 vs. 4 patients, in the context of serious concerns about the methodology that were identified during a site visit to the facility where the images were analyzed. I think we should point out the inherent uncertainty of a comparison of 4 patients to 4 controls, where the company chooses to ignore the other 4 treated patients. It would be irresponsible to base an accelerated approval on a selected finding comparing 4 vs. 4 patients where FDA can legitimately question the relevance of the measurement as well as its validity.

I'll also note that Eric's backgrounder simply brushes off the applicant's data comparing the 4th biopsy in ~12 patients with longstanding treatment to pre-treatment or untreated controls (see pp 72-73 in Serepta's backgrounder). This looks compelling, but we don't agree with it. If we don't believe their analyses on pp 72-73, we have to say why we disagree. We also need to explain, in understandable language, why 37% positive fibers doesn't mean 37% of normal dystrophin (see their figure 27, page 73).

I think it is critically important to explain why % positive fibers is not a measure of dystrophin content. This is because a “positive” fiber can be a fiber that shows barely any staining at all, so that “percent positive fibers” grossly overestimates that actual dystrophin content. I think we need to explain this very clearly. One of the things you could show is the utter lack of correlation between % positive fibers and Western Blot (below – $R = 0.42$). If you had to pick a slope out of this plot, it would be 5: 5% positive fibers per percent by Western Blot. That means that if we were to extrapolate to, for example, 50% dystrophin by Western Blot, there would be $50 \times 5 = 250\%$ positive fibers. We should also mention that just showing dystrophin doesn't prove it is functional.

Here's the plot comparing Western blot to PPF:



Ellis

From: Farkas, Ronald
Sent: Monday, December 14, 2015 7:36 PM
To: Bastings, Eric; Temple, Robert; Unger, Ellis; Dunn, Billy
Subject: RE: Eleteplirsen AC package

Because time is short, I'm emailing everyone.

The typical AC cover memo states that the views expressed in the package are those of the primary review team, and that supervisory staff and senior management are only partially aware of the details, and may entirely disagree with the primary review staff. To me, this pretense is not acceptable for the eteplirsen AC meeting. I strenuously object to cover material for the eteplirsen AC meeting that does not make clear that the concerns expressed are shared by supervisory staff and senior management. You can decide on how high in the chain that goes.

Thanks

Ron

From: Bastings, Eric
Sent: Monday, December 14, 2015 6:15 PM
To: Temple, Robert; Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: Eleteplirsen AC package

Bob, Ellis,

Attached are the documents that will constitute the eteplirsen AC package.

I suggest you begin with the cover memo, then read the CDTL memo, to finish with the Stats review.

I'm sure you know the timeline is very compressed.

Thanks.

Eric

Philips, Howard

From: Hank Fuchs <HFuchs@bmrn.com>
Sent: Wednesday, December 16, 2015 7:46 PM
To: Choy, Fannie (Yuet)
Cc: Temple, Robert; Camilla Simpson; Barbara Winslow; Brad Glasscock; Amy Waterhouse
Subject: Re: Drisapersen - BioMarin follow up
Attachments: Response to 10Dec2015 FDA T-con.docx

Hi Fannie,

We are not planning to submit (b) (4).

(b) (4)

Thank you for your diligent attention to this.

Best regards,

Hank

From: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Sent: Wednesday, December 16, 2015 3:36 PM
To: Hank Fuchs
Cc: Choy, Fannie (Yuet)
Subject: RE: Drisapersen - BioMarin follow up

Dear Dr. Fuchs,

Reference is made to your pending NDA 206031 for drisapersen submitted on June 26, 2015. We have the following information request in response to your Dec 15, 2015 email attached below. We ask that you respond to this request as soon as possible or by tomorrow (Thursday 12/17/15) morning.

(b) (4)

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

From: Nicole Persson [<mailto:nicole.r.persson@bmrn.com>] **On Behalf Of** Hank Fuchs
Sent: Tuesday, December 15, 2015 6:19 PM
To: Temple, Robert
Cc: Choy, Fannie (Yuet); [REDACTED] (b) (4)
Subject: Drisapersen - BioMarin follow up

Dear Drs. Temple and Dunn,



I look forward to continued dialog.

Best regards and thanks,

Hank Fuchs
Chief Medical Officer
BioMarin Pharmaceutical, Inc.

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[Kyndrisa] (drisapersen)

(b) (4)



[Kyndrisa] (drisapersen)

(b) (4)



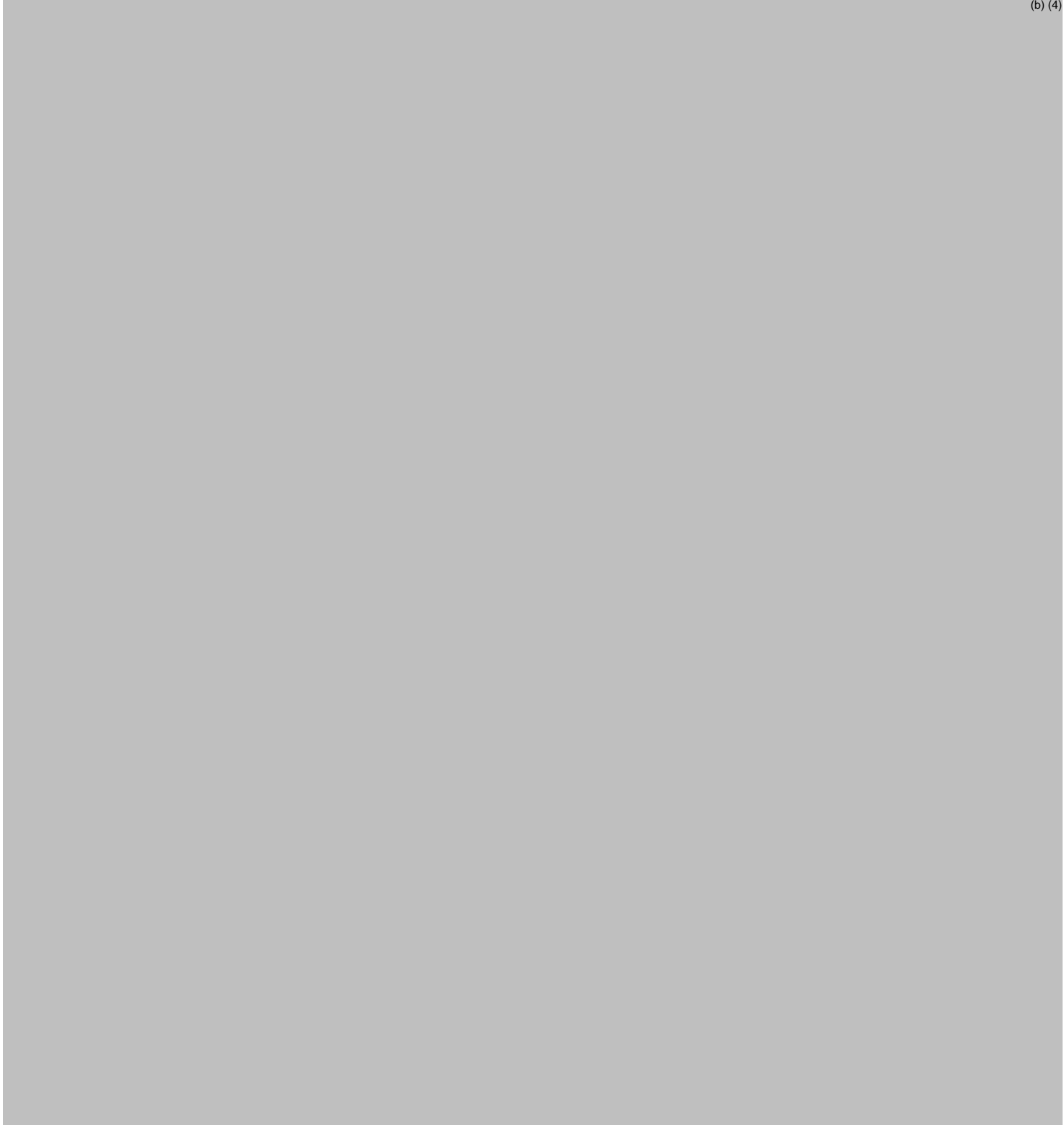
[Kyndrisa] (drisapersen)

(b) (4)



[Kyndrisa] (drisapersen)

(b) (4)



[Kyndrisa] (drisapersen)

(b) (4)



Philips, Howard

From: Unger, Ellis
Sent: Friday, December 18, 2015 10:05 AM
To: Temple, Robert
Subject: FW: redacted-ish eteplirsen review
Attachments: Eteplirsen CDTL memo Thurs PM_EU.docx

Here again....

From: Unger, Ellis
Sent: Friday, December 18, 2015 12:29 AM
To: Farkas, Ronald
Cc: Bastings, Eric; Dunn, Billy; Temple, Robert
Subject: RE: redacted-ish eteplirsen review

Ron,

It's a comprehensive review!

I did find some passages that I thought were inflammatory and unnecessary, and I marked or removed them.

Mostly, if you can find the time tomorrow, I think it would definitely benefit from reorganization. The stuff in the appendix should be included in the main document, and just presented once. I'd present the overview of drug development, then mRNA, dystrophin protein, clinical efficacy, and safety. For each section, I'd present it in the usual way – methods, findings, interpretation, +/- critique (strengths/limitations).

I'd put in a table of the findings for dystrophin, like this.

Patient	Western Blot	% positive fibers
A	2.05	18.5
B	1.15	19.1
C	0.38	33.5
D	1.62	24.0
E	0.52	21.5
F	0.98	12.8
G	0	7.1
H	2.47	20.7
I	0.96	28.2
J	0	1.4
N	0.14	4.5

Also, I think when you read through it all, you'll find some redundancy.

In the interest of transparency/efficiency, I'm cc'ing the others.

Ellis

From: Farkas, Ronald

Sent: Thursday, December 17, 2015 1:24 PM

To: Unger, Ellis

Subject: redacted-ish eteplirsen review

MEMORANDUM

DATE: December 8, 2015

FROM: Ronald Farkas, M.D., Ph.D.
Clinical Team Leader
Division of Neurology Products, CDER, FDA

TO: Members and Invited Guests of the Peripheral and Central Nervous Systems
Drugs Advisory Committee (PCNS AC)

SUBJECT: Clinical Team Leader Memo for New Drug Application (NDA) 206488, for the use
of Exondys 51 (eteplirsen) for the treatment of Duchenne muscular dystrophy in
patients with mutations amenable to exon 51 skipping

Philips, Howard

From: Bastings, Eric
Sent: Monday, December 21, 2015 5:22 PM
To: Unger, Ellis; Temple, Robert
Cc: Dunn, Billy; Farkas, Ronald
Subject: Draft points to consider

Bob, Ellis,

Here are draft points to consider:

1. Consider the data for dystrophin expression, including the following
 - a. Experimental methods, including consideration of accuracy, reliability, reproducibility, etc.
 - b. Potential clinical meaning, including consideration of amount of dystrophin relative to patients with Becker muscular dystrophy, functionality of the truncated dystrophin, and percent of muscle fibers with detectable dystrophin.
2. Consider the data for clinical measures, including the following
 - a. Design and potential interpretability of Study 201/202, including consideration of a) the placebo-controlled period, and b) comparison of the open-label experience to natural history.
 - b. Results of Study 201/202 in the context of the study design.
3. Consider the possible design of any future efficacy and safety studies that might be necessary.

Any edit?

Eric

Philips, Howard

From: Unger, Ellis
Sent: Monday, December 21, 2015 3:29 PM
To: Farkas, Ronald; Bastings, Eric
Cc: Dunn, Billy; Temple, Robert; Choy, Fannie (Yuet)
Subject: Eteplirsen AC package latest stats review
Attachments: 206488 Eteplirsen Stats review.doc

Here's the latest stats review I have.

Ellis



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 206488

Drug Name: EXONDYS 51™ (eteplirsen)

Indication(s): Duchenne muscular dystrophy (DMD)

Applicant: Sarepta

Date(s): Submission date: 6/26/2015
PDUFA Date: 2/26/2016

Review Priority: Priority Review

Biometrics Division: Division I, Office of Biometrics (HFD -710)

Statistical Reviewer: Xiang Ling, Ph.D.

Concurring Reviewers: Kun Jin, Ph.D., Team Leader
Jim Hung, Ph.D., Director

Medical Division: Division of Neuropharm (HFD -120)

Clinical Team: Christopher Breder, M.D., Ph.D.
Ronald Farkas, M.D., Ph.D., Team Leader

Project Manager: Fannie Choy

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1 EXECUTIVE SUMMARY

The data, overall, did not provide statistical evidence to support the efficacy of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

The only randomized controlled study submitted by the applicant, Study 201, can only be considered as exploratory because of study design and statistical analysis issues. In Study 201, patients were randomized to receive 50 or 30 mg/kg eteplirsen, or placebo. The study endpoints were assessed through Week 24. The statistical analysis plan of Study 201 did not include a method for statistical adjustment for testing multiple doses and/or multiple endpoints. The primary endpoint in Study 201 was the percent of dystrophin positive fibers in muscle biopsy tissue. The interpretation of the immunohistochemistry raw data is discussed in the clinical review. There was no nominally significant difference between eteplirsen 50 mg/kg, eteplirsen 30mg/kg and placebo for the 6MWT, which was the key clinical endpoint in Study 201.

The comparison of eteplirsen with historical controls, as proposed by the applicant in the open-label extension of Study 201 (called Study 202 by the applicant), is statistically uninterpretable, as this open-label extension did not have a prespecified statistical analysis plan, and had an inadequate control for bias. Among the potential sources of bias in the open-label extension of Study 201 are possible differences in various factors between eteplirsen-treated patients and the selected historical control cohort unaddressed by the applicant's attempt to match patients, the potential selection bias due to the *post-hoc* identification of the control cohort by the applicant, and other known sources of bias with the use of a historical control.

2 INTRODUCTION

2.1 Overview

Study 201 is the only randomized, double-blind, placebo-controlled study in this application. It was conducted at a single site in US in 12 subjects with genotypically confirmed DMD. Efficacy was assessed through the first 24 weeks of this study, while safety was assessed through Week 28. Upon completion of Study 201, all 12 patients were enrolled into an open-label extension study (Study 202) to continue receiving once-weekly treatment with eteplirsen. Study 202 was still ongoing at the time of NDA submission and interim study results were submitted for a cumulative 168 weeks of treatment, from Week 1 in Study 201 through the interim data cut at Week 140 in Study 202.

A historical control cohort was identified from 2 DMD patient registries for comparison to eteplirsen-treated patients in Study 201/202.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directories: [\\CDSESUB1\evsprod\NDA206488\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\dmd-51](#) and [\\CDSESUB1\evsprod\NDA206488\0006\m5\datasets](#).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The key clinical efficacy endpoint results were reproduced by this reviewer from the raw data. Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The first patient was enrolled in Study 201 on July 18, 2011 and the study was completed on February 29, 2012. Protocol 201 was amended 7 times, 3 of them were implemented after the study was initiated and the last version was dated January 07, 2012. In Amendment 6 (dated November 04, 2011), the protocol changed the endpoint of 6-Minute Walk Test (6MWT) from exploratory endpoint to a secondary endpoint. In Amendment 7 (dated January 07, 2012), the duration of the study was extended from 24 to 28 weeks. The efficacy analyses were only specified in the statistical analysis plan (SAP), dated February 20, 2012.

Study 201 was not designed as a clinical efficacy study and not powered for efficacy analysis. The primary endpoint was the percent of dystrophin positive fibers as measured in muscle biopsy tissue, i.e., a biomarker. The key clinical secondary endpoint, 6MWT, was specified midway through the trial and the analyses were not specified until the trial was close to completion.

Study Design

This is a randomized, single-center, double-blind, placebo-controlled, multiple-dose study to assess the efficacy, safety, tolerability, and PK of once-weekly i.v. infusions of eteplirsen in subjects with genotypically confirmed DMD with an appropriate genetic lesion. Eligible subjects were randomized to receive 50 or 30 mg/kg eteplirsen or placebo, then placebo subjects were further randomized to 1 of 2 groups to create 4 treatment groups as shown in Table 1. Groups 1 and 2 received 50 or 30 mg/kg eteplirsen once a week for 28 weeks. Group 3a received placebo once a week for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks, and Group 3b received

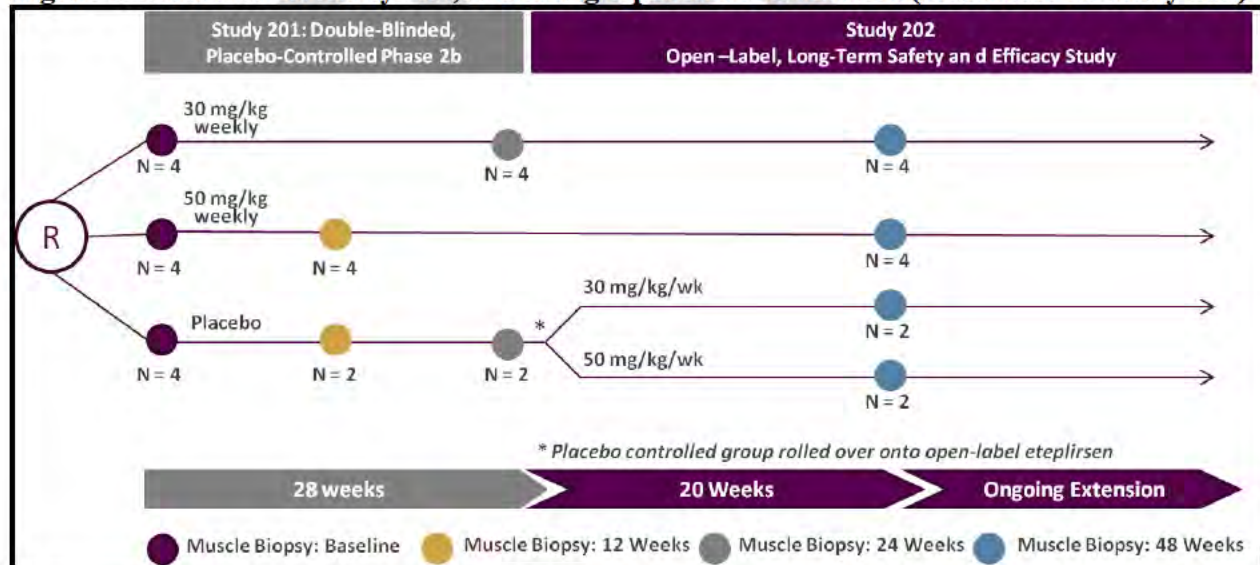
placebo once a week for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks. Beginning Week 25, all parties were aware that all subjects were receiving either 50 or 30 mg/kg eteplirsen.

Table 1: Treatment Groups

Group	N	Treatment
1	4	50 mg/kg eteplirsen IV once weekly for 28 weeks
2	4	30 mg/kg eteplirsen IV once weekly for 28 weeks
3a	2	Placebo IV for 24 weeks then 50 mg/kg eteplirsen for 4 weeks
3b	2	Placebo IV for 24 weeks then 30 mg/kg eteplirsen for 4 weeks

All patients underwent muscle biopsies at baseline for analysis of exon skipping and dystrophin expression. Repeat biopsies were performed at Week 12 for patients in Group 1 and Group 3a and at Week 24 for patients in Group 2 and Group 3b. Efficacy was assessed through the first 24 placebo-controlled weeks of this study, while safety was assessed through Week 28. Upon completion of this study, all 12 patients were rolled into an open-label extension (called Study 202 by the applicant) to continue receiving once-weekly treatment with eteplirsen for additional 212 weeks. In the open-label extension, all patients underwent a third muscle biopsy from the deltoid muscle at Week 20 and optionally a fourth muscle biopsy at approximately Week 140.

Figure 1. Overview of Study 201, Including Open-label Extension (Described as Study 202)



Efficacy Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint is the change from baseline in percent of dystrophin positive fibers as measured in the muscle biopsy tissue using immunohistochemistry (IHC) at Week 12 for groups 1 and 3a and at Week 24 for groups 2 and 3b.

Key Efficacy Endpoints:

1. Changes from Baseline in CD3, CD4, and CD8 lymphocyte counts in muscle biopsy tissue at Week 12 for groups 1 and 3a and at Week 24 for groups 2 and 3b.
2. Changes from Baseline to Week 24 in 6-Minute Walk Test (6MWT).

The following clinical assessments were described as exploratory endpoints in the protocol (Amendment 7, dated 07 January 2012), but are included as key secondary endpoints together with 6MWT in the SAP (dated February 20, 2012):

- Timed 4 Step Test.
- Maximum voluntary isometric contraction test (MVICT) to measure elbow flexion and extension, knee flexion and extension, and grip strength.
- Timed 10-meter run from the North Star Ambulatory Assessment (NSAA).
- NSAA total score.

There is no clear description of hierarchal ordering among all those secondary endpoints. In the open-label extension (described as Study 202) only 6MWT is included as primary clinical endpoint.

3.2.2 Statistical Methodologies

Testing and summary statistics of all efficacy endpoints will combine placebo subjects into a single group. Some efficacy assessments including 6MWT were performed on Days 1 and 2 of the Week 1 (baseline), Week 12, and Week 24 visits and once at the Week 4, 8, 16, and 20 visits. On those visits where 2 tests were performed, the maximum/best observed value is used for the primary analysis. If data for any one visit day are missing, then the non-missing value from the same visit is used.

Efficacy Analysis Population

The efficacy analysis set is the Full Analysis Set (FAS), consisting of all subjects randomized into the study who received any amount of study drug.

Statistical Analysis Method

For this exploratory study, all statistical analyses are conducted at two-sided alpha level of 0.05. No multiplicity adjustment was specified for testing multiple doses and/or multiple endpoints, so all p-values are exploratory only.

The primary efficacy endpoint, the change from baseline in percent of dystrophin positive fibers, was analyzed by comparing the 50 mg/kg eteplirsen treatment group at Week 12 to the combined placebo treatment group, and the 30 mg/kg eteplirsen treatment group at Week 24 to the combined placebo treatment group, using the ANCOVA for ranked data with Baseline values and duration of DMD as covariates.

The analysis of changes from baseline to Week 24 in the clinical assessment parameters (6MWT, Timed 4 Step Test, MVICT, Timed 10-meter run, and NSAA total score) was based on a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) with treatment (placebo, 30 mg/kg, 50 mg/kg), time, and treatment-by-time interaction terms as fixed effects, subject nested within treatment as random effects, with the Baseline value and time since DMD diagnosis as covariates. A first-order autoregressive (AR1) covariance structured matrix is used. The treatment comparison is made between each of the active treatments and placebo. The same MMRM analysis described above would be repeated to compare the combined eteplirsen groups to placebo.

If there was strong evidence suggesting that data for any endpoint deviated from normal distribution, then ANCOVA for ranked data was to be utilized.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patients were recruited for this study nationwide across the US. A total of 12 patients were randomized and all patients received scheduled infusions of study medication and completed the study as planned. All patients were 7 to 10-year old male and, except for one patient of Asian descent, all were white. The time since DMD diagnosis ranged from 18 to 112 months, with a median duration of 57 months. Numerically, there appears to be some imbalance in baseline 6MWT among the treatment groups (Table 2).

Table 2: Demographic and Baseline Disease Characteristics

Parameter		Placebo to Eteplirsena	Eteplirsen			All Patients
			30 mg/kg	50 mg/kg	All Eteplirsen	
		N = 4	N = 4	N = 4	N = 8	N = 12
Age	Mean	8.5	9.3	8.5	8.9	8.8
	Median	8.5	9	8.5	9	9
	Min, Max	7, 10	9, 10	7, 10	7, 10	7, 10
Mutation, n (%)	45-50	0	2 (50.0)	1 (25.0)	3 (37.5)	3 (25.0)
	48-50	0	1 (25.0)	0	1 (12.5)	1 (8.3)
	49-50	3 (75.0)	0	2 (50.0)	2 (25.0)	5 (41.7)
	50	1 (25.0)	0	0	0	1 (8.3)
	52	0	1 (25.0)	1 (25.0)	2 (25.0)	2 (16.7)
6MWT, meters	Mean	394.5	355.3	396	375.6	381.9
	Median	379	359	395	380.5	380
	SD	42.25	74.78	26.61	56.34	50.92
	Min, Max	364, 456	261, 442	365, 429	261, 442	261, 456
Time since DMD diagnosis, months	Mean	50.3	52.5	66.5	59.5	56.4
	Median	51	57	68	57	57
	SD	13.74	14.06	44.29	31.33	26.4
	Min, Max	36, 63	32, 64	18, 112	18, 112	18, 112

^a Includes both 30 mg/kg and 50 mg/kg

Source: Table 10-2 and 10-3 of the CSR.

3.2.4 Results and Conclusions

3.2.4.1 Analyses of the Primary Endpoint

The following analyses were based the fiber data derived by the applicant. The validity of the immunohistochemistry (IHC) raw data is beyond the scope of this review, and is addressed in the clinical review, to which the reader is referred for interpretation of the IHC results.

There was no statistically significant difference between the 50 mg/kg eteplirsen group and placebo at Week 12 ($p=0.958$; Table 3). At Week 24, the mean percentage of dystrophin-positive muscle fibers was higher in the eteplirsen 30 mg/kg group than the placebo. Patients treated with 30 mg/kg eteplirsen demonstrated 23% increase in the mean percentage of dystrophin positive fibers from baseline to Week 24. There appeared to be no increases from baseline in placebo patients. The nominal p value (0.002) for the comparison between eteplirsen 30 mg/kg group and the placebo group can only be considered exploratory, as there was no plan to control the type 1 error due to multiple comparisons, and the other comparison between 50mg/kg and placebo in Study 201 was negative.

Table 3: Dystrophin-Positive Fibers Detected by IHC with MANDYS106

Time point		Placebo	30 mg/kg Eteplirsén N = 4	50 mg/kg Eteplirsén N = 4
Baseline	Mean	15.64	18.19	11.00
	Median	15.58	17.80	11.51
	SD (SE)	10.742 (5.371)	5.501 (2.751)	4.668 (2.334)
	Min, Max	3.2, 28.2	11.9, 25.3	5.4, 15.6
On-Treatment	Mean	11.59	41.14	11.79
	Median	9.44	38.77	11.81
	SD (SE)	7.130 (3.565)	10.097 (5.049)	4.456 (2.228)
	Min, Max	5.7, 21.7	32.7, 54.3	6.4, 17.2
Change from Baseline	Mean	-4.05	22.95	0.79
	Median	-6.13	23.46	2.52
	SD (SE)	5.834 (2.917)	5.792 (2.896)	7.099 (3.549)
	Min, Max	-8.5, 4.5	15.9, 29.0	-9.3, 7.4
	p-value ^a		0.002	0.958

Source: CSR Table 11-1 and Table 14.2.1.1.2, confirmed by FDA reviewer.

^aBased on ANCOVA model for ranked data with treatment (placebo, 30 mg/kg, 50 mg/kg) as a fixed effect and baseline value and time since DMD diagnosis as covariates.

3.2.4.2 Analyses of 6MWT

As shown in Table 4, placebo-treated patients experienced a mean decline of 17.3 meters in 6MWT from baseline to Week 24, while patients in the 30 and 50 mg/kg eteplirsén groups showed mean declines of 134.8 and 2.3 meters, respectively. ANCOVA for ranked data showed no nominally significant differences between the treatment groups. The result of the MMRM analysis showed a nominally statistically significant difference between the placebo and 30 mg/kg eteplirsén groups, in favor of placebo (p=0.026; Table 4).

Table 4: Analysis Results of Change from Baseline in 6MWT

	Placebo	30mg/kg Eteplirsen N = 4	30mg/kg Eteplirsen mITT N = 2	50mg/kg Eteplirsen N = 4
Baseline				
Mean	394.5	355.3	407	396
Median	379	359	407	395
SD(SE)	42.25(21.12)	74.78(37.39)	49.50(35.00)	26.61(13.30)
Min, Max	364, 456	261, 442	372, 442	365, 429
Week 24				
Mean	377.3	220.5	394.5	393.8
Median	377.5	204	394.5	403.5
SD (SE)	19.00 (9.50)	203.14 (101.57)	51.62 (36.50)	53.67 (26.84)
Min, Max	354, 400	43, 431	358, 431	325, 443
Change at Week 24				
Mean	-17.3	-134.8	-12.5	-2.3
Median	-12	-116	-12.5	1.5
SD (SE)	28.06 (14.03)	144.71 (72.36)	2.12 (1.50)	29.89 (14.95)
Min, Max	-56, 11	-296, -11	-14, -11	-40, 28
treatment effect*		-102.4		25.6
95% CI *		(-192.2, -12.5)		(-62.7, 113.8)
P-value *		0.026		0.563

*Based on mixed model repeated measures (MMRM).

Source: Table 14.2.5.2.1 and Table 14.2.5.2.2 of Study 201 CSR.

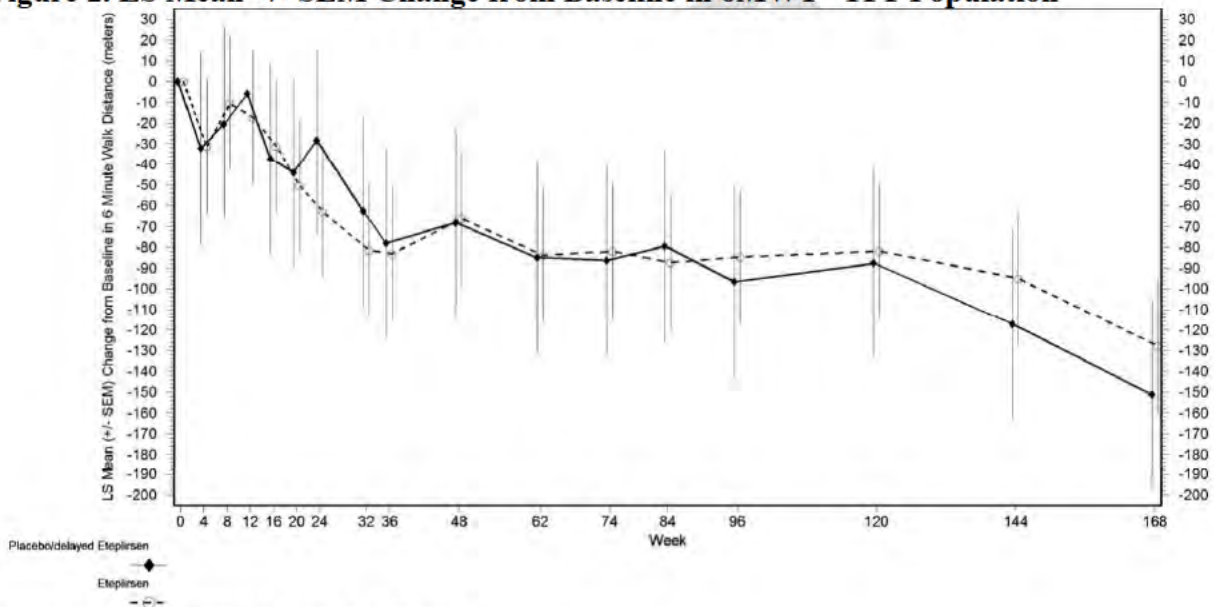
The applicant stated that the large decline in the 30 mg/kg eteplirsen group was attributable to Patients 009 and 010, who showed signs of rapid disease progression within weeks after enrollment. Therefore, the applicant conducted *post-hoc* analyses using Modified Intent-to-Treat (mITT) Population which excluded those 2 patients. For the mITT population, the mean change from baseline to Week 24 in MWT was a decline of 12.5 meters for the 30 mg/kg eteplirsen group. Both ANCOVA on ranked data and the MMRM analysis showed no nominally significant differences between the treatment groups in mITT.

The mITT population was not pre-specified in the SAP. Moreover, the mITT was defined based on the outcome data (instead of enrollment criteria or baseline character). Therefore, analysis on the mITT population could be misleading.

3.2.4.3 Analyses of the open-label extension study (described by the applicant as Study 202)

The 6MWT at Week 168 was compared between the combined eteplirsen group and placebo/delayed eteplirsen group. Analyses on ITT population did not achieve nominal statistical significance ($p=0.68$ by MMRM). The changes from baseline in 6MWT by assessment week for the combined eteplirsen group and placebo/delayed eteplirsen group are shown in Figure 2.

Figure 2. LS Mean $\pm$ SEM Change from Baseline in 6MWT - ITT Population



Source: Figure 14.2.5.2.2.1 of Study 202 CSR.

3.2.4.4 Comparison against Historical Controls

Historical Control Cohort

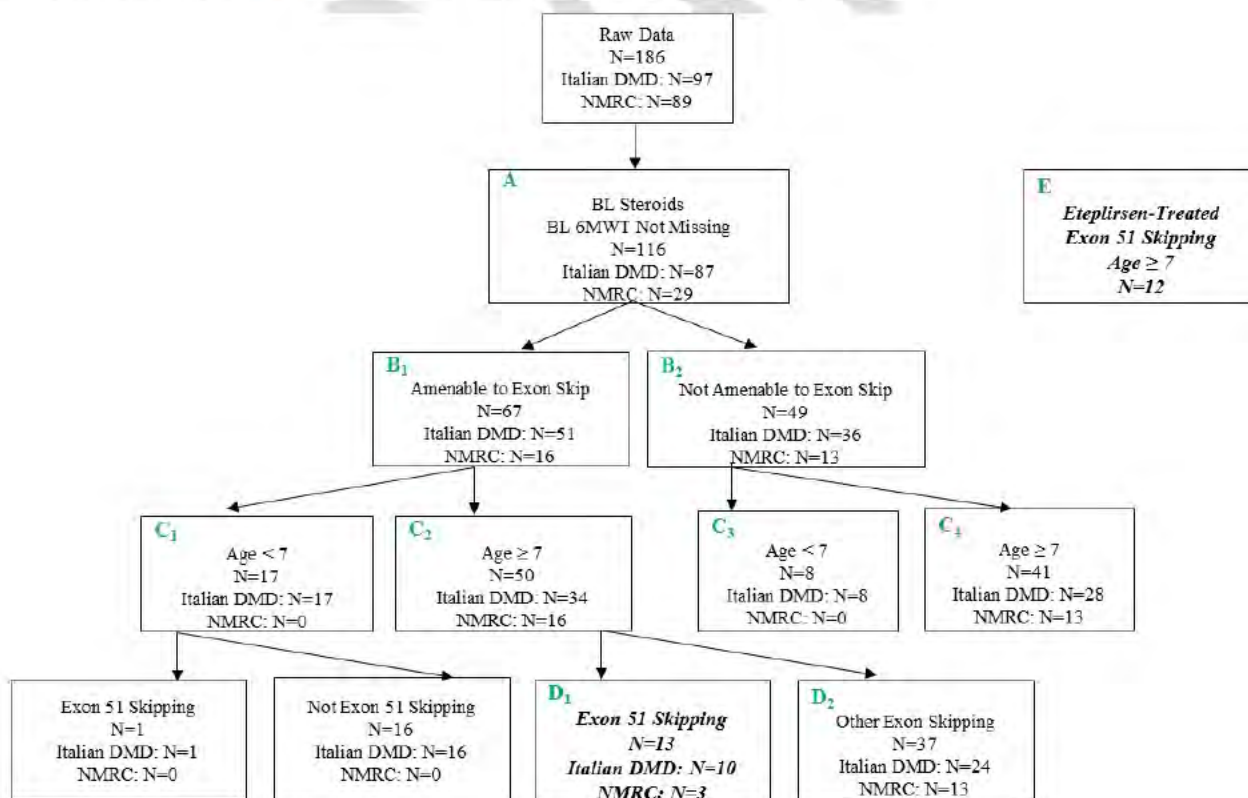
The comparison of eteplirsen with historical controls was not part of an adequate and well-controlled study. The applicant obtained historical data after observations were made for the eteplirsen patients. Historical data were obtained from 2 DMD patient registries (Italian DMD Registry and the Leuven Neuromuscular Reference Center – NMRC) for comparison to eteplirsen-treated patients. The following filters were applied to try to match patients in the historical control cohort:

1. Corticosteroid use at Baseline (use/non-use)
2. Sufficient longitudinal data for 6MWT available
3. Age ≥ 7 years
4. Genotype amenable to any exon skipping therapy
5. Genotype amenable to exon 51 skipping therapy

The Italian DMD registry is a longitudinal multicenter observational cohort study involving 11 tertiary neuromuscular centers in Italy. Patients were recruited between January 2008 and June 2010 and were to be followed for at least three years. The Italian DMD cohort contained the 6MWT results at Baseline (Month 0) and at Months 12, 24, and 36, with age and steroid use entered for each visit and with genotype information for 97 patients. Of these patients, 10 valid cases were identified based on applying the 5 filters.

The NMRC registry was an observational, single center, cohort study of DMD up to 17.5 years of age attending the NMRC between January 2007 and September 2012. The NMRC dataset contained 6MWT results at various time points, the patient's age and steroid use at the same time points, and genotype information for 89 patients. However, discrete visit designations (i.e., Baseline, Month 12, etc.) were not identified in the dataset. The first time points with non-zero meters on the 6MWT assessment for patients who were ≥ 7 years of age and on a steroid, were designated as the Baseline visit. Only 3 cases were identified based on applying filters (Figure 3).

Figure 3: Historical Controls and Eteplirsen-Treated Cohort



Source: Figure 1 of Study SR-15-031 CS.

Applicant’s Comparison of Eteplirsen with Historical Control

The results for 6MWT in eteplirsen-treated patients compared with historical controls matched on all 5 criteria mentioned above are shown in Table 5. The difference in LS mean change from baseline on 6MWT at 36 months was 141 meters. The nominal p-value reported by the applicant is not meaningful because the open label extension with historical control comparison was not an adequate and well-controlled study, for the reasons described below.

Table 5: Applicant’s Result of 6MWT in Eteplirsen Compared to Historical Controls

Patients Included	Groups Compared		Age	6MWT Baseline	6MWT Month 36**
HC + eteplirsen-treated, Steroid-Treated, Amenable to Exon 51 Skipping, ≥7 years old	HC	N	13	13	11
		Mean / LS Mean ^a (SE)	9.45 (0.403)	357.6 (18.51)	115.1 (33.54)
		Min, Max	7.3, 11.8	200, 458	
	eteplirsen-treated	N	12	12	12
		Mean / LS Mean ^a (SE)	9.41 (0.342)	363.2 (12.18)	256.4 (33.11)
		Min, Max	7.3, 11.0	256, 416	

* LS Mean for 6MWT Month 36 only

** LS Mean difference =141 and p=0.009 at month 36.

Source: Applicant’s analyses with output table modified by the reviewer.

Reviewer’s Discussion and Conclusion of the Historical Control Study

According to the ICH E10 guidance on Control Group and Related Issues in Clinical Trials, the major and well-recognized limitation of externally controlled (including historical control) trials is inability to control bias. The test group and control group can be dissimilar with respect to a wide range of observable and unobservable factors that could affect outcome. It may be possible to match the historical control group to the test group in observed factors but there is no assurance for any unobserved factors. “The lack of randomization and blinding, and the resultant problems with lack of assurance of comparability of test group and control group, make the possibility of substantial bias inherent in this design and impossible to quantitate.”

Because of the serious concern about the inability to control bias, the use of the external control design is restricted only to unusual circumstances.

1. ICH E10 states that “an externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable...” However, such prior belief does not exist for eteplirsen.
2. ICH E10 states that “use of external controls should be limited to cases in which the endpoints are objective...” However, performance on the 6-minute walk test can be

influenced by motivation. Patients may not achieve maximal 6MWT due to concerns of falling or injury, or patients could try harder with encouragement and with the expectation that the drug might be effective.

3. Pocock's criteria¹ for acceptability of a historical control group require that "the methods of treatment evaluation must be the same," and "the previous study must have been performed in the same organization with largely the same clinical investigators." This is especially important when assessing endpoints such as 6MWT, in contrast to hard endpoints such as mortality. For this NDA, these requirements are not met.

Moreover, the historical control group was identified *post-hoc* in this NDA, leading to potential selection bias that cannot be quantitated. If a historical control is to be utilized, selection of the control group and matching on selection criteria should be prospectively planned without knowing the outcome of the drug group and control group.

Based on ICH E10, "a consequence of the recognized inability to control bias is that the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials." The success criteria for this historical control study were not discussed or pre-specified in the protocol.

Given all these concerns, including issues of comparability of eteplirsen-treated patients and historical control cohort patients, the fact that 6MWT is not a "hard" efficacy endpoint, the potential of selection bias due to the *post-hoc* identification of the control cohort by the applicant, and all the known pitfalls with the use of historical controls, the comparison of the eteplirsen with the historical control is not statistically interpretable.

3.3 Evaluation of Safety

Please see the clinical review.

¹ Pocock SJ. The combination of randomized and historical controls in clinical trials. *Journal of Chronic Diseases*. 1976; 29:175–188.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses are not applicable as the study 201 was conducted at a single site in the US and all 12 patients were 7 to 10-year old male and, except for one patient of Asian descent, all were white.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study 201 was designed as an exploratory study. No multiplicity adjustment was specified for testing multiple doses and/or multiple endpoints.

The sample sizes of both Study 201 and the historical control study are very small. The robustness of the study result is a concern since a single patient can change the results substantially. The interpretation of results is also difficult because the sample may not represent the DMD patient population at large. Small studies can be useful for hypothesis generating but usually do not have the ability to provide definitive evidence for a drug's effect.

5.2 Collective Evidence

In Study 201, there was no statistically significant difference between the 50 mg/kg eteplirsen group and placebo at Week 12 ($p=0.958$). Treatment with 30 mg/kg eteplirsen for 24 weeks increased the mean percentage of dystrophin-positive muscle fibers in DMD patients compared to placebo, however, the nominal p value (0.002) can only be considered exploratory due to the lack of multiplicity control.

The MMRM analysis of 6MWT at Week 24 in Study 201 showed a statistically significant difference between the placebo and 30 mg/kg eteplirsen groups, in favor of placebo ($p=0.026$). There was no statistically significant difference between the 50 mg/kg eteplirsen group and the placebo ($p=0.563$). These results must be considered as exploratory only.

The open-label extension with historical control is not statistically interpretable.

5.3 Conclusions and Recommendations

The data overall did not provide statistical evidence to support the efficacy in subjects who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

Philips, Howard

From: Unger, Ellis
Sent: Monday, December 21, 2015 7:30 PM
To: Bastings, Eric; Temple, Robert; Dunn, Billy; Farkas, Ronald
Cc: Blount, Aprile
Subject: RE: Draft points to consider
Attachments: Sarepta PTC _Bob Temple.pdf

All,

Bob took a look at these yesterday and discussed a bit. Here is a shot at some edits (I haven't looked at them yet). I'm "off" but I'll be looking for these tomorrow. Hopefully, some of all of us can discuss by email and/or phone so we can get there.

And I appreciate everyone's hard work on this and drisa. They are not easy...

And having said that, I hope you all have happy holidays and enjoy some time off with your family and friends.

See you in January...

Ellis

From: Bastings, Eric
Sent: Monday, December 21, 2015 5:22 PM
To: Unger, Ellis; Temple, Robert
Cc: Dunn, Billy; Farkas, Ronald
Subject: Draft points to consider

Bob, Ellis,

Here are draft points to consider:

1. Consider the data for dystrophin expression, including the following
 - a. Experimental methods, including consideration of accuracy, reliability, reproducibility, etc.
 - b. Potential clinical meaning, including consideration of amount of dystrophin relative to patients with Becker muscular dystrophy, functionality of the truncated dystrophin, and percent of muscle fibers with detectable dystrophin.
2. Consider the data for clinical measures, including the following
 - a. Design and potential interpretability of Study 201/202, including consideration of a) the placebo-controlled period, and b) comparison of the open-label experience to natural history.
 - b. Results of Study 201/202 in the context of the study design.
3. Consider the possible design of any future efficacy and safety studies that might be necessary.

Any edit?

Eric



Philips, Howard

From: Bastings, Eric
Sent: Tuesday, December 22, 2015 2:42 PM
To: Choy, Fannie (Yuet)
Cc: Temple, Robert; Unger, Ellis; Farkas, Ronald; Blount, Aprile; Dunn, Billy
Subject: Eteplirsen FDA briefing materials cover memo
Attachments: Eteplirsen AC Cover.pdf; Eteplirsen AC Cover.doc

Here is the final cover memo.

Eric

MEMORANDUM

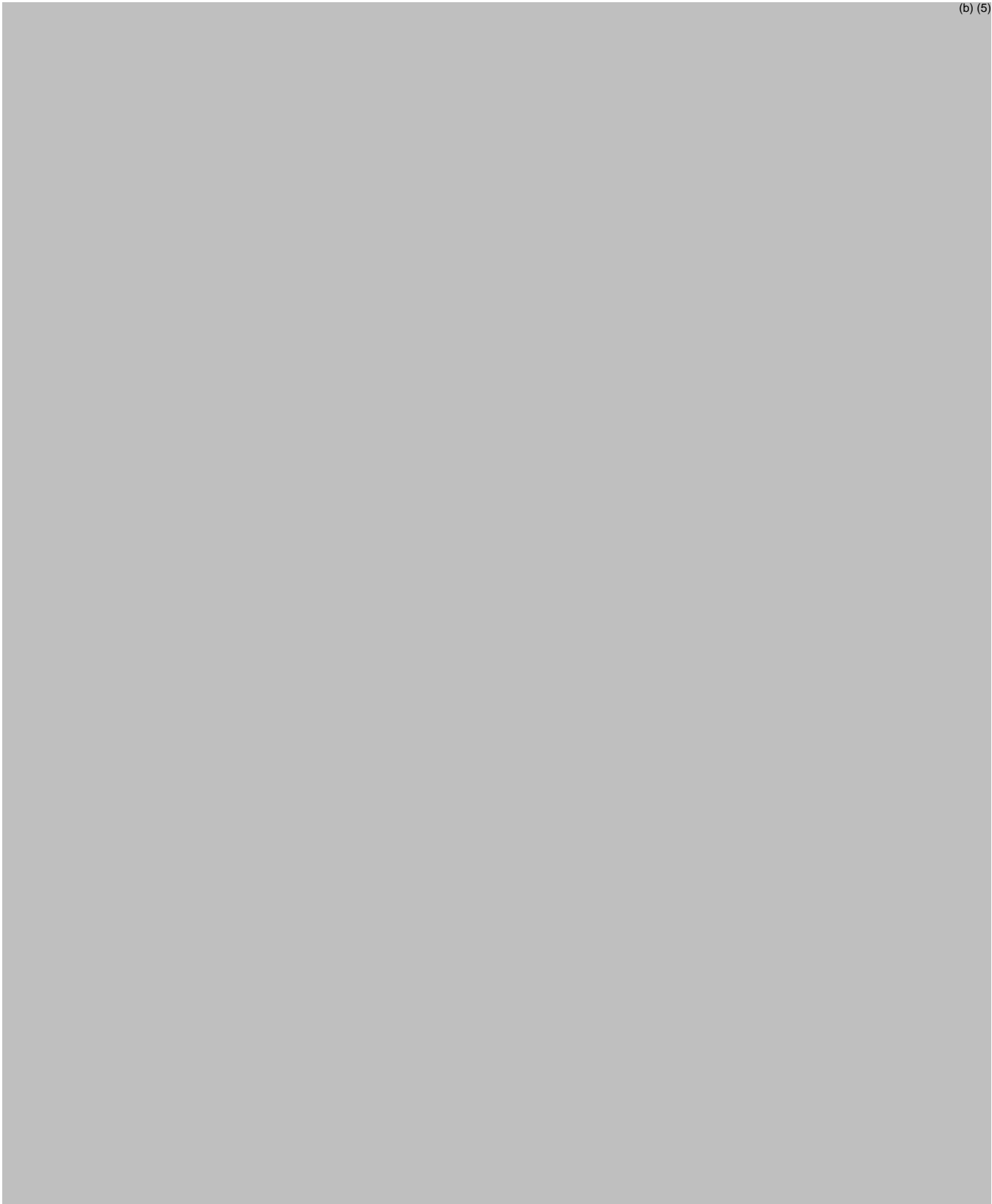
(b) (5)



13 pages of draft language have been withheld as b(5) immediately following this page

MEMORANDUM

(b) (5)



14 pages of draft language have been withheld as b(5) immediately following this page

Philips, Howard

From: Temple, Robert
Sent: Thursday, December 24, 2015 11:56 AM
To: Woodcock, Janet
Subject: Re: Draft Eteplirsen background document for Jan 22 AC Mtg

Ellis, that sounds right. I did not recall that line but it seems unnecessary.
Sent from my BlackBerry 10 smartphone.

From: Woodcock, Janet
Sent: Thursday, December 24, 2015 11:13 AM
To: Unger, Ellis
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Draft Eteplirsen background document for Jan 22 AC Mtg

I am fine with this, it is clearly written, except the last paragraph where it states “(b) (5)” . Since we have done accelerated approvals in the past in rare diseases based on pretty thin evidence, I see this as drawing a line in the sand that is not necessary or well delineated, and in fact Congress has opined in several laws subsequent to the '62 amendments on what we should do about accelerated approval for rare diseases (these are just as much the law of the land as the original) and I don't think the Division needs to offer a legal opinion to the AC, nor is that usually done. However, that is just my input and the Division Director may do as he sees fit. Thanks for sending. I think Ron's document is also clear and the tone is reasonable. jw

From: Unger, Ellis
Sent: Friday, December 18, 2015 4:59 PM
To: Woodcock, Janet
Cc: Jenkins, John K; Temple, Robert
Subject: Draft Eteplirsen background document for Jan 22 AC Mtg

Janet,

Here's a draft of the background document for the upcoming eteplirsen AC meeting. Given the visibility here, this was a joint project of DNP and ODE-I, and John has weighed in. Comments welcome. Ron Farkas is still working on his review document. I've also attached the company's backgrounder.

Ellis

Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Wednesday, January 06, 2016 1:14 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Bastings, Eric; Farkas, Ronald
Cc: Choy, Fannie (Yuet); Ngo, Diem-Kieu (CDR,USPHS); Choi, Moon Hee
Subject: Posting AC Materials /eteplirsen

All,

I have contacted Diem regarding the request to post the eteplirsen AC materials on Friday 1/15/16. Since this AC has a sponsor, both Sarepta and the FDA backgrounds will need to be posted at the same time. Therefore, we will need to have concurrence from Sarepta. In addition, Sarepta is planning on sending an addendum, and it should also be posted at the same time.

As this might set a precedent, her group is discussing with the lawyers and others. She will get back to us.

Thanks
Fannie

P.S. Final Agenda and Questions will still be posted 2 days before the meeting.

Philips, Howard

From: Woodcock, Janet
Sent: Thursday, January 07, 2016 12:52 PM
To: Jenkins, John K; Unger, Ellis; Clarke, Mary Beth
Cc: Temple, Robert; Locicero, Colleen L; Dunn, Billy
Subject: RE: Drisa CR action - release of Etep backgrounder

I think it is important to release the eteplirsin package quite early. Sure, it is unusual, but what about these development programs is not unusual? Would not delay the etep package so much. The community really needs to see the data and talk among themselves. jw

From: Jenkins, John K
Sent: Thursday, January 07, 2016 12:49 PM
To: Unger, Ellis; Woodcock, Janet; Clarke, Mary Beth
Cc: Temple, Robert; Locicero, Colleen L; Dunn, Billy; Jenkins, John K
Subject: RE: Drisa CR action - release of Etep backgrounder

Ellis

The timing is tricky. I copied Mary Beth and Janet since we discussed this some yesterday at CDER Small Staff and Mary Beth was going to check with ACS on when they can be ready to post the eteplirsin package. I understand your concern about posting the AC background package the same week as the drisapersen CR, but we are going to need to consider carefully the merits, which are high, of releasing the AC background package earlier than the usual 48 hours. Is there no way we can issue the drisapersen letter by COB tomorrow?

John

From: Unger, Ellis
Sent: Thursday, January 07, 2016 12:39 PM
To: Jenkins, John K
Cc: Temple, Robert; Locicero, Colleen L; Dunn, Billy
Subject: Drisa CR action - release of Etep backgrounder

John,

As you know, Janet was interested in releasing the eteplirsin AC package out on the internet sooner than the usual 48 hours prior to the AC meeting, in order to give the DMD community time to digest it. The AC meeting is Friday, Jan. 22nd.

It's clear that we're not going to be in a position to send the Drisa CR letter to the applicant until early next week. Thus, if we were to release the Etep AC package 7 (or more) days before the 1/22 meeting, we would be CR'ing the Drisa NDA the same week we release the background package on eteplirsin. And the public might think we were going out of our way to release two pieces of bad news in rapid succession.

In light of this, my sense is to wait until the week of the AC meeting to post the Eteplirsin package. Monday of that week is a holiday (MLK Day), so the earliest would be Tuesday – 72 hours before the AC meeting. But I think releasing the package at ANY point before the usual 48 hours will draw quite a bit of attention. So I've come to believe that releasing it on Wednesday, 1/20, 48 hours before the meeting, is the best course of action here.

Please let me know what you think.

Thanks,

Ellis

Philips, Howard

From: Temple, Robert
Sent: Thursday, January 07, 2016 10:52 AM
To: Dunn, Billy; Unger, Ellis; Bastings, Eric
Subject: RE: Posting AC Materials /eteplirsen

I think that's the right plan. I do very much want to have the letter to look at over the weekend.

From: Dunn, Billy
Sent: Thursday, January 07, 2016 10:26 AM
To: Unger, Ellis; Bastings, Eric; Temple, Robert
Subject: RE: Posting AC Materials /eteplirsen

I guess that is kind of in Bob's court, though I think it would be challenging. I sent him my memo before I left, and while I could file it in dartrts remotely, I am fully booked the rest of this week so I will not be able to deal with preparing the final CR letter for Bob, though I have asked the team to get a final draft ready this week so I can get it to Bob promptly upon my return. Assuming Bob is ready to finalize his memo next week, and nothing crops up at the last minute when he and I look over final materials, I anticipated we would issue the CR early next week.

Billy

From: Unger, Ellis
Sent: Wednesday, January 06, 2016 3:46 PM
To: Bastings, Eric; Temple, Robert; Dunn, Billy
Subject: RE: Posting AC Materials /eteplirsen

Assuming we send the CR letter on drisapersen next week when Billy gets back from leave (i.e., Jan 11th to 15th), releasing the eteplirsen backounder 1 week early could mean sending the CR on drisa the same week we release of the eteplirsen background materials. I suspect Janet was hoping we'd do the CR this week, and not next week.

Would there be any way to send the CR letter to Biomarin this Friday?

If not, we might, with the support of John and Janet, revert to releasing the eteplirsen backounder the usual 48 hours prior to the ACM. Then the bad news would be separated by a week.

From: Bastings, Eric
Sent: Wednesday, January 06, 2016 3:35 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy
Subject: RE: Posting AC Materials /eteplirsen

In this situation, I am not sure it would be wise to negotiate with Sarepta an early posting of the package. I would vote for forgetting about that idea and posting as usual.

Eric

From: Unger, Ellis
Sent: Wednesday, January 06, 2016 3:30 PM
To: Choy, Fannie (Yuet); Temple, Robert; Dunn, Billy; Bastings, Eric; Farkas, Ronald

Cc: Ngo, Diem-Kieu (CDR,USPHS); Choi, Moon Hee

Subject: RE: Posting AC Materials /eteplirsen

Talking with the lawyers – always a good idea...

From: Choy, Fannie (Yuet)

Sent: Wednesday, January 06, 2016 1:14 PM

To: Unger, Ellis; Temple, Robert; Dunn, Billy; Bastings, Eric; Farkas, Ronald

Cc: Choy, Fannie (Yuet); Ngo, Diem-Kieu (CDR,USPHS); Choi, Moon Hee

Subject: Posting AC Materials /eteplirsen

All,

I have contacted Diem regarding the request to post the eteplirsen AC materials on Friday 1/15/16. Since this AC has a sponsor, both Sarepta and the FDA backgrounds will need to be posted at the same time. Therefore, we will need to have concurrence from Sarepta. In addition, Sarepta is planning on sending an addendum, and it should also be posted at the same time.

As this might set a precedent, her group is discussing with the lawyers and others. She will get back to us.

Thanks

Fannie

P.S. Final Agenda and Questions will still be posted 2 days before the meeting.

Philips, Howard

From: Unger, Ellis
Sent: Thursday, January 07, 2016 6:11 PM
To: Bastings, Eric; Temple, Robert
Cc: Farkas, Ronald; Dunn, Billy
Subject: RE: Sarepta DRAFT questions (dec 7 draft).doc

Not sure how to address A3 ([REDACTED] (b) (5)). With respect to the sentence you want added back, I suggest a variation:

Importantly, accelerated approval is based both on the likelihood that the endpoint that is reasonably likely to predict efficacy (surrogate marker or intermediate clinical endpoint) and on the adequacy of the data showing the effect, including the effect size. In other words, *substantial evidence* is needed to support both clinical endpoints and surrogate endpoints intended to support accelerated approval. Accelerated approval cannot be used to compensate for weak or inconsistent clinical findings.

From: Bastings, Eric
Sent: Thursday, January 07, 2016 5:36 PM
To: Unger, Ellis; Temple, Robert
Cc: Farkas, Ronald; Dunn, Billy
Subject: RE: Sarepta DRAFT questions (dec 7 draft).doc

This looks good.

I responded to comment A2, and also am not sure how you want to address comment A3.

Eric

From: Unger, Ellis
Sent: Thursday, January 07, 2016 5:15 PM
To: Bastings, Eric; Temple, Robert
Cc: Farkas, Ronald; Dunn, Billy
Subject: RE: Sarepta DRAFT questions (dec 7 draft).doc

I made some edits. . See what you think. Note my addition of a "[REDACTED] (b) (5)." See if you are ok with that.

Ellis

From: Bastings, Eric
Sent: Thursday, January 07, 2016 3:39 PM
To: Temple, Robert; Unger, Ellis
Cc: Farkas, Ronald; Dunn, Billy
Subject: Sarepta DRAFT questions (dec 7 draft).doc

Bob, Ellis,

Here are the revised questions for the Sarepta AC.

Please send me your edits. AC staff deadline is tomorrow. Thanks.

Eric

Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Friday, January 08, 2016 10:28 AM
To: Rogers, Hobart; Bastings, Eric; Bhattaram, Atul; Bonson, Katherine R; Braver, Elisa; Breder, Christopher D; Dunn, Billy; Farkas, Ronald; Freed, Lois M; Harris, Danielle; Hawver, David; Heimann, Martha R; Jin, Kun; Kelley, Laurie; Kozauer, Nicholas; Krudys, Kevin; Ling, Xiang; Locicero, Colleen L; Men, Angela; Moukhtara, Aline; Myers, Deborah; Peters, Tracy; Pratt, Robert; Rao, Ashutosh; Temple, Robert; Unger, Ellis; Ware, Jacqueline H; Wilson, Wendy; Woody, Dahlia; Wu, Ta-Chen; Zerislassie, Ermias
Cc: Hung, Hsien Ming J; Grimstein, Christian; El Hage, Antoine N; Bauer, Larry J; Choy, Fannie (Yuet); Kelley, Laurie; El Hage, Antoine N
Subject: FW: Addendum to Sarepta's BD for Jan 22 PCNS
Attachments: Sarepta PCNSDAC BD Addendum Final.pdf

Dear review team,

Please see attached.

Thanks!
Fannie

From: Choi, Moon Hee
Sent: Friday, January 08, 2016 9:46 AM
To: Choy, Fannie (Yuet)
Cc: Ngo, Diem-Kieu (CDR,USPHS); Farkas, Ronald; Dunn, Billy; Bastings, Eric
Subject: Addendum to Sarepta's BD for Jan 22 PCNS
Importance: High

Hi Fannie,

Attached is the addendum to Sarepta's BD that we received this morning.

Thanks.

Moon

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

**PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE**

January 22, 2016

**ETEPLIRSEN BRIEFING DOCUMENT ADDENDUM
NDA 206488**



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

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

FDACDER0002917

INTRODUCTION

Sarepta and the FDA have no more critical challenge than to reliably bridge and extend the benefits of medical innovation to patients. Eteplirsen has been developed as an innovative therapy, customized to treat a unique set of DMD genetic mutations, those which are amenable to skipping exon 51.

This addendum provides updated efficacy data as requested by FDA. It will also address Sarepta's position on the FDA's existing authority and mandate to exercise flexibility in the evaluation of data for a rare disease such as DMD. Finally, Sarepta will provide clarification of comments in the FDA briefing document that we believe are key inaccuracies.

UPDATED ETEPLIRSEN CLINICAL EFFICACY DATA: WEEK 216 LOSS OF AMBULATION AND 6-MINUTE WALK TEST RESULTS

Summary of Year 4 Loss of Ambulation (LOA) Status by Kaplan-Meier Analysis

A summary of the Kaplan-Meier analysis results comparing Year 4 LOA rates of eteplirsen-treated subjects and external controls is provided below.

Study 201/202 (n=12): 2 LOAs, 10 ambulatory, %LOA = 16.7%.

External control (n=13): 10 LOAs, 1 ambulatory, 2 missing data at year 4; %LOA = 89.7% by Kaplan-Meier analysis taking into account missing data cases; $p=0.004$ by log-rank test.

Six-Minute Walk Test

The eteplirsen NDA was based on a large significant advantage of over 100 meters on the 6MWT for the eteplirsen-treated boys compared to external control boys at Year 3. This magnitude of effect was consistent and verified by several sensitivity analyses including those adjusting for covariates of baseline age and 6MWT (**Section 6.5.1.1 of Sarepta's briefing document**).

Subsequent to the NDA submission, the FDA requested additional Study 201/202 data through Week 216; the requested 6MWT data are provided in [Table 1](#). All 10 of the eteplirsen boys who were ambulant at time of NDA submission remain able to walk at Week 216. Their ages at this point in the study range from 11.8 years to 15.2 years, with 4 of the boys aged 14 or older. This is in contrast to what was stated in the FDA Briefing Document for drisapersen, "*by age 10-14, DMD patients become wheel chair bound*" (Peripheral and Central Nervous System Drugs Advisory Committee Meeting November 24, 2015; NDA 206031 Briefing Document for Drisapersen, page 28).

In addition, Year 4 data for the external control patients amenable to exon 51 skipping have recently become available, are is provided in [Table 2](#).

Table 1: Study 201/202 Subjects (n=12) with Results of 6MWT at Year 4

Dose Group	Subject Number	Baseline 6MWT	Year 3 6MWT	Year 4 6MWT	Age at Year 4
Placebo to 30 mg/kg	007	374	312	197	11.7
	008	346	100	55	14.2
Placebo to 50 mg/kg	005	374	247	143	11.7
	013	400	301	230	14.3
30 mg/kg	002	416	378	349	12.7
	006	355	359	332	14.2
	009	330	0	0	13.9
	010	256	0	0	13.9
50 mg/kg	003	366	324	192	11.0
	004	389	355	221	12.5
	012	351	298	237	14.6
	015	401	483	400	13.3

Table 2: External Control Subjects (n=13) with Results of 6MWT at Year 4

Subject Number	Baseline 6MWT	Year 3 6MWT	Year 4 6MWT	Age at Year 4
(b) (6)	380	195	*Missing	12.6
	295	35	0	13.3
	380	0	0	12.0
	329	218	0	12.8
	388	0	0	12.1
	388	0	0	14.1
	325	0	0	11.3
	458	362	300	14.2
	200	0	0	15.5
	373	273	0	13.0
	327	0	0	15.5
	451	240	0	15.2
	355	*Missing	*Missing	12.3

* External control patients with missing 6MWT data at Year 4.

** Of note, patients (b) (6) and (b) (6) were subsequently reported to have loss of ambulation with “0” meters on the 6MWT at ~4.5 years. In addition, external control patient (b) (6) was known to have lost ambulation with a 6MWT of “0” at 4.8 years.

Table 3: Summary of Year 4 6MWT Difference in Mean Change from Baseline between Study 201/202 Subjects and External Controls by Model (estimated mean difference, p-value)

Model	MMRM N= 12/13	ANCOVA N=12/11
Covariate: Baseline 6MWT	146.5, p=0.003	150.3, p=0.002
Covariates: Baseline 6MWT, Age	143.1, p=0.004	156.1, p=0.002
Rank transformed data analyzed Covariate: Baseline 6MWT	8.4, p=0.004	8.7, p=0.001

Conclusion

Based on available data for LOA and 6MWT status at 4 years, Study 201/202 patients performed better than EC patients in a statistically significant and clinically meaningful manner.

FLEXIBILITY REGARDING EVIDENCE REQUIRED TO MEET THE SUBSTANTIAL EVIDENCE STANDARD

FDA’s existing authority allows for the use of scientifically-driven flexibility in the application of the statutory standards for approval, in particular through the accelerated approval pathway for serious or life-threatening diseases as codified in the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on 09 July 2012. While application of regulatory flexibility has been most prevalent in the areas of oncology and HIV/AIDS, nowhere is the use of such flexibility more impactful than in the case of new therapies for the treatment of serious and life-threatening rare diseases. The need for innovative and flexible approaches to FDA review across divisions increases as more rare disease therapies are being developed, where the contextual knowledge of patients and their diseases often evolves in parallel with clinical development.

Authority for such flexibility is borne directly from federal regulations which state in part “[w]hile the statutory [substantial evidence of effectiveness] standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards.” The regulations go on to empower use of this flexibility by requiring the FDA “to exercise its scientific judgment to determine the kind and quantity of data and information... required to provide for a particular drug to meet the statutory standards” (21 CFR 314.105(c)). More recently, FDA affirmed in draft guidance that “[t]here is no specific minimum number of patients that should be studied to establish effectiveness and safety of a treatment for any rare disease.” (Guidance for Industry - Rare

Diseases: Common Issues in Drug Development, August 2015). Utilizing this authority, FDA allows for the broadest application of flexibility for new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists (21 CFR §312.80).

Congress embraced this flexible approach to drug evaluation in enacting Title IX of FDASIA in 2012. That law provided both the Findings and Sense of Congress with respect to FDA's authority to grant accelerated approval for drugs for serious and life-threatening diseases where the effect on a surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict clinical benefit. Uncertainty about whether clinical benefit would be verified and the possibility of undiscovered risks are the reasons that accelerated approval is reserved for drugs intended to treat serious conditions, such as the use of eteplirsen in the treatment of Duchenne muscular dystrophy. Importantly, FDA acknowledged that approval under such a pathway may involve *"fewer, smaller, or shorter clinical trials than is typical for a traditional approval..."* (FDASIA Section 901(a)(1)(C)) and that *"trials using external controls, such as historically controlled trials, may be considered adequate and well-controlled, and may provide or contribute to evidence of efficacy to support approval."* (FDA Guidance for Industry: *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment*, June 2015). There are numerous examples where FDA's flexibility has established regulatory precedent in rare diseases, including those described in the Sarepta briefing document and:

- Carbaglu[®] (carglumic acid): approved in March 2010 for treatment of N-acetylglutamate synthase (NAGS) deficiency based on a case series from fewer than 20 patients and comparison to a historical control group.
- Ceptrotin[®] (human plasma derived protein C concentrate): approved in March 2007 for the treatment of severe congenital Protein C deficiency based on a study of 18 patients using a comparison to historical control data.

Such variation in the type and quantity of evidence used by the FDA to assess the efficacy of novel therapeutic agents underscores the Agency's flexible approach to meeting standards for drug approval. It is clear in the context of the review of drugs for rare diseases FDA has the authority—and specific direction from Congress—to exercise flexibility in considering all of the available data.

CLARIFICATION OF KEY INACCURACIES IN THE FDA BRIEFING DOCUMENT

Dystrophin Analytical Methodology:

FDA Statement	Sarepta Clarification
<i>“It is important to note that the applicant digitally processed dystrophin images in their background material (images in Appendix 12) in such a way that low intensity values were preferentially increased to produce a higher intensity and higher contrast image.”</i> (FDA BD page 29 of PDF)	The digitally processed images referenced by FDA in this statement were included in Sarepta’s briefing document for demonstration purposes only, and it is far more important to note that the referenced images were not used in the analysis of fiber intensity, nor to score dystrophin-positive fibers.
<i>“Biomarker studies on the 4th biopsy obtained at Week 180 were conducted by the applicant with technical advice from FDA. However, the reliability of results remains questionable for a number of reasons, including the lack of independent confirmation.”</i> (FDA BD page 30 of PDF)	Methodology for dystrophin analyses of the fourth biopsy tissue samples, including confirmatory assessments of percent dystrophin-positive fibers (PDPF) analysis performed by 3 independent pathologists, were agreed with FDA prior to conducting any analyses of the fourth biopsy tissue samples. In accordance with the mutually agreed-upon protocols for the assessment of dystrophin-positive fibers in DMD muscle biopsy samples from the fourth biopsy obtained at Week 180, 3 independent pathologists performed a blinded assessment of the randomized muscle fiber microscopy images, which independently confirmed the results obtained by the pathologist at Nationwide Children’s Hospital (NCH). Assessment of PDPF at NCH indicated a significant increase in PDPF score ($p < 0.001$) relative to untreated control samples. This increase in PDPF score was confirmed by the 3 independent pathologists ($p < 0.001$).
<i>“Random measurement error can be large in comparison to the estimated amount of dystrophin.”</i> (FDA BD page 31 of PDF)	The random measurement error of our Western blot protocol for measurement of dystrophin levels was well below the observed difference between untreated and treated Week 180 biopsy samples. A rigorous validation of the Western blot method was reviewed by the FDA prior to Week 180 biopsy analysis. Validation data demonstrated a %CV of +/- 50% and a linear range ($R^2 > 0.9$) of sensitivity extending as low as 0.25% of normal.
<i>“There is no simple or reliable way to compare estimates of dystrophin amount derived from immunofluorescence with estimates derived from Western blot.”</i> (FDA BD page 35 PDF).	Correlation between dystrophin quantification by Western blot and IHC methods has been demonstrated by multiple laboratories (Taylor, 2012; Anthony, 2011; Anthony, 2014; Hathout, 2015 FDA Workshop on Measuring Dystrophin).

FDA Statement	Sarepta Clarification
<i>“In this context, the applicant selected three BMD patients as comparators for the Week 180 dystrophin studies, one of whom had low dystrophin level of about 2% of normal. However, the BMD patients selected by the applicant do not appear representative, and this patient may correspond to one of the rare BMD patients with very low dystrophin levels.”</i> (FDA BD page 34 of PDF)	BMD patient samples were not chosen to be representative; rather, they were selected in response to an FDA request to assess the relationship between dystrophin as measured by Western blot and immunofluorescence fiber intensity. Therefore, BMD samples were obtained that represented low, middle, and higher ranges of dystrophin expression. A comparable Western blot analysis-IHC correlation was presented by Hathout, et al. (MDA 2015 Scientific Conference poster, FDA-NIH workshop on measuring dystrophin, 2015), where BMD biopsies were chosen to represent low- and mid-level dystrophin expression. Consistently, their BMD low patient biopsy was 2% of normal.

Potential Clinical Impact:

FDA Statement	Sarepta Clarification
<i>“With these two comparisons of eteplirsen to placebo, there was a positive finding for only the lower dose (30 mg/kg) and for just one of the two time points (the later time point). The lack of an effect with the higher dose group tends to undermine the finding in the lower dose group and the lack of even a positive trend at the earlier time point (with a higher dose) sheds doubt on the finding at a later time point.”</i> (FDA BD page 7 of PDF)	The study was designed to see whether dose (50 mg/kg vs. 30 mg/kg) or duration was the most important criterion to enable consistent dystrophin production. • Duration of therapy was observed to be the critical variable when interpreting dystrophin levels. 12 weeks does not represent a clinically relevant duration of therapy (FDA BD page 26 of PDF). • Significant dystrophin levels were by measured at Week 24 for the 30 mg/kg dose, and, importantly, at Weeks 48 and 180 for both the 30 and 50 mg/kg doses by all dystrophin assay methods.
<i>“Arguably, placebo-treated patients who were blinded to treatment assignment from other controlled trials are more appropriate as matched controls than registry patients, as they may receive special care and attention as trial participants, and may be more highly motivated.”</i> (FDA BD page 13 of PDF)	The placebo patients from another study as referenced by the FDA are not appropriate for comparison with the eteplirsen-treated patients (FDA BD pages 8, 9, 40-44, and 50 of the PDF): Baseline characteristics are not comparable between eteplirsen and the proposed placebo group: • Placebo group included boys <7 years old • Placebo group included many patients with baseline 6MWT >440 meters which is outside the eteplirsen trial’s inclusion criteria Placebo patients were followed for only one year, whereas eteplirsen-treated patients were followed for 3 or more years:

FDA Statement	Sarepta Clarification
	• By virtue of the ambulatory requirement at study entry, older placebo patients (e.g. ≥ 11 years) were a group of pre-selected, better performing subjects. • The first year of an 11-year-old-at-baseline placebo patient (i.e. 11-12 years old) to the third year of a 9-year-old boy with 3 years of eteplirsen treatment (i.e. 11-12 years old) is not a valid comparison due to the difference in duration of observation, as well as the biased selection of the 11-year-old ambulatory placebo boy, irrespective of both patients having the same age at last assessment. • Comparison of eteplirsen-treated patients to the appropriately matched external control shows that more than one year is required to observe a divergence in disease progression between the two groups.
<i>“The robustness of the study result is a concern since a single patient could change the results substantially.”</i> (FDA BD page 69 of PDF)	This statement is inaccurate. A comprehensive sensitivity analysis was performed in order to address any potential issue regarding robustness of the data. Specifically: • Two patients were removed: the best performing eteplirsen and the worst performing external control patient. • Results demonstrated a robust 6MWT treatment advantage of >100 meters with nominal significance.
<i>“Finally, as the sponsor’s natural history study proceeded, some patients left to enter interventional clinical trials, further decreasing the similarity of the natural history cohort to the eteplirsen patients.”</i> (FDA BD page 47 of PDF)	The 2 external control patients who entered interventional trials did not diminish the comparability of the natural history cohort. Two types of sensitivity analyses were performed to confirm the magnitude of difference remained over 100 meters and maintained nominal significance: • MMRM using all available data • Last Observation Carried Forward imputation (conservative analysis assuming that the 2 control patients did not decline)

Regulatory Feedback:

FDA Statement	Sarepta Clarification
<i>“As the duration of exposure in Study 202 increased, the applicant proposed comparing the clinical course of treated patients to historical controls.”</i> (FDA BD page 38 of PDF)	The proposal to compare with historical control patients originated from the FDA. Specifically, a requirement to compare the clinical course of treated patients in Study 202 to matched patient-level historical control data was made by the FDA at the March 2014 guidance meeting, and reiterated at the September 2014 pre-NDA meeting. Sarepta had proposed an open-label confirmatory study comparing treated patients to

FDA Statement	Sarepta Clarification
	concurrent (not historical) untreated patients with exon deletions not amenable to skipping exon 51 (i.e. the PROMOVI study).

Philips, Howard

From: Temple, Robert
Sent: Friday, January 08, 2016 11:09 AM
To: Blount, Aprile
Subject: FW: Sarepta DRAFT questions (dec 7 draft).doc
Attachments: Sarepta DRAFT questions (Jan 7 draft).doc.html

I can't find Eric's original. This is Ellis's but you need to change to my markup of Eric's. High priority.

From: Unger, Ellis
Sent: Thursday, January 07, 2016 5:15 PM
To: Bastings, Eric; Temple, Robert
Cc: Farkas, Ronald; Dunn, Billy
Subject: RE: Sarepta DRAFT questions (dec 7 draft).doc

I made some edits. . See what you think. Note my addition of a “(b) (5).” See if you are ok with that.

Ellis

From: Bastings, Eric
Sent: Thursday, January 07, 2016 3:39 PM
To: Temple, Robert; Unger, Ellis
Cc: Farkas, Ronald; Dunn, Billy
Subject: Sarepta DRAFT questions (dec 7 draft).doc

Bob, Ellis,

Here are the revised questions for the Sarepta AC.

Please send me your edits. AC staff deadline is tomorrow. Thanks.

Eric

Philips, Howard

From: Unger, Ellis
Sent: Sunday, January 10, 2016 9:55 PM
To: Dunn, Billy; Bastings, Eric; Temple, Robert
Cc: Blount, Aprile
Subject: FW: Draft questions for etep AC mtg
Attachments: Sarepta AC Questions_1 jkj_eu.doc

I made a few typo corrections to John's edited version, and posed a couple of new Qs.

We'll need to hear back from Janet before finalizing.

I'll be at work tomorrow, though not 100% healthy.

Ellis

From: Unger, Ellis
Sent: Sunday, January 10, 2016 9:53 PM
To: Jenkins, John K
Cc: Temple, Robert; Blount, Aprile
Subject: RE: Draft questions for etep AC mtg

John,

Thanks for edits. Please let us know which way Janet wants to go on [REDACTED] (b) (5).

Ellis

From: Jenkins, John K
Sent: Sunday, January 10, 2016 2:16 PM
To: Unger, Ellis
Cc: Temple, Robert; Blount, Aprile; Jenkins, John K
Subject: RE: Draft questions for etep AC mtg

Ellis

See attached. Lots of edits. I like the idea of [REDACTED] (b) (5).

John

PS: I would like to have a seat at the table for this meeting. Please let the AC staff know.

From: Unger, Ellis
Sent: Friday, January 08, 2016 3:50 PM
To: Jenkins, John K

Cc: Temple, Robert; Blount, Aprile

Subject: Draft questions for etep AC mtg

Hi John,

Could you take a look at these? We originally aimed

(b) (5)

(b) (5)

Thanks,

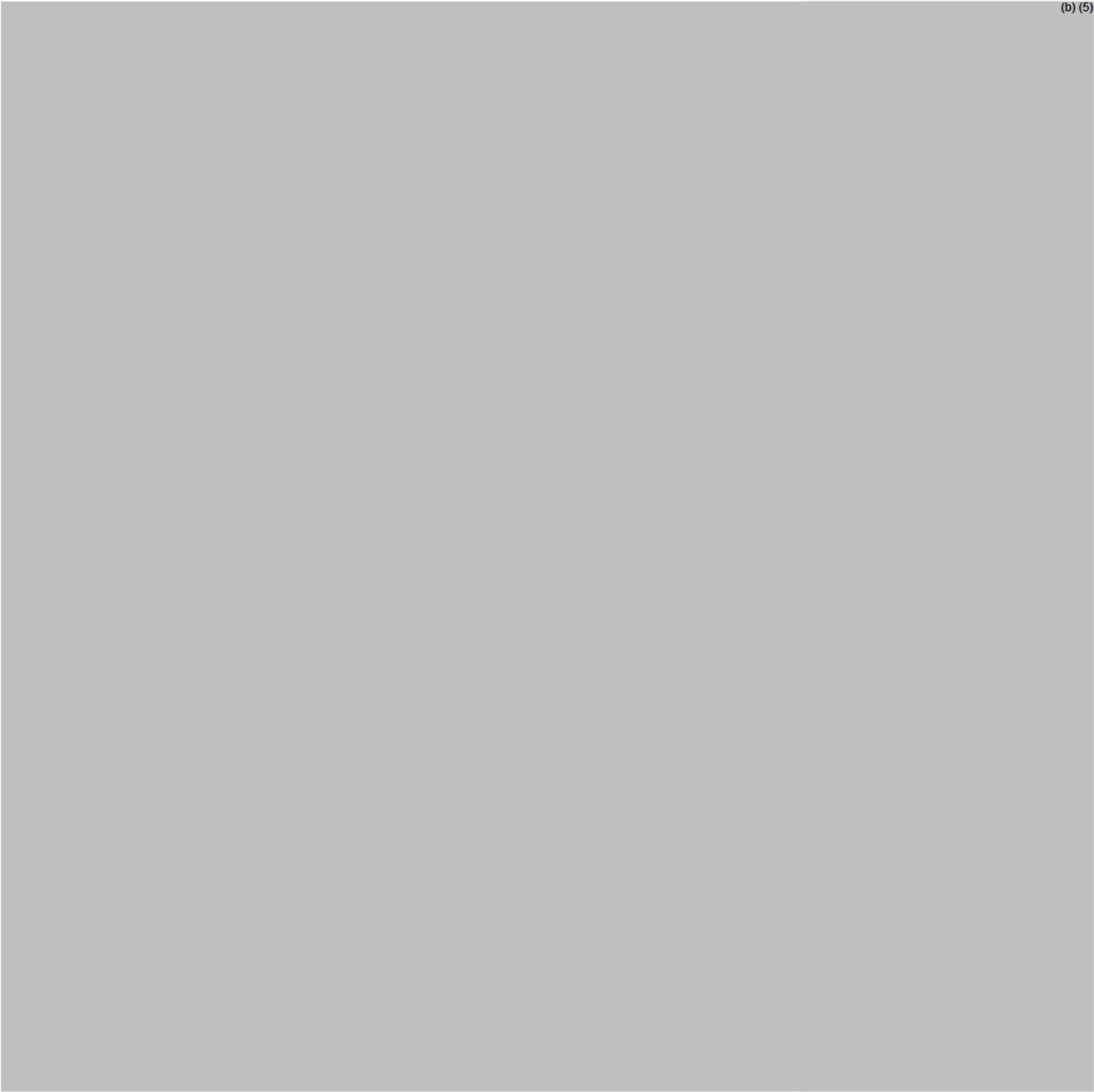
Ellis

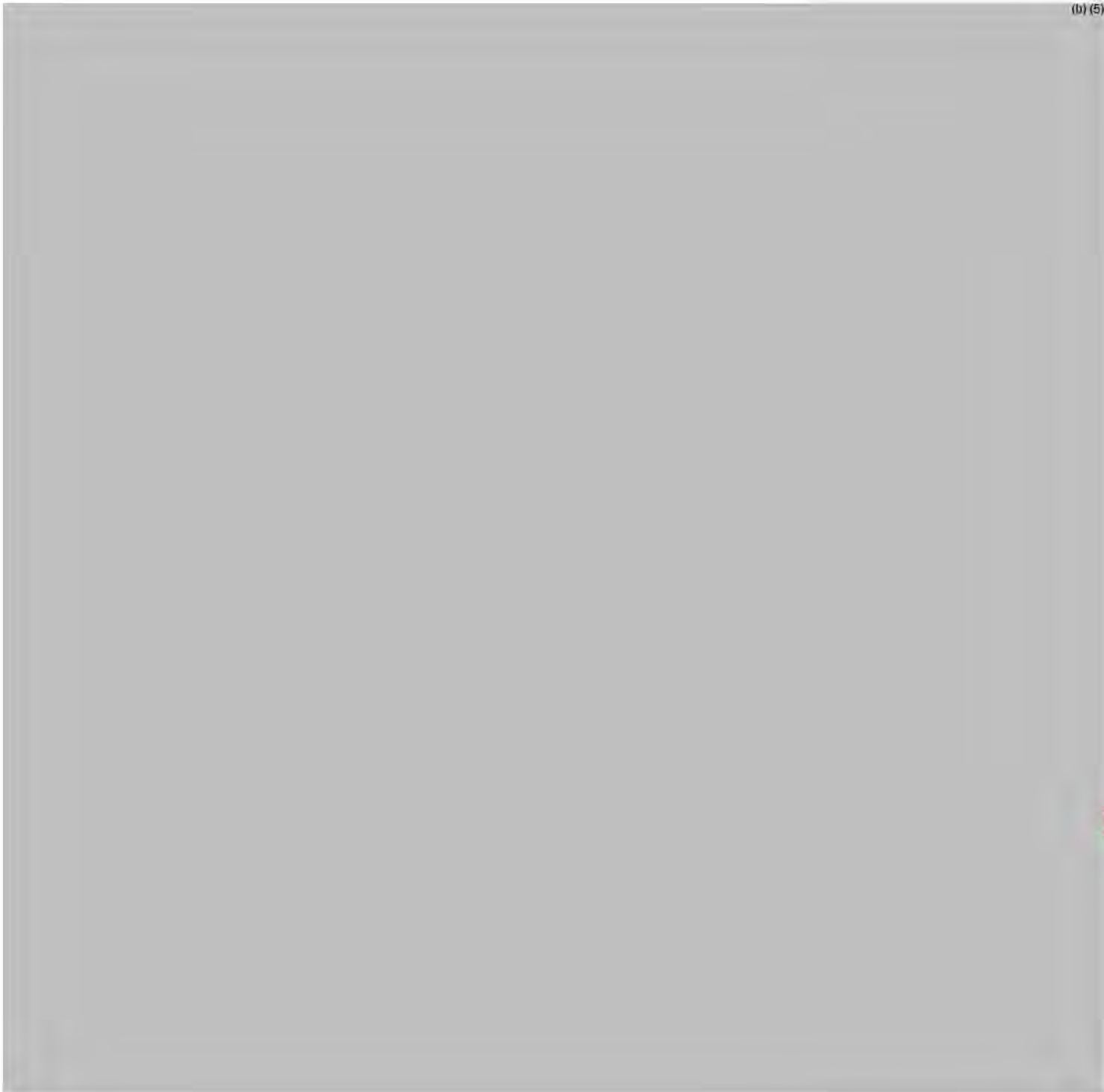
AC QUESTIONS

(b) (5)



(b) (5)





(b) (5)

(b) (5)

(b) (5)

Philips, Howard

From: Temple, Robert
Sent: Monday, January 11, 2016 1:53 PM
To: Blount, Aprile
Subject: FW: (b) (4) for drisapersen
Attachments: 206031_drisapersen_(b) (4).doc.html

From: Dunn, Billy
Sent: Wednesday, December 30, 2015 2:30 AM
To: Temple, Robert
Subject: (b) (4) for drisapersen

Bob,

(b) (4)

Billy

Philips, Howard

From: Farkas, Ronald
Sent: Monday, January 11, 2016 8:53 PM
To: Unger, Ellis; Dunn, Billy; Temple, Robert
Cc: Bastings, Eric
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

(b) (4)

Thanks
Ron

From: Unger, Ellis
Sent: Monday, January 11, 2016 7:44 PM
To: Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

(b) (4)

From: Dunn, Billy
Sent: Monday, January 11, 2016 7:08 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile; Unger, Ellis
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Additional final edits from Bob. This is the final. Bob is sending this to John and Janet.

From: Dunn, Billy
Sent: Monday, January 11, 2016 6:45 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Final letter, clean copy.

From: Dunn, Billy
Sent: Monday, January 11, 2016 6:42 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Final letter in tracked changes.

From: Dunn, Billy
Sent: Monday, January 11, 2016 5:45 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

The final letter is attached. Bob and I are meeting now to make a final review of the letter [REDACTED] (b) (4). We will be coming to Ron to clarify the 3 highlighted statements.

From: Choy, Fannie (Yuet)
Sent: Monday, January 11, 2016 10:36 AM
To: Temple, Robert; Dunn, Billy
Cc: Bastings, Eric; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Here's the version with Dr. Temple's comments.

Thanks
Fannie

Philips, Howard

From: Temple, Robert
Sent: Monday, January 11, 2016 7:49 PM
To: Unger, Ellis; Dunn, Billy; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Not going till tomorrow. We'll look at these.

From: Unger, Ellis
Sent: Monday, January 11, 2016 7:44 PM
To: Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

(b) (4)

From: Dunn, Billy
Sent: Monday, January 11, 2016 7:08 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile; Unger, Ellis
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Additional final edits from Bob. This is the final. Bob is sending this to John and Janet.

From: Dunn, Billy
Sent: Monday, January 11, 2016 6:45 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Final letter, clean copy.

From: Dunn, Billy
Sent: Monday, January 11, 2016 6:42 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Final letter in tracked changes.

From: Dunn, Billy
Sent: Monday, January 11, 2016 5:45 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

The final letter is attached. Bob and I are meeting now to make a final review of the letter (b) (4). We will be coming to Ron to clarify the 3 highlighted statements.

From: Choy, Fannie (Yuet)
Sent: Monday, January 11, 2016 10:36 AM
To: Temple, Robert; Dunn, Billy
Cc: Bastings, Eric; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Here's the version with Dr. Temple's comments.

Thanks
Fannie

Philips, Howard

From: Temple, Robert
Sent: Monday, January 11, 2016 7:06 PM
To: Jenkins, John K
Subject: RE: I plan to attend the eteplirsen LCM today

I will be sending you and JW a “final” version of the CR letter. Barring an amazing turnaround, I expect that action will not be till tomorrow.

From: Jenkins, John K
Sent: Monday, January 11, 2016 1:48 PM
To: Dunn, Billy; Unger, Ellis; Temple, Robert
Subject: I plan to attend the eteplirsen LCM today

Let me know if that is a problem.

BTW, Janet agrees

(b) (5)

Philips, Howard

From: Diggs, Felicia
Sent: Tuesday, January 12, 2016 6:33 PM
To: CDER 120 Calendar; Rosenberg, Amy; Blount, Aprile; Rao, Ashutosh; Bhattaram, Atul; Dunn, Billy; Breder, Christopher D; Throckmorton, Douglas C; Unger, Ellis; Bastings, Eric; Choy, Fannie (Yuet); Hung, Hsien Ming J; Ware, Jacqueline H; Woodcock, Janet; Jenkins, John K; Jin, Kun; LaVange, Lisa; Kozauer, Nicholas; Moscicki, Richard; Guidos, Robert; Temple, Robert; Farkas, Ronald; Kweder, Sandra L; Nevius, S Edward; Ligon, Sharnell (CDER); Tandon, Veneeta; Ling, Xiang; Diggs, Felicia
Subject: CD-Brief Presentation for AC Meeting on Eteplirsen_ Updated with Slide Presentation
Attachments: Eteplirsen CD Briefing.pptx

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.



Eteplirsen

Duchenne Muscular Dystrophy In Patients with Mutations Amenable to Skipping Exon 51

FDA Efficacy Review

(b) (5)

72 pages of draft language have been withheld as b(5) immediately following this page

Philips, Howard

From: Temple, Robert
Sent: Tuesday, January 12, 2016 9:41 AM
To: Farkas, Ronald; Unger, Ellis; Dunn, Billy
Cc: Bastings, Eric
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

(b) (4)

From: Farkas, Ronald
Sent: Monday, January 11, 2016 8:53 PM
To: Unger, Ellis; Dunn, Billy; Temple, Robert
Cc: Bastings, Eric
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

(b) (4)

Thanks
Ron

From: Unger, Ellis
Sent: Monday, January 11, 2016 7:44 PM
To: Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

(b) (4)

From: Dunn, Billy
Sent: Monday, January 11, 2016 7:08 PM

To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile; Unger, Ellis
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Additional final edits from Bob. This is the final. Bob is sending this to John and Janet.

From: Dunn, Billy
Sent: Monday, January 11, 2016 6:45 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald; Blount, Aprile
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Final letter, clean copy.

From: Dunn, Billy
Sent: Monday, January 11, 2016 6:42 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Final letter in tracked changes.

From: Dunn, Billy
Sent: Monday, January 11, 2016 5:45 PM
To: Choy, Fannie (Yuet); Temple, Robert
Cc: Bastings, Eric; Farkas, Ronald
Subject: RE: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

The final letter is attached. Bob and I are meeting now to make a final review of the letter (b) (4) We will be coming to Ron to clarify the 3 highlighted statements.

From: Choy, Fannie (Yuet)
Sent: Monday, January 11, 2016 10:36 AM
To: Temple, Robert; Dunn, Billy
Cc: Bastings, Eric; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: 2016-01-08_NDA206031_drisapersen_DRAFTCR Ltr-RT.doc

Here's the version with Dr. Temple's comments.

Thanks
Fannie

Philips, Howard

From: Farkas, Ronald
Sent: Tuesday, January 12, 2016 10:58 AM
To: Temple, Robert; Dunn, Billy
Subject: RE: Drisaperson CR

(b) (4)

Thanks
Ron

From: Temple, Robert
Sent: Tuesday, January 12, 2016 10:49 AM
To: Dunn, Billy; Farkas, Ronald
Subject: FW: Drisaperson CR

Can you think of what to add re this?

From: Woodcock, Janet
Sent: Tuesday, January 12, 2016 9:57 AM
To: Temple, Robert; Jenkins, John K
Subject: RE: Drisaperson CR

(b) (4)

(b) (4) Thank you. jw

From: Temple, Robert
Sent: Monday, January 11, 2016 7:20 PM
To: Jenkins, John K; Woodcock, Janet
Subject: Drisaperson CR

I am forwarding the drisaperson CR letter. We hope to get it out tomorrow.

Philips, Howard

From: Temple, Robert
Sent: Tuesday, January 12, 2016 6:02 PM
To: Jenkins, John K; Unger, Ellis; Bolek, Michelle; Dunn, Billy; Woodcock, Janet (Janet.Woodcock@fda.hhs.gov)
Subject: RE: Edits to talk points on BioMarin drisapersen CR letter (Duchenne Muscular Dystrophy)

I am waiting for JW's comment on her suggested change.

From: Jenkins, John K
Sent: Tuesday, January 12, 2016 6:00 PM
To: Unger, Ellis; Bolek, Michelle
Cc: Diggs, Felicia; Walsh, Sandy; Rawlings, Kimberly; Shreeve, Chris; Temple, Robert; Woodcock, Janet; Dunn, Billy
Subject: Re: Edits to talk points on BioMarin drisapersen CR letter (Duchenne Muscular Dystrophy)

Has the CR letter issued?

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Unger, Ellis
Sent: Tuesday, January 12, 2016 5:46 PM
To: Bolek, Michelle; Jenkins, John K
Cc: Diggs, Felicia; Walsh, Sandy; Rawlings, Kimberly; Shreeve, Chris; Temple, Robert; Woodcock, Janet; Dunn, Billy
Subject: RE: Edits to talk points on BioMarin drisapersen CR letter (Duchenne Muscular Dystrophy)

Michelle,

In terms of a spokesperson,

If the question is about the CR specifically, it should go to Dr. Temple or to me. Dr. Temple is the subject matter expert here, as he is the signatory on this NDA. I will note, however, that Dr. Woodcock indicated a few weeks ago that she wanted to be available to field questions from the press and/or DMD community, if necessary, so she might want to be looped in.

General questions about drug development for patients with DMD should go to the Division Director – Dr. Billy Dunn.

Ellis

From: Unger, Ellis
Sent: Tuesday, January 12, 2016 5:38 PM
To: Bolek, Michelle; Jenkins, John K
Cc: Diggs, Felicia; Walsh, Sandy; Rawlings, Kimberly; Shreeve, Chris
Subject: RE: Edits to talk points on BioMarin drisapersen CR letter (Duchenne Muscular Dystrophy)

It seems OK as it is, but I suggest the following (if you agree and if you don't need to go through multiple levels of approval). I'm not a big fan of "functionality." We are talking about human beings here, not iPhone apps.

(b) (4)

In terms of spokesperson – I'll get back to you in a second.

From: Bolek, Michelle
Sent: Tuesday, January 12, 2016 5:15 PM
To: Jenkins, John K; Unger, Ellis
Cc: Diggs, Felicia; Walsh, Sandy; Rawlings, Kimberly; Shreeve, Chris
Subject: RE: Edits to talk points on BioMarin drisapersen CR letter (Duchenne Muscular Dystrophy)

Thank you – I will update the talking points accordingly.
Michelle

Michelle M. Bolek, MPH
Office of Communications
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
O: 301-796-2973
BB: 240-447-4682
michelle.bolek@fda.hhs.gov

From: Jenkins, John K
Sent: Tuesday, January 12, 2016 4:59 PM
To: Bolek, Michelle; Unger, Ellis
Cc: Diggs, Felicia; Walsh, Sandy; Rawlings, Kimberly; Shreeve, Chris
Subject: RE: Edits to talk points on BioMarin drisapersen CR letter (Duchenne Muscular Dystrophy)

What is captured is not what was intended. We wanted to remove (b) (4) from the statement and say something like (b) (4)

From: Bolek, Michelle
Sent: Tuesday, January 12, 2016 12:25 PM
To: Jenkins, John K; Unger, Ellis
Cc: Diggs, Felicia; Walsh, Sandy; Rawlings, Kimberly; Shreeve, Chris
Subject: Edits to talk points on BioMarin drisapersen CR letter (Duchenne Muscular Dystrophy)

Edits were made to the talking points per discussion at small staff. Please see the track changes in the attachment and highlighted in the body of the email below. Let us know if there are any concerns with the changes made.

Please also let us know who the spokesperson would be if we get questions around the general topic of DMD drug development or work being done with advocacy groups.

Talking points for advocates, media, public, patients, etc. regarding the issuance of a CR letter to Biomarin for drisapersen

(b) (4)

Michelle M. Bolek, MPH
Office of Communications
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
O: 301-796-2973
BB: 240-447-4682
michelle.bolek@fda.hhs.gov

Philips, Howard

From: Temple, Robert
Sent: Wednesday, January 13, 2016 7:18 PM
To: Jenkins, John K; Unger, Ellis
Cc: Blount, Aprile; Dunn, Billy; Bastings, Eric; Woodcock, Janet; Unger, Ellis
Subject: RE: Draft questions for etep AC mtg

OK, I did not understand.. Completely agree that our own analysis of the data in the historical control study is critical, including the recent data that seem to make it stronger (which we just got, as I understand it, and have not yet analyzed). Given their essentially total reliance on these data as the basis for approval, it would be hard to identify anything more critical.

From: Jenkins, John K
Sent: Wednesday, January 13, 2016 7:07 PM
To: Temple, Robert; Unger, Ellis
Cc: Blount, Aprile; Dunn, Billy; Bastings, Eric; Woodcock, Janet; Unger, Ellis
Subject: Re: Draft questions for etep AC mtg

I did not see our own analyses of the historical data from the two databases. Do we agree that they selected the right patients? Do we agree with their analyses? The sponsor has pivoted to the historical data as their primary evidence and on its surface the effect looks large. We need to have all our analyses to address this if we think is unreliable. Combined with the testimonials these data could lead to a positive vote for approval, very odd given the CR issued today for drisal with tons more data.

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Temple, Robert
Sent: Wednesday, January 13, 2016 7:03 PM
To: Jenkins, John K; Unger, Ellis
Cc: Blount, Aprile; Dunn, Billy; Bastings, Eric; Woodcock, Janet; Unger, Ellis
Subject: RE: Draft questions for etep AC mtg

But we do present our own historical control, don't we.? Aren't the data that we discussed showing the drisaperson placebo data that analysis?

From: Jenkins, John K
Sent: Wednesday, January 13, 2016 6:58 PM
To: Unger, Ellis
Cc: Temple, Robert; Blount, Aprile; Dunn, Billy; Bastings, Eric; Woodcock, Janet; Unger, Ellis
Subject: Re: Draft questions for etep AC mtg

I think the key point as I understand it was that there was no prospective plan to do a historical comparison when the trial started. We later suggested they try to get historical data for comparison when they were telling us they were making "gobbs" of dystrophin and the boys were "stable" or improving. I don't know how involved we were in their planning the historical comparison. I'm also surprised we are not presenting our own historical comparison since we also have the data. Are we essentially agreeing with what they did, just expressing concerns about the interpretability? If not, why is our focus on the same 13 controls and the placebo patients? What happened to all the pharmacometrics analyses?

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Unger, Ellis
Sent: Wednesday, January 13, 2016 6:35 PM
To: Jenkins, John K
Cc: Temple, Robert; Blount, Aprile; Dunn, Billy; Bastings, Eric; Woodcock, Janet; Unger, Ellis
Subject: RE: Draft questions for etep AC mtg

Thanks, John. All of that makes sense.

We appreciate the edits, although Bob and I are a bit concerned about continuing to insist that the comparison of the clinical data from 201/202 to historical controls was “unplanned.” Of course, it was originally unplanned, but then we encouraged the company, with some cautions, to make the comparison. The company pointed out Monday that they resent the notion that, with a failed trial on their hands, they just willy-nilly made the comparison to the registry data.

So we are proposing this edit:

(b) (5)

Please let me know what you think.

Also – you mentioned that you wanted a seat at the table. I presume you haven’t changed your mind, but I just wanted to verify.

Ellis

From: Jenkins, John K
Sent: Wednesday, January 13, 2016 5:31 PM
To: Unger, Ellis
Cc: Temple, Robert; Blount, Aprile; Dunn, Billy; Bastings, Eric; Jenkins, John K; Woodcock, Janet
Subject: RE: Draft questions for etep AC mtg

Ellis

See attached for my proposed edits.

(b) (5)

(b) (5)

John

From: Unger, Ellis
Sent: Tuesday, January 12, 2016 6:46 PM
To: Jenkins, John K
Cc: Temple, Robert; Blount, Aprile; Dunn, Billy; Bastings, Eric
Subject: RE: Draft questions for etep AC mtg

John,

Here's our latest version of the Qs for the eteplirsen AC (hopefully final). I've also attached a tracked changes version from the last one you edited.

Ellis

From: Jenkins, John K
Sent: Sunday, January 10, 2016 2:16 PM
To: Unger, Ellis
Cc: Temple, Robert; Blount, Aprile; Jenkins, John K
Subject: RE: Draft questions for etep AC mtg

Ellis

See attached. Lots of edits. I like the idea of [REDACTED] (b) (5)

John

PS: I would like to have a seat at the table for this meeting. Please let the AC staff know.

From: Unger, Ellis
Sent: Friday, January 08, 2016 3:50 PM
To: Jenkins, John K
Cc: Temple, Robert; Blount, Aprile
Subject: Draft questions for etep AC mtg

Hi John,

Could you take a look at these? We originally aimed [REDACTED] (b) (5)

[REDACTED] (b) (5)

Thanks,

Ellis

Philips, Howard

From: Temple, Robert
Sent: Wednesday, January 13, 2016 12:41 PM
To: Choy, Fannie (Yuet)
Cc: Locicero, Colleen L
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

I would have to skip an existing meeting, but I would plan to do that.

From: Choy, Fannie (Yuet)
Sent: Wednesday, January 13, 2016 12:37 PM
To: Temple, Robert; Unger, Ellis; Bastings, Eric; Dunn, Billy; Farkas, Ronald; Rao, Ashutosh
Cc: Blount, Aprile
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

The alternate is Tuesday January 26th 4:00pm – 5:00 pm.

Our plan was to have a short TC with Sarepta before briefing Dr. Woodcock. If the briefing is at 4pm 1/26, will 11a or 12noon work for the TC with Sarepta? Thanks

From: Temple, Robert
Sent: Wednesday, January 13, 2016 12:31 PM
To: Unger, Ellis; Bastings, Eric; Choy, Fannie (Yuet); Dunn, Billy; Farkas, Ronald; Rao, Ashutosh
Cc: Blount, Aprile
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

I have a meeting then but could skip or move.

From: Unger, Ellis
Sent: Wednesday, January 13, 2016 11:51 AM
To: Bastings, Eric; Choy, Fannie (Yuet); Temple, Robert; Dunn, Billy; Farkas, Ronald; Rao, Ashutosh
Cc: Blount, Aprile
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

That time doesn't work for me either, although I might be able to get the conflicting meeting rescheduled.

From: Bastings, Eric
Sent: Wednesday, January 13, 2016 11:36 AM
To: Choy, Fannie (Yuet); Temple, Robert; Unger, Ellis; Dunn, Billy; Farkas, Ronald; Rao, Ashutosh
Cc: Blount, Aprile
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

It does not work for me. I asked Felicia if she has any opening on 1/26 or 1/27.

Eric

From: Choy, Fannie (Yuet)
Sent: Wednesday, January 13, 2016 11:18 AM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh
Cc: Blount, Aprile
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

Sorry...I meant to ask if 3-4 pm would work for everyone.

From: Choy, Fannie (Yuet)
Sent: Wednesday, January 13, 2016 10:17 AM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh
Cc: Blount, Aprile
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

Hi,

Dr. Woodcock has a hearing on 1/28/16 and will need to push the meeting to 1/28/16 @ 3pm. Felicia is checking whether 3-4 pm would work.

Thank you,
Fannie

-----Original Appointment-----

From: Diggs, Felicia
Sent: Tuesday, December 08, 2015 12:11 PM
To: Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Choy, Fannie (Yuet); Dunn, Billy; Breder, Christopher D; Rao, Ashutosh; Ware, Jacqueline H; Bhattaram, Atul; Ligon, Sharnell (CDER); Blount, Aprile; CDER 120 Calendar; Kozauer, Nicholas
Subject: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting
When: Thursday, January 28, 2016 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: CDER WO BLD 51 Room 6139

Date 1/28/16 2:00 p.m. – 3:00 p.m.

WO BLDG, 51, Rm. 6139

Topic: Discuss application eteplirsen, NME (NDA 206488) Post Advisory Committee Meeting

CDER Staff Contacts: Fannie Choy, RPMS

CDER Executive Operations Staff Contact: Felicia Diggs, DEO liaison

Invited Attendees: Janet Woodcock, Richard Moscicki, Robert Guidos, John Jenkins, Doug Throckmorton, Robert Temple, Felicia Diggs, Sharnell Ligon, Fannie Choy, Ellis Unger, Billy Dunn, Eric Bastings, Ronald Farkas, Veneeta Tandon, Christopher D Breder, Ashutosh Rao, Evelyn Mentari, Sally Jo Yasuda, Alice Hughes, Jackie Ware

Reason for Briefing: The purpose of this meeting is to discuss the outcome and plan of actions for application eteplirsen, NME (NDA 206488) post advisory committee meeting held on January 22, 2016. Eteplirsen proposed indication is for the treatment of patients with Duchene muscular dystrophy due to a deletion in the dystrophin gene that is amenable to exon 51 skipping.

Philips, Howard

From: Unger, Ellis
Sent: Thursday, January 14, 2016 6:56 PM
To: Woodcock, Janet; Jenkins, John K
Cc: Temple, Robert
Subject: Eteplirsen AC Mtg - We decided (b) (5)

Janet and John,

We gathered up the senior leadership of DNP and ODE-I and had a 90-minute discussion about the (b) (5)
.

In the end, we were all pretty much on the fence (b) (5) Without anyone making a compelling
argument for why we (b) (5)
.

(b) (5)

So the Division will present the data and its concerns, and we will all do our level best to search objectively for the truth.

And thank you for considering this decision on short notice.

Ellis

COMPLETED

Rou
cc Ellis

1/14/2016



U.S. Food and Drug Administration
Protecting and Promoting Public Health

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Eteplirsen

(b) (5)

(u) (2)

44 pages of draft language have been withheld as b(5) immediately following this page

Temple, Robert

From: Unger, Ellis
Sent: Monday, January 18, 2016 11:14 PM
To: Bastings, Eric; Farkas, Ronald; Dunn, Billy; Temple, Robert
Subject: RE: Main slide deck
Attachments: Eteplirsen CD Briefing Jan 18 draft.pptx

They look pretty good. I made a number of editorial changes and a few substantive changes. Some are just suggestions. There are also questions. I tried to show questions and issues in red font.

See, in particular, slides 6, 26, 27, 33, 40, 42, 43, 49, 52, 55, 56, 57, 61, 70, 74, 76, 80, 81, 82-85, 88, 92, and 94. I would delete the slide about (b) (5)

Ellis

From: Bastings, Eric
Sent: Monday, January 18, 2016 3:37 PM
To: Farkas, Ronald; Unger, Ellis
Cc: Dunn, Billy
Subject: Main slide deck

Here are my edits to the main slide deck. Ron may want to add a few things that we discussed today (e.g., (b) (5)

(b) (4)
I added some details (b) (5)
(b) (5)

The plan will be for Billy to include in his initial comments concepts about FDA standards for approval, and introduce the Sarepta development program.

Ron and Ash will make the main presentation.

If time allows, I would like to give closing arguments.

Eric

Philips, Howard

From: Dunn, Billy
Sent: Wednesday, January 20, 2016 12:33 PM
To: Jenkins, John K; Unger, Ellis; Woodcock, Janet; Temple, Robert
Cc: Bastings, Eric; Blount, Aprile; Clarke, Mary Beth; Peterson, Jayne E
Subject: RE: Eteplirsen AC - possible postponement B/O snow

We have just completed another inclement weather meeting. I was on the phone, but it is clear that there is considerable anxiety on the part of all involved that we need to get the word out ASAP. All 25 folks that attended the meeting agreed that the meeting should be postponed. I was asked to pass on that DACCM, OHCA, and PASE, and Facilities are all strongly recommending postponement of the meeting and are very concerned that we have not yet announced the decision. Several participants brought up concerns regarding inability to ensure staff would be present to manage the meeting and concerns about the safety of our staff in attempting to travel home.

Billy

From: Jenkins, John K
Sent: Wednesday, January 20, 2016 8:51 AM
To: Dunn, Billy; Unger, Ellis; Woodcock, Janet; Temple, Robert
Cc: Bastings, Eric; Blount, Aprile; Clarke, Mary Beth; Peterson, Jayne E; Jenkins, John K
Subject: RE: Eteplirsen AC - possible postponement B/O snow

Including Mary Beth and Jayne so they are aware of the division recommendation.

If we do postpone the meeting to (b) (5), we may be able to consider the new data submitted by Sarepta last week to be a major amendment and extend the PDUFA goal date by up to 3 months. This would allow more time to fully evaluate these new data, particularly the suggestion that all boys in the historically controlled cohort have stopped walking.

John

From: Dunn, Billy
Sent: Wednesday, January 20, 2016 8:37 AM
To: Unger, Ellis; Woodcock, Janet; Jenkins, John K; Temple, Robert
Cc: Bastings, Eric; Blount, Aprile
Subject: RE: Eteplirsen AC - possible postponement B/O snow

We had an inclement weather planning meeting yesterday with about 15 folks. We asked a lot of pointed questions and received some strong advice to announce the postponement as early as possible this morning, if we were going to do so. There was also strong advice to us (which I was opposed to at the time, but now agree with) to postpone. We have a backup date of (b) (5) already in place.

The weather models remain well-aligned overnight. "Computer models that came in between 9 p.m. and midnight forecast very substantial to historic snowfall amounts for the D.C. area Friday into Saturday night or Sunday morning." "Computer models, without exception, are forecasting over 10 inches of snow in the D.C. area with a few throwing around 20 inch plus numbers."

Some of the issues that were stressed to us during our planning meeting yesterday:

- The earlier we get the word out the better
- A last minute postponement will cause more disruption than advance notice this morning
- Many attendees will be traveling today, not tomorrow, particularly those coming from Europe

- AC members will decline to travel here because of the effects of the weather on return travel
- If the government closes early on Friday, we will be required to end the AC prematurely
- There was strong advice to us that “we will look much worse postponing later rather than earlier”
- Travel, both air and road, is likely to be highly disrupted or impossible later on Friday

Given the logistical challenges for many of the planned attendees, the more advance notice they have the better, despite the disappointment of a postponement. Further complicating the issue is that road travel later on Friday will be difficult and dangerous.

For these reasons, although it was not my preference yesterday, my strong recommendation is to announce as early as possible this morning that we have postponed the AC.

Billy

From: Unger, Ellis
Sent: Tuesday, January 19, 2016 4:51 PM
To: Woodcock, Janet; Jenkins, John K; Temple, Robert
Cc: Dunn, Billy; Bastings, Eric; Blount, Aprile
Subject: RE: Eteplirsen AC - possible postponement B/O snow

Janet,

We are waiting at this point, and we (DNP/OND-I) are strongly in favor of going ahead with the meeting this Friday as planned. But holding the meeting would not be possible if the Government is closed apparently.

We are scheduled to have another t-con at noon tomorrow.

Supposedly the computer weather models have strongly converged on an East Coast storm Friday into Saturday – high probability/high impact. I would say that if the models are still predicting a large snowfall as of noon tomorrow, their consensus will be to postpone.

Do you want them to wait until the end of the day tomorrow before making a decision?

Ellis

From: Woodcock, Janet
Sent: Tuesday, January 19, 2016 4:34 PM
To: Unger, Ellis; Jenkins, John K; Temple, Robert
Cc: Dunn, Billy; Bastings, Eric; Blount, Aprile
Subject: RE: Eteplirsen AC - possible postponement B/O snow

I would prefer waiting until we know more. jw

From: Unger, Ellis
Sent: Tuesday, January 19, 2016 2:00 PM
To: Jenkins, John K; Woodcock, Janet; Temple, Robert
Cc: Dunn, Billy; Bastings, Eric; Blount, Aprile
Subject: Eteplirsen AC - possible postponement B/O snow

We just got off the phone with advisors and consultants, OCOMM, etc. We heard that we may have to postpone, obviously, and have decided to make a decision tomorrow AM or late AM based on forecasts at the time. (DNP and ODE-I will not be the decision-makers.)

There is a backup date - (b) (5) but you should know that such a delay would mean that we'd miss the goal date.

Sent from my BlackBerry.

Philips, Howard

From: Temple, Robert
Sent: Thursday, January 21, 2016 1:56 PM
To: Unger, Ellis; Choi, Moon Hee; Choy, Fannie (Yuet)
Cc: Ngo, Diem-Kieu (CDR,USPHS); Farkas, Ronald; Dunn, Billy; Bastings, Eric; Blount, Aprile
Subject: RE: DNP Availability to Discuss Meeting Date for Eteplirsen

I think Dr. Woodcock has already told Texas she will not be coming and I would do the same. We both intend to go to the A.C.

From: Unger, Ellis
Sent: Thursday, January 21, 2016 11:33 AM
To: Choi, Moon Hee; Choy, Fannie (Yuet)
Cc: Ngo, Diem-Kieu (CDR,USPHS); Farkas, Ronald; Dunn, Billy; Bastings, Eric; Temple, Robert; Blount, Aprile
Subject: RE: DNP Availability to Discuss Meeting Date for Eteplirsen

I don't know whether DNP is available, but I am available on 2/23.

It looks like Dr. Temple will be in Texas at a conference. It would not be desirable for Dr. Temple to miss the meeting, but it would be OK for him to miss if necessary.

But I see that Dr. Woodcock is also on the ICD2 meeting agenda – scheduled to participate in a roundtable discussion on 2/23. So I suggest you check with her office.

Ellis

<https://www.utexas.edu/pharmacy/ce/conferences/icdd/agenda.html>

From: Choi, Moon Hee
Sent: Thursday, January 21, 2016 11:26 AM
To: Choy, Fannie (Yuet)
Cc: Ngo, Diem-Kieu (CDR,USPHS); Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: DNP Availability to Discuss Meeting Date for Eteplirsen
Importance: High

Hi Fannie,

Can you see if DNP would be available for a quick tcon to discuss rescheduling the eteplirsen meeting?

Also, attached you will find the draft FR Notice and Sign-off Clearance Record with the (b) (5) meeting date. Please only revise the yellow highlighted items. Please obtain the Office and Division Director signatures as we need to submit the new FR ASAP if we are to move forward with the (b) (5) date.

Thanks so much and I look forward to hearing from you.

Moon

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

**PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE**

January 22, 2016

Ellen
P 31

**ETEPLIRSEN BRIEFING DOCUMENT
NDA 206488**



Sarepta Therapeutics, Inc.
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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
6MWT	6-Minute Walk Test
AA	Accelerated Approval
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AUC	area under the concentration time curve
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
AVI-4658	eteplirsen
BL	Baseline
BLQ	below the limit of quantification
BMD	Becker muscular dystrophy
BMI	body mass index
BUN	blood urea nitrogen
CDC	Centers for Disease Control
CK	creatine kinase
CLPL	plasma clearance
C _{max}	maximum concentration
CYP	cytochrome P450 enzymes
CXMD	canine X-linked muscular dystrophy
DAPC	dystrophin-associated protein complex
DMD	Duchenne muscular dystrophy
DMD gene	dystrophin gene
ECG	electrocardiogram
ECHO	echocardiogram
EDB	extensor digitorum brevis
EF	ejection fraction
EK	Egen Klassifikation
ELISPOT	enzyme-linked immunosorbent spot assay

FDA	Food and Drug Administration
FVC	forced vital capacity
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practices
hDMD	humanized DMD mouse model
HR	heart rate
ICC	interclass correlation coefficient
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IM	intramuscular, intramuscularly
IND	Investigational New Drug
INR	international normalized ratio
IV	intravenous, intravenously
LOCF	last observation carried forward
LVEF	left ventricular ejection fraction
Max	maximum
mdx	dystrophic mouse model
MEP	maximum expiratory pressure
Min	minimum
MIP	maximum inspiratory pressure
MMRM	mixed model repeated measure
MVICT	maximum voluntary isometric contraction testing
NA	not applicable
NDA	New Drug Application
NHP	non-human primates
NMRC	Neuromuscular Reference Center
N/n	number
nNOS	nitric oxide synthase
NOAEL	no observed adverse effect level
NSAA	North Star Ambulatory Assessment
PDPF	Percentage of dystrophic positive fibers
PFTs	pulmonary function tests
PK	pharmacokinetic

PMO	Phosphorodiamidate morpholino oligomer
PODCI	Pediatric Outcomes Data Collection Instrument
PPMD	Parent Project Muscular Dystrophy
PT	prothrombin time
PUL	Performance Upper Limb Scale
QMT	quantitative muscle testing
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAM	step activity monitor
SD	standard deviation
SOC	System Organ Class
t _{1/2}	elimination half life
TA	tibialis anterior
TEAE	treatment emergent adverse event
ULN	upper limit of normal
United Kingdom	UK
US	United States
V _{ss}	apparent volume of distribution at steady-state
WB	Western blot

1. EXECUTIVE SUMMARY

Sarepta Therapeutics (Sarepta) is seeking accelerated approval (AA) for eteplirsen (administered as weekly 30 mg/kg IV infusions) for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping therapy. This executive summary provides an overview of the attributes of the eteplirsen development program that specifically meet the criteria listed below as requirements for accelerated approval. A complete description of each of the clinical and nonclinical results of the development program for eteplirsen is provided in respective sections of this briefing document that follow this executive summary.

Regulatory Framework

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) codified FDA's accelerated approval authority. The statute provides that FDA may grant AA of a product:

- *“for a serious or life-threatening disease or condition”*
- *that “has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.”*

The AA pathway means that there will be an acceptable degree of uncertainty about whether the therapy will actually result in the anticipated clinical benefit. This uncertainty is addressed by the requirement that “appropriate post-approval studies to verify and describe the predicted effect” would usually be underway at the time of approval.

This uncertainty about whether the ultimate clinical benefit will be achieved is accounted for by the requirement that a product approved under the accelerated approval program have:

- *“appropriate post-approval studies to verify and describe the predicted effect,”* which are generally referred to as confirmatory postmarketing studies. FD&C Act §506(c)(2)(A). FDA's regulations explain that at the time of accelerated approval, the *“[p]ostmarketing studies would usually be studies already underway.” 21 C.F.R. §314.510.*

Examples of FDA's Flexibility

Historically, FDA has exercised some form of regulatory flexibility in the approval of new drugs for serious and rare conditions with unmet medical needs (Sasinowski 2015). Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs. "Adequate and well-controlled studies" must have *“a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.” 21 C.F.R. §314.126(b)(2).* FDA recognizes historically controlled studies, where *“[t]he results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition...,”* to be "adequate and well-controlled." 21 C.F.R. §314.126(b)(2)(v). In

prior drug approvals, FDA has determined that studies with small numbers of patients, as well as comparison to untreated historical controls, were adequately and well-controlled and thus met the “substantial evidence” standard of effectiveness.

Examples of such regulatory precedents are as follows:

- Myozyme (alglucosidase alfa) was approved on April 28, 2006 for the treatment of patients with infantile onset Pompe disease. The approval precedent reflects the use of a natural history database to create a subgroup-matched historical control, selecting patients from the broader population with efficacy that meet certain prognostic factors (e.g., age, age of onset, documented phenotype).
- Cresemba (isavuconazonium) was approved on March 6, 2015 for the treatment of adults with invasive aspergillosis and invasive mucormycosis.
- Cholbam (cholic acid) was approved on March 17, 2015 for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs), and as adjunctive treatment of peroxisomal disorders (PDs), including Zellweger spectrum disorders.

Regulatory History: Brief Summary

The regulatory history of eteplirsen is non-traditional, in that the primary efficacy outcome results are based on a small Phase 2 study which was compared to natural history control data obtained from 2 observational studies. After multiple discussions and interactions during 2013 to 2015, FDA provided a pathway for a “fileable” NDA for accelerated approval of eteplirsen and also agreed on the design of two confirmatory studies. The flexibility demonstrated by FDA was due to the serious, fatal nature of DMD, the absence of approved therapies, evidence that the drug induces the production of de novo dystrophin and has a measurable effect on functional outcomes. Additional detail is provided in [Section 3.4](#) and [Appendix 1](#).

Eteplirsen Is Intended to Treat a Rare Serious Medical Condition

Duchenne Muscular Dystrophy (DMD) is a serious, progressively debilitating, and ultimately fatal inherited X-linked neuromuscular disease. DMD is caused by mutations in the dystrophin gene that disrupt the mRNA reading frame, resulting in a lack of dystrophin, a critically important part of the protein complex that connects the cytoskeletal actin of a muscle fiber to the extracellular matrix. In the absence of dystrophin, patients with DMD follow a predictable disease course. Affected boys develop muscle weakness in the first few years of life, lose the ability to walk during childhood, and usually require respiratory support by their late teens. Loss of functional abilities leads to loss of independence and increasing caregiver burden. Once lost, these abilities cannot be recovered. Despite improvements in the standard of care, such as the use of glucocorticoids, DMD is an irreversible fatal disease and patients usually die of respiratory or cardiac failure in their mid to late 20s.

The prevalence of DMD in the US is approximately 9,000 to 12,000. Approximately 13% of DMD patients have mutations of the dystrophin gene that are amenable to therapies that skip exon 51, which corresponds to ~1,300-1,900 patients in the US. Genetic testing for DMD can readily and reliably identify patients amenable to exon 51 skipping therapy.

High Unmet Medical Need in DMD despite Current Standard of Care

There are no approved therapies in the US for DMD. Current standard of care guidelines for the treatment of DMD include the administration of glucocorticoids in conjunction with palliative interventions. While glucocorticoids can delay the loss of ambulation and other correlates of disease progression, they do not sufficiently ameliorate symptoms, modify the underlying genetic defect or address the absence of functional dystrophin characteristic of DMD. Moreover, glucocorticoid use is often limited by numerous side effects. Most importantly, glucocorticoids do not alter the ultimate fatal nature of the disease course.

Eteplirsen is a Targeted Therapy Specifically Designed to Treat DMD Patients Amenable to Exon 51 Skipping

The direct cause of DMD is an absence or near absence of functional dystrophin, a critical structural protein that protects muscle from injury. Normal dystrophin links intracellular actin filaments of a muscle fiber (via N-terminus) to the cell membrane and extracellular matrix (via C-terminus) acting as a “molecular shock absorber”. DMD mutations amenable to exon 51 skipping therapies impair the reading of pre-mRNA resulting in an inability to assemble the correct amino acids for construction of the C-terminus of the dystrophin protein. Eteplirsen’s mechanism of action is to remove exon 51 of the pre-mRNA, thereby shifting the pre-mRNA “reading frame”, enabling the reading of the remaining protein including assembly of the C-terminus. This mechanism is similar to a clinically milder form of dystrophinopathy, Becker’s muscular dystrophy (BMD), where the naturally occurring mutation(s) results in a shortened central domain (missing amino acids corresponding to deleted exons), but correct in-frame reading of the pre-mRNA distal to the deleted exon(s), thus enabling assembly of the correct amino acids for construction of the C-terminus and dystrophin functionality is retained.

Eteplirsen is a Structurally Unique Phosphorodiamidate Morpholino Oligomer

Eteplirsen belongs to a distinct class of novel synthetic antisense RNA therapeutics known as Phosphorodiamidate Morpholino Oligomers (PMO). Eteplirsen’s sequence of 30 nucleobases is complementary to a specific target sequence within exon 51 of dystrophin pre-mRNA. It is structurally distinct from RNA and other RNA analogues (such as 2’-O-methyl phosphorothioates) through its specific use of 6-membered morpholino rings and uncharged phosphorodiamidate linkages throughout the oligomer. PMOs are distinct from other classes of clinical-stage synthetic antisense oligonucleotides, which typically have a 5-membered ribose ring and negatively charged phosphorothioate linkages.

- The PMO backbone was designed to resist enzymatic degradation and provide stability *in vivo*.
- In nonclinical studies, minimal non-specific protein binding, likely due to the uncharged phosphorodiamidate linkages, is observed.

Pivotal Study 201/202 Design

Study 201 is a completed double-blind, placebo-controlled study of eteplirsen in 12 ambulatory boys with DMD mutations amenable to exon 51 skipping. Eligible patients were randomized to receive weekly IV infusions of 30 mg/kg (N = 4), 50 mg/kg eteplirsen (N = 4) or placebo (N = 4) for the first 24 weeks.

- Following completion of the 24-week double-blind, placebo-controlled period, the 4 patients originally randomized to placebo rolled over to o eteplirsens of 30 mg/kg (N = 2) or 50 mg/kg (N = 2) at Week 25. All 1. continued receiving weekly eteplirsens in the ongoing extension Study : 3 years.
- The primary clinical endpoint of the single arm 202 study was the 6MWT, and % dystrophin-positive fibers was the primary pharmacodynamic endpoint. Clinical outcomes of North Star Ambulatory Assessment (NSAA), pulmonary function tests (PFT), loss of ambulation (LOA), and other functional measures were supportive. Clinical outcomes have been collected through Week 168 for the 12 patients enrolled in Studies 201/202.
- Given the relatively short 24-week placebo control period, the FDA requested that Sarepta obtain external control data from DMD registries with longitudinal 6MWT data. After partnering with leading DMD experts, Sarepta identified 12 international DMD registries with extensive clinical data. Of these, 2 registries were selected based on the availability of longitudinal 6MWT data for external control comparisons.
- The external control groups were comparable to the eteplirsens treated boys in terms of the key prognostic factors for DMD progression used as inclusion criteria for Study 201/202, baseline age, 6MWT and representation of genetic subtype; 2 external control groups were identified:
 - A highly comparable group with DMD mutations amenable to exon 51 skipping therapy (N = 13) (primary external control group)
 - A larger group of boys with DMD mutations amenable to any kind of exon skipping therapy (N = 50) (secondary external control group)

Sarepta?
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for

The comparison of clinical outcomes versus untreated External Control data on 6MWT and additional supportive endpoints is the basis for eteplirsens's submission to the FDA.

Eteplirsens Treatment Demonstrates an Effect on the "Intermediate" Clinical Endpoint 6MWT – That Is Reasonably Likely to Predict a Clinical Benefit

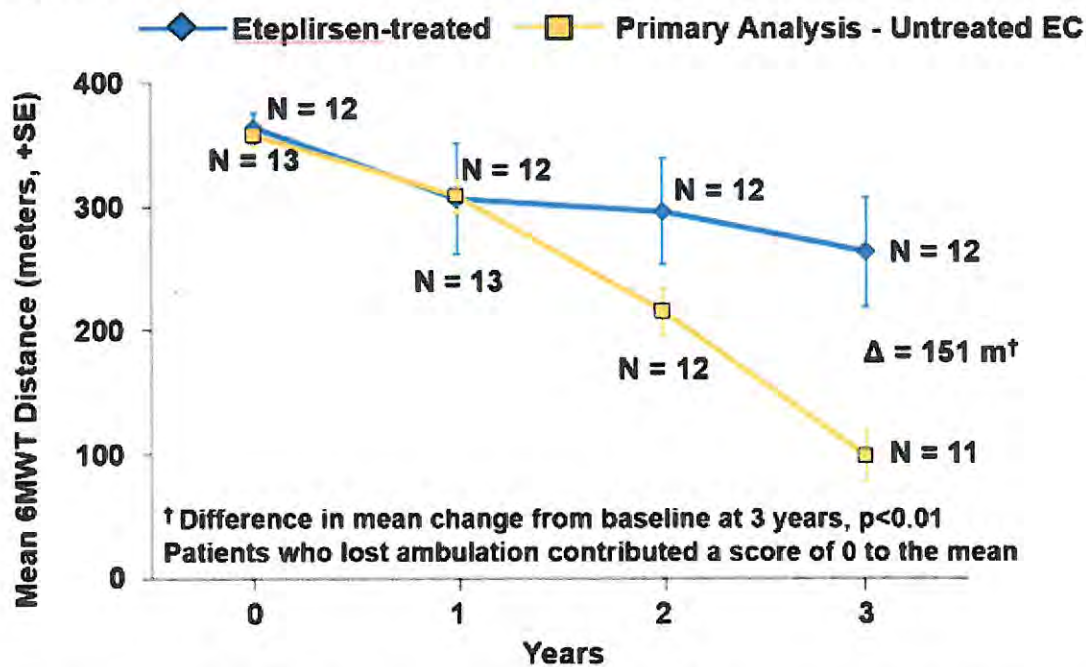
6 Minute Walk Test

Given the pivotal role of ambulation in daily human function and the impact of its inevitable loss in DMD, the 6MWT was agreed upon with FDA as the "intermediate" clinical efficacy outcome for Accelerated Approval. As the majority of the 6MWT data from eteplirsens was from a single arm study, FDA requested that data from external DMD registries be obtained for comparison of the long-term clinical outcomes; primarily the 168-week longitudinal 6MWT data from the eteplirsens 202 Phase 2b study. The pre-specified criteria for external control selection paralleled the Study 201/202 inclusion criteria which selected for a relatively homogeneous population that would be expected to decline on the 6MWT. Of note, in both Study 201/202 and the external registries, the 6MWT was conducted in a standardized manner according to international guidelines.

Not true, any evidence of that?

There was a high degree of homogeneity and comparability between eteplirsen and untreated external control patients for baseline characteristics including age, 6MWT and representation of DMD genetic subtypes. Moreover, uniformity of DMD care between the 2 patient groups was shown with high compliance to international DMD care guidelines, including the longitudinal use of steroids, physical therapy and orthotic devices.

Eteplirsen treated patients from pivotal Study 201/202 (N = 12) demonstrated a durable and large magnitude of effect, a 151 meter advantage, over the course of 3 years, when compared to a highly comparable external control (EC) of similarly aged untreated boys with DMD mutations amenable to exon 51 skipping (N = 13). This treatment effect manifested in a divergence of the trajectory of disease following the first year of eteplirsen therapy.



When compared to a larger external control group of DMD patients amenable to any exon skipping therapy (N = 50), there was a substantive advantage of 79 meters for patients treated with eteplirsen at Year 3. This larger group of DMD patients provides a more conservative comparison, which is representative of the broader DMD patient population amenable to exon skipping.

A series of sensitivity analyses of the 6MWT results accounting for covariates of age and baseline 6MWT consistently demonstrated a clinically relevant advantage for the eteplirsen treated group compared to the external control patients with exon 51 skippable mutations. Nominal p values associated with the sensitivity analyses continued to be significant.

The 151 meter difference between eteplirsen and external control exon 51 patients (N = 13) is clinically significant and statistically persuasive.

Eteplirsen Treatment Demonstrates an Effect on a Potential Surrogate Endpoint (dystrophin) - That Is Reasonably Likely to Predict a Clinical Benefit

Novel Dystrophin Production

Eteplirsen mechanism of action has been established via RT-PCR testing and sequencing which showed exon skipping and also the presence of internally shortened dystrophin mRNA in all eteplirsen-treated patients evaluated to date.

Significant dystrophin production was demonstrated as early as Week 24 of pivotal Study 201 with increased levels of percent dystrophin positive muscle fibers (PDPF) and dystrophin intensity, compared to pre-treatment values. Moreover, the 24-week findings were confirmed by an independent review by 3 pathologists.

Sustained dystrophin production was shown through Week 180 by three assays, with complementary detection techniques each showing significant increases in dystrophin including percent dystrophin positive fibers, dystrophin intensity by fluorescence and Western Blot. The methodology for dystrophin testing was developed in consultation with FDA.

Week 180 Dystrophin Assays	Untreated (Mean % Dystrophin of Normal)	Treated (Mean % Dystrophin of Normal)	Difference of Means (Treated vs. Untreated)	P-Value
PDPF	1.12%	17.39%	+16.27%	<0.001
Intensity	9.41%	22.61%	+13.20%	<0.001
Western Blot	0.08%	0.93%	+0.85%	<0.007

Supportive Endpoints of Loss of Ambulation, NSAA and PFTs Consistent with 6MWT

Loss of Ambulation

Ambulatory compromise and loss of ambulation are hallmarks of the progressive muscle degeneration characteristic of DMD. Once confined to a wheelchair, other symptoms tend to follow in rapid succession. Consistent with results of the 6MWT, fewer eteplirsen treated boys lost ambulation (2/12; 16.7%) compared to the external control patients who were amenable to exon 51 skipping therapy (6/13; 46.2%) or compared to the external cohort of boys with mutations amenable to any exon 51 skipping (18/50; 36%).

later

Northstar Ambulatory Assessment (NSAA)

The NSAA is a clinician-reported outcome instrument specifically designed to measure function in ambulatory patients with DMD. The 17-items are scored on an ordinal scale and include assessments of abilities such as rising from the floor, climbing and descending a step, 10-meter walk/run and lifting the head. In both Studies 201/202 and the external Italian Telethon registry, the NSAA was performed according to standardized published methods.

In the comparison of baseline NSAA, both the eteplirsen treated patients and untreated external control patients (exon 51) had impaired and/or lost functional abilities with a total score of 24.9 and 22.0 out of a possible 34 total score. Over the first year, both the eteplirsen treated boys and the Italian Telethon group declined in NSAA function. However, following Year 1, the decline in function for the eteplirsen group became slower and by the end of Year 3 there was a

no Δ

~3 point greater decline for the untreated boys. The 3-point difference is of clinical relevance and may represent loss or impairment of up to 3 activities.

Rise Time

The ability to rise from supine is a critical activity for DMD patients and it is one of the early abilities to be lost in DMD and is predictive of loss of ambulation. In the analysis comparing the ability to rise from a supine position (without external support) 92% vs 88% of eteplirsen treated vs Italian Telethon patients had this ability at baseline. However at the end of Year 3, 55% of eteplirsen treated boys had maintained the ability to rise whereas only 14% of the Italian Telethon patients maintained this ability.

Pulmonary Function Tests

Respiratory function in DMD is progressively impaired over time as the dystrophic process affects respiratory muscles, including the diaphragm leading to significant morbidity and mortality. Pulmonary function data from DMD patients who received eteplirsen for approximately 3 years were compared to patient level data. Eteplirsen treated boys had slower deterioration of respiratory muscle function as measured by FVC %predicted (annual decrease of 3.2%) when compared to a cohort of patients in the same age range (annual decrease of 5.8%). Additionally, based on review of published literature MEP %predicted and MIP %predicted may also decline more slowly with eteplirsen treatment, although the comparison is limited.

Safety

The safety profile of eteplirsen has been characterized in 114 patients with DMD amenable to exon 51 skipping therapies, including 88 patients who have received doses of 30 mg/kg or higher. Safety monitoring has included frequently scheduled clinical and/or laboratory assessments for infusion reactions, renal toxicity, hepatotoxicity, coagulopathy, and cutaneous and cardiac-related events with no apparent signal for significant safety risks.

The drug is well tolerated as evidenced by the low rates of serious or severe or adverse events leading to discontinuation of study drug.

- The favorable tolerability of eteplirsen is demonstrated by low rates of treatment emergent SAEs (N = 2; 1.8%) and AEs resulting in study drug discontinuation (N = 1; 0.9%).
- The most common ($\geq 10\%$ of patients) TEAEs occurring in patients treated with eteplirsen at the clinical dose of ≥ 30 mg/kg and observed at higher rates than reported for placebo were headache, vomiting, cough, procedural pain, upper respiratory infection, arthralgia, contusion, excoriation, nasopharyngitis, and nasal congestion.
 - The majority of events were mild and resolved with ongoing study drug.
 - Many events may be reflective of the types of conditions that occur in a pediatric population with DMD.
- Three mild events were considered potential adverse drug reactions due to the temporal relationship with eteplirsen administration: erythema, flushing, and mild temperature elevation.

- Adverse Events of Special Interest (i.e., cardiac, renal, hepatic, coagulopathy, infusion and cutaneous reactions, and leukopenia) and related safety laboratory parameters were reviewed and no apparent safety signal was detected.

Favorable Benefit Risk Profile of Eteplirsen

The favorable benefit of eteplirsen is demonstrated by multiple endpoints presenting both clinical and pharmacodynamics evidence showing that eteplirsen offers boys with DMD (who are amenable to exon 51 skipping) an effective treatment.

- Eteplirsen mechanism of action and production of novel dystrophin has been established by pharmacodynamic data from 36 patients across 4 studies;
 - Significant differences in dystrophin production when compared to baseline or untreated controls as early as Week 24 and sustained through Week 180 using methodology developed in collaboration with FDA
- Primary endpoint of 6MWT (intermediate endpoint for accelerated approval) demonstrates that eteplirsen offers boys a significantly slower rate of decline in ambulation, endurance, and muscle function as measured by the 6MWT over a 3-year treatment period compared to highly comparable untreated external controls.
 - Large and significant effect compared to external control of 151 meters
 - Importantly, fewer eteplirsen treated boys experienced loss of ambulation
- Other supportive endpoints are directionally consistent with results of the 6MWT, including NSAA and pulmonary function test.

This clinical benefit is accompanied by a safety profile that indicates that eteplirsen is well tolerated with no apparent signal of significant safety risks. Although the safety dataset of 114 patients may not detect very rare events and therefore carries the potential risk of uncertainty, this needs to be weighed against the certainty of relentless disease progression and premature death for boys with DMD. Continued safety surveillance of ongoing clinical trials, post-marketing pharmacovigilance, along with a planned DMD registry, will provide an evolving understanding of the safety profile of eteplirsen.

Confirmatory studies to verify the clinical benefit of eteplirsen are underway

Sarepta is committed to the completion of confirmatory trials that will not only verify the clinical benefit of eteplirsen using the 6MWT and other functional endpoints, but will also contribute to the safety profile of eteplirsen.

Furthermore, Sarepta is not only committed to confirming the efficacy of eteplirsen but also understanding its PMOs, and expanding the development of the PMO platform to address other less common types of genetic variants of DMD, with a planned study in boys with DMD with genetic mutations amenable to exon 45 and exon 53 skipping therapies.

2. OVERVIEW OF DUCHENNE MUSCULAR DYSTROPHY (DMD)

2.1. Onset and Progression

Duchenne muscular dystrophy (DMD) is a rare, serious, life threatening, degenerative neuromuscular disease with a recessive X-linked inheritance. Caused by mutations in the dystrophin gene, DMD is characterized by the absence, or near absence, of functional dystrophin protein, leading to relentlessly progressive deterioration of skeletal muscle function from early childhood, and premature death, usually by 30 years of age.

The progression of DMD follows a predictable course. Biochemical and molecular evidence of myofiber membrane instability are typically evident from shortly after birth (Chen 2005); however, clinical manifestations of ongoing muscle damage are usually obscured by otherwise normal growth and maturation during infancy. In fact, initial symptoms of DMD are often not reported until 2-3 years of age, with patients being diagnosed, on average at approximately 4 to 5 years of age (Bushby 2010a; Ciafaloni 2009; van Ruiten 2014). Initial symptoms of DMD most often include waddling gait, toe walking, falls, and delayed speech (Ciafaloni 2009; van Ruiten 2014). Compared with healthy, same-age peers, the achievement of motor milestones in patients with DMD is delayed, and performance on tests of motor function, such as timed function tests, is markedly impaired (Beenakker 2005; McDonald 2010a; McDonald 2010b).

Functional improvements due to natural growth are observed heterogeneously in boys younger than age 7, until the characteristic degeneration and loss of muscle tissue outpaces maturational development and physical growth (McDonald 2010b, Mazzone 2013). At 7 years of age the disease trajectory for DMD has been observed to decline in a relentless and progressively precipitous fashion. Once this threshold is crossed, disease trajectory is predictively negative and 6MWD decreases more rapidly each year (Mendell 2015; Mazzone 2013; Pane 2014b). At this time, DMD boys who were steadily gaining in physical function, albeit at a slower rate than their healthy age-matched peers, begin a progressive decline. This age dichotomy is supported by literature; in a 3 year longitudinal dataset boys who entered into observation prior to age 7 demonstrated improvement for the first two years, with decline observed by the third year when the mean age of the cohort was over 8 years (Pane 2014b; Mendell 2015).

By 8 years of age, most DMD patients lose the ability to rise from the floor and climb stairs, have an increasingly labored gait, and often fall while walking. By 10 to 14 years of age, most have become wheelchair dependent. Once confined to a wheelchair, other symptoms tend to follow in rapid succession. There is gradual loss of upper limb, trunk, and neck function, such that self-grooming, toileting, bathing, dressing, unsupported sitting, and eating become impaired or impossible, severely affecting patient quality of life, as well as that of caregiver and families (Bendixen 2012; Bendixen 2014; Buyse 2012; Buyse 2015; Hahn 1997; Magliano 2014; Uzark 2012).

While few, if any, respiratory symptoms have been reported in the earliest stages of DMD, data from recent natural history studies in patients with DMD suggest that from the time pulmonary function testing (PFT) is first performed, usually at the ages of 4 or 5 years, percent predicted values for forced vital capacity (FVC) and maximum inspiratory (MIP) and expiratory (MEP) pressures decline (Khirani 2014; Mayer 2015). Diaphragmatic muscles progressively weaken

during adolescence, and patients often require ventilation support in their mid to late teens (Bushby 2010a; Bushby 2010b).

There is also an increased risk of cardiomyopathy with DMD (Thomas 2012), which usually manifests after 10 years of age as dilated cardiomyopathy with reduced left ventricular ejection fraction. The prevalence of cardiomyopathy has been shown to increase with age and disease progression, with 10% to 20% of patients affected between 6 and 13 years of age and over 60% of patients ≥ 18 years affected (Spurney 2014). Historically, patients with DMD died from respiratory or cardiac failure in their late teens or early 20s (Brooke 1989; Eagle 2002). Although recent studies suggest that use of ventilation support, steroids, surgery, diet and other supportive measures may increase life span by several years (Kohler 2009; Bushby 2010a; Bushby 2010b; Moxley 2010), DMD remains fatal by early adulthood.

2.2. Diagnosis and Determination of Mutation

Historically, diagnosis of DMD had to be confirmed by muscle biopsy; however, genetic testing for DMD has become a common part of the diagnostic process in treatment centers in the US and Europe, thereby reducing the need for muscle biopsies. The use of newer methods of testing, such as next generation sequencing, has greatly improved the sensitivity and accuracy of genetic testing for DMD and ensures that patients amenable to exon 51 skipping can be readily and reliably identified (Wei 2014; Bovolenta 2012). Importantly, in the US, even patients and families lacking or having insufficient insurance coverage are able to access genetic testing for DMD at no cost through the “Decode Duchenne” program, which was launched by Parent Project Muscular Dystrophy (PPMD).

2.3. Current Treatments for DMD and Unmet Medical Need

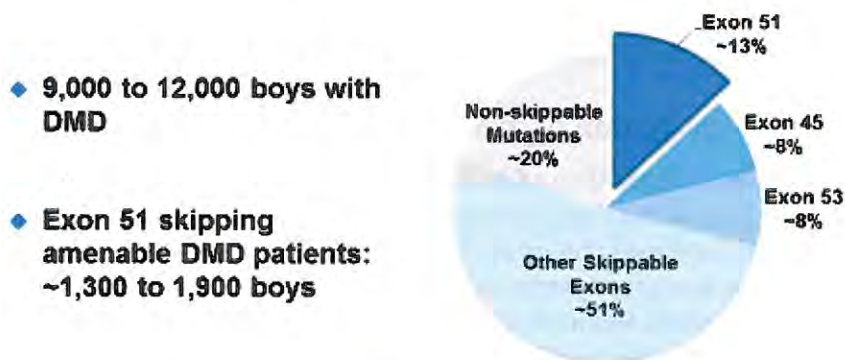
There is no approved therapy for DMD in the US. Currently, uniform standard of care guidelines for treatment of patients with DMD in the US and Europe include the administration of glucocorticoids in conjunction with nutritional, orthopedic, respiratory, cardiac, pain, psychosocial, and other palliative interventions (Bushby 2010a; Bushby 2010b). Aside from glucocorticoids, none of these interventions have been shown to impact loss of ambulation. Although glucocorticoids can delay the loss of ambulation as well as the onset of respiratory dependence, scoliosis, and cardiomyopathy (Beenakker 2005; Biggar 2006; Pradhan 2006; Manzur 2009; Schram 2013; Henricson 2013a), they do not sufficiently ameliorate symptoms or address the underlying genetic mutation and lack of functional dystrophin. Moreover, glucocorticoid use is often limited by numerous side effects, including weight gain, behavioral changes, hypertension, hyperglycemia and osteoporosis. Thus, there remains a high unmet medical need for treatments in patients with DMD.

2.4. Epidemiology

The worldwide incidence of DMD is 1 in 3,500-5,000 newborn boys, irrespective of geographical region, race, or population density (Zaharieva 2013; Mendell 2012; Moat 2013). The prevalence of DMD in the United States (US) is estimated to be approximately 9,000 to 12,000. The most common cause of DMD is deletion mutations of one or more DMD exons, accounting for approximately two-thirds of DMD cases (Aartsma-Rus 2009; Bladen 2015). Approximately 13% of all DMD patients have mutations amenable to therapies that skip

exon 51, corresponding to approximately 1,300-1,900 patients in the US who would potentially benefit from exon 51 skipping therapy (Figure 1). Another 16% percent have mutations amenable to treatment by skipping exons 45 (8%) and 53 (8%), and an additional 51% have mutations amenable to treatment by skipping other exons. Thus, hypothetically, exon skipping PMO therapies could potentially address treatment needs for approximately 80% of all DMD mutations.

Figure 1: US Prevalence of Patients with Exon 51 Skippable Deletions and other DMD Mutations



Source: Adapted from [Aartsma-Rus 2009](#).

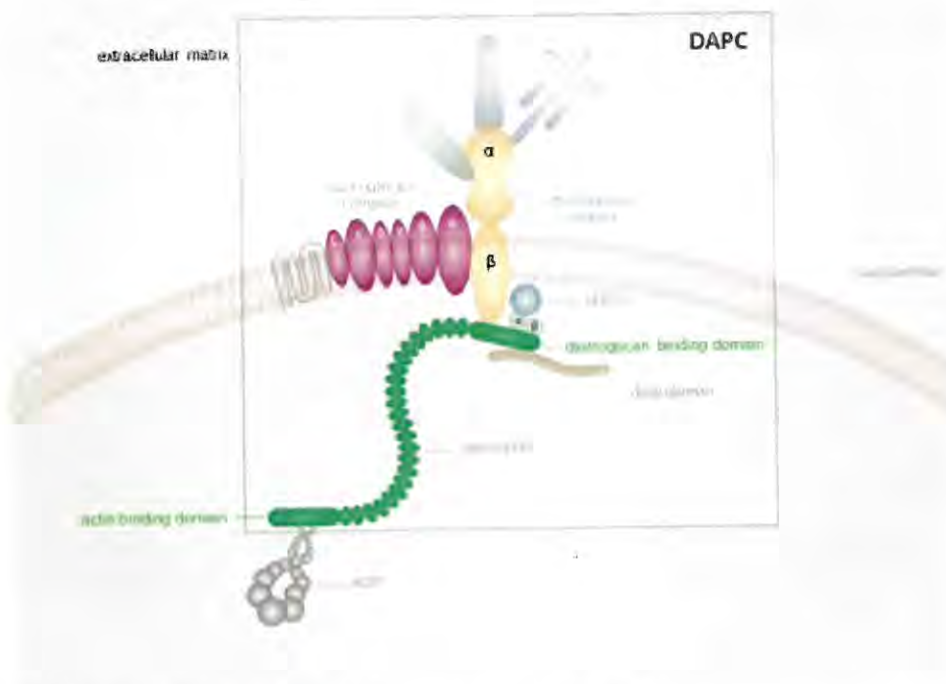
2.5. Pathophysiology and Role of Dystrophin

2.5.1. Dystrophin in Normal Muscle

Dystrophin is a low abundance (<0.1%) protein in muscle tissue with a slow translation time (~16h) and low turnover (half-life of ~2 months) ([Wu 2012](#); [Tennyson 1995](#); [Hoffman 1987](#)).

Dystrophin is a critical structural protein that protects muscle from strain-induced injury. Often referred to as a “molecular shock absorber”, dystrophin links the intracellular actin filaments of a muscle fiber to the cell membrane and surrounding extracellular matrix through its interaction with the dystrophin-associated protein complex (DAPC). Dystrophin binds directly to cytoplasmic actin through its *N-terminal actin-binding domain* and localizes to the sarcolemma and the DAPC via its *C-terminal dystroglycan binding domain* ([Figure 2](#)). Together, dystrophin and the other components of the DAPC protect muscle from the forces of repeated contraction and relaxation ([Kobayashi 2012](#)).

Figure 2: The DAPC in Normal Muscle



Abbreviations: DAPC = dystrophin associated protein complex.
Adapted from Kobayashi 2012.

2.5.2. Dystrophin Protein in DMD and BMD

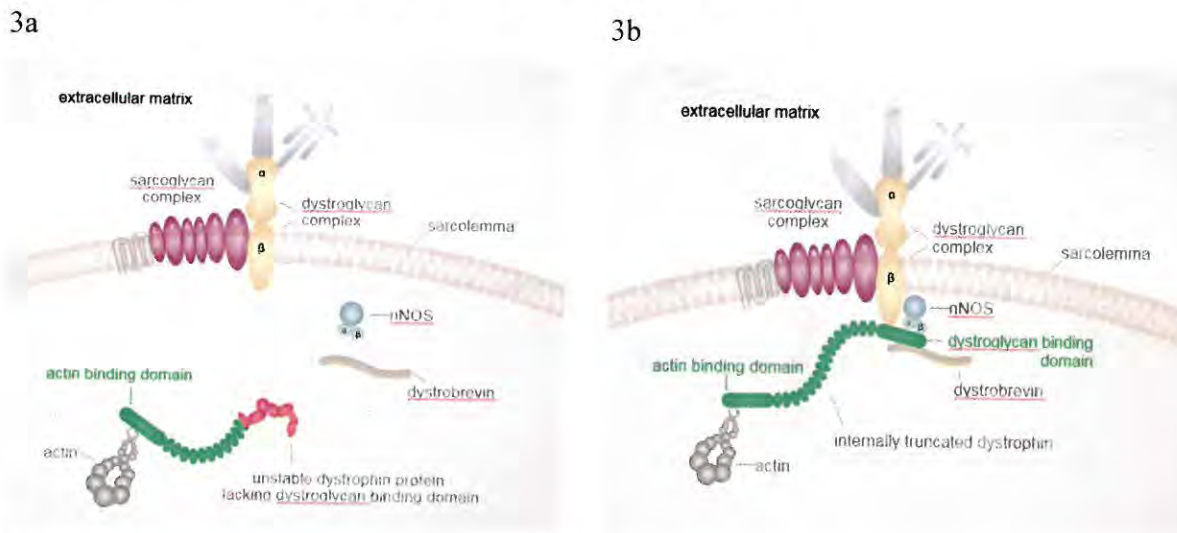
Mutations in the gene encoding dystrophin give rise to a spectrum of neuromuscular disorders called dystrophinopathies. The most common mutations are whole exon deletions, which, depending on the exon(s) deleted, result in severe and fatal DMD or the significantly milder dystrophinopathy, Becker muscular dystrophy (BMD).

Whole exon deletions that disrupt the mRNA reading frame, also referred to as “out-of-frame deletions” are the primary cause of DMD. Out-of-frame mutations prevent translation of functional dystrophin protein downstream of the mutation, creating an unstable protein lacking a *C-terminal dystroglycan binding domain* (Figure 3A). The absence of functional dystrophin prevents the connection between the intracellular cytoskeleton and the cell membrane leading to repeated cycles of cellular inflammation, degeneration, and cumulative damage to muscle. Over the clinical course of DMD, the inherent ability of muscle cells to repair and regenerate is exhausted and muscle is progressively replaced by fibrotic tissue and fat (Blake 2002; Emery 2002).

In contrast, whole exon deletions that do not disrupt the mRNA reading frame, also referred to as “in-frame deletions”, are usually associated with BMD. Such mutations result in a dystrophin protein missing amino acids in the central domain of the dystrophin protein; however, the C- and N-terminal binding domains are retained. (Figure 3B). Due to this preservation of functional dystrophin, BMD patients generally have a much later onset of symptoms, a milder and slower

disease course, and a near normal life expectancy (McDonald 1995; Bushby 1993a; Bushby 1993b; Kaspar 2009).

Figure 3: The DAPC in DMD (3a) and BMD (3b) Muscle



Adapted from Kobayashi 2012.

2.5.3. Relationship of Dystrophin to DMD and BMD Severity

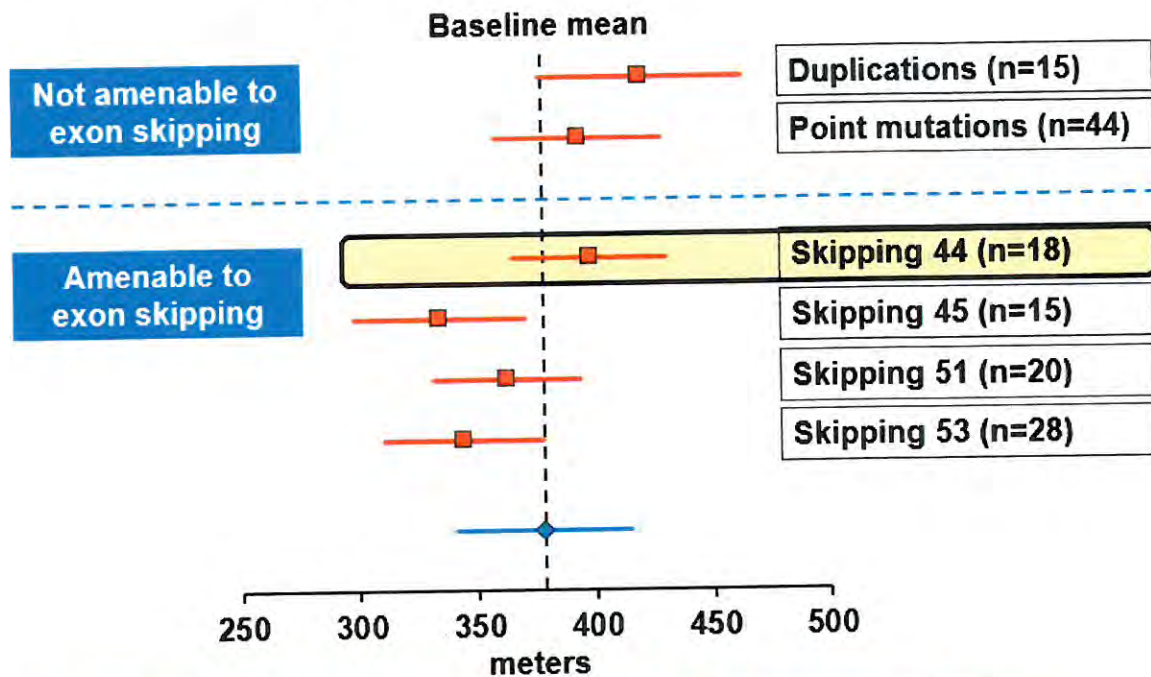
The clinical literature has not established a linear relationship between dystrophin expression and clinical course of dystrophinopathies (Hoffman 1988; Bushby 1993b; Bushby 1992; Taylor 2012; Nicholson 1993; Hoffman 1989; Anthony 2014; van den Bergen 2014; Goldberg 1998; Lenk 1996). A review of publications identified 82 DMD and 137 BMD patients with sufficient clinical detail to categorize their disease course and dystrophin levels (Western blot). In BMD expression of dystrophin by Western Blot has been variable with estimates from the literature ranging from 3% to 78% of normal muscle levels (van den Bergen 2014). Dystrophin levels, while lower overall in patients with DMD, were highly variable among both patient groups, and did not appear to correlate linearly with disease severity.

One of these studies (van den Bergen 2014) evaluated 33 BMD patients whose dystrophin levels were based on biopsies of the anterior tibialis muscle. In this individual study, there was also no linear relation found between dystrophin levels and muscle strength or age at different disease milestones. This finding led the authors to posit that the presence of a relatively small amount of dystrophin may be sufficient to result in a disease course that is milder than DMD.

An example of the presence of low levels of dystrophin resulting in a milder disease course is also demonstrated by genetic variations of DMD. Many DMD patients express very low levels of dystrophin attributable to spontaneous exon skipping that occurs naturally. The sporadic muscle fibers expressing dystrophin are referred to as “revertant” fibers. In particular, patients amenable to exon 44 skipping have been shown to express higher levels of dystrophin than are typically seen in DMD patients due to the phenomenon of naturally occurring revertant muscle fibers (Anthony 2014).

Corresponding to the presence of some dystrophin, patients with DMD amenable to skipping exon 44 experience a milder disease course compared to other types of DMD (Anthony 2014). A recent study conducted in a cohort of 191 similarly aged boys with DMD (Panc 2014a) examined the relationship between DMD genotypes and distance walked on the 6-Minute Walk Test (6MWT). Patients amenable to exon 44 skipping walked further (a mean distance of 398 meters) compared to boys with DMD amenable to skipping exons 45, 51, and 53 who walked mean distances of 334, 362, and 344 meters, respectively (Figure 4). A recent study of 513 steroid treated boys with DMD also demonstrated that Exon 44 amenable patients declined at a slower rate than the overall DMD population over 24-months on the North Star Ambulatory Assessment (NSAA) ($p < 0.01$) (Ricotti 2015).

Figure 4: Comparison of 6MWT Performance in Patients with DMD Mutations Amenable to Exon Skipping



◆ Whole cohort n=191 (includes 51 patients with Other deletions not shown)

Source: Adapted from: Panc 2014a. Figure shows mean distance walked on the 6MWT in patients with different DMD mutations relative to the mean distance walked by the whole cohort.

In summary, published literature indicates that the presence of functional dystrophin results in milder disease course in patients with BMD and DMD mutations amenable to exon 44 skipping. Although a linear correlation between the amount of dystrophin and clinical course has not been established, it is clear that the presence of some dystrophin results in disease amelioration.

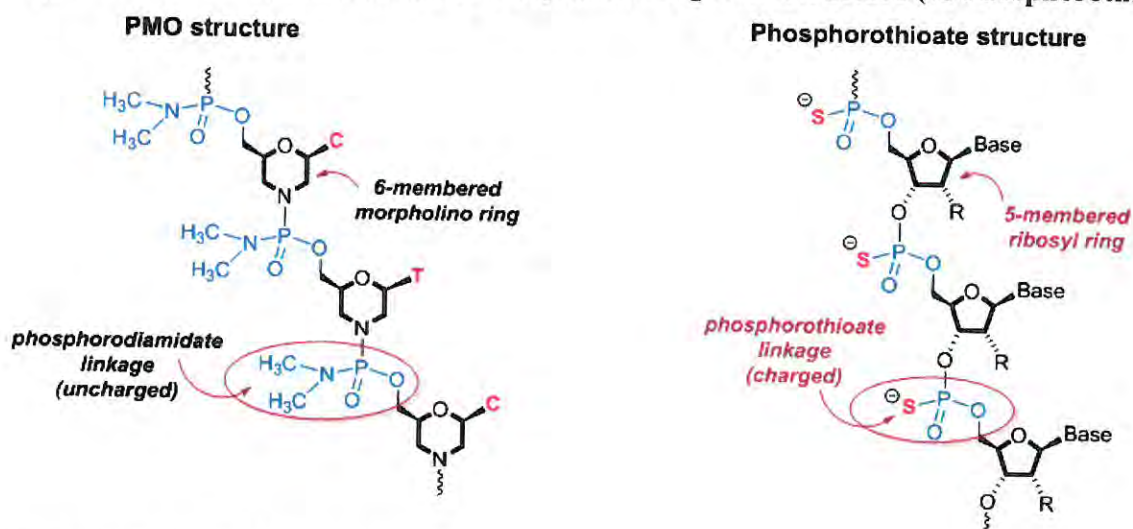
3. ETEPLIRSEN DEVELOPMENT

3.1. Background Information on Eteplirsen Injection

Eteplirsen belongs to a distinct class of novel synthetic antisense RNA therapeutics called Phosphorodiamidate Morpholino Oligomers (PMO), which are a redesign of the natural nucleic acid structure (Figure 5). PMOs offer specific clinical potential advantages that have been documented in vivo.

- PMOs incorporate modifications to the sugar ring of RNA that protect it from enzymatic degradation by nucleases in order to ensure stability in vivo. PMOs are distinguished from natural nucleic acids and other antisense oligonucleotide classes in part through the use of 6-membered synthetic morpholino rings, which replace the 5-membered ribofuranosyl rings found in RNA, DNA and many other synthetic antisense RNA oligonucleotides.
- The uncharged phosphorodiamidate linkages specific to PMOs are considered to potentially confer reduced off-target binding to proteins. PMOs have a phosphorodiamidate linkage that links each morpholino ring instead of the negatively charged phosphorothioate linkage used in other clinical-stage synthetic antisense RNA oligonucleotides.
- The sequence of eteplirsen's 30 nucleobases is designed to be complementary to a specific target sequence within exon 51 of dystrophin pre-mRNA. Each morpholino ring in eteplirsen is linked to one of four heterocyclic nucleobases found in DNA (adenine, cytosine, guanine, and thymine).

Figure 5: Phosphorodiamidate Morpholino Oligomer Structure (vs Phosphorothioate)



The chemical name for eteplirsen is:

RNA, [P-deoxy-P-(dimethylamino)] (2',3'-dideoxy-2',3'-imino-2',3'-seco) (2'a→5') (C-m⁵U-C-C-A-A-C-A- m⁵U-C-A-A-G-G-A-A-G-A- m⁵U-G-G-C-A- m⁵U- m⁵U- m⁵U-C- m⁵U-A-G), 5'-[P-[4-[[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]carbonyl]-1-piperazinyl]-N,N-dimethylaminophosphonamidate]

Note “m⁵U” stands for 5-methyluracil (i.e., thymine).

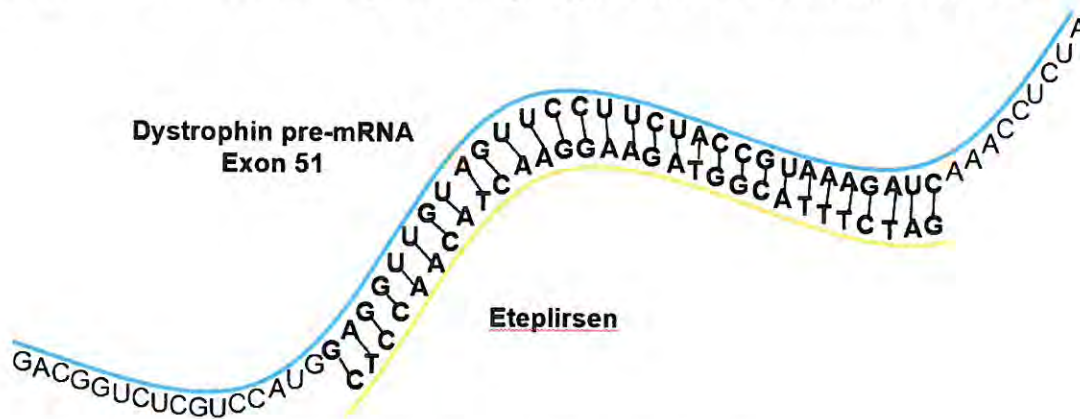
3.2. Rationale for Development and Mechanism of Action

A potential therapeutic approach to the treatment of DMD caused by out-of-frame mutations in the *DMD* gene is suggested by the milder form of dystrophinopathy known as BMD, which is caused by in-frame mutations. The ability to convert an out-of-frame mutation to an in-frame mutation would hypothetically preserve the mRNA reading frame and produce an internally shortened yet functional dystrophin protein. Eteplirsen was designed to accomplish this.

Eteplirsen targets dystrophin pre-mRNA and induces skipping of exon 51, so it is excluded or skipped from the mature, spliced mRNA transcript. By skipping exon 51, the disrupted reading frame is restored to an in-frame mutation. While DMD is comprised of various genetic subtypes, eteplirsen was specifically designed to skip exon 51 of dystrophin pre-mRNA. DMD mutations amenable to skipping exon 51 include deletions of exons contiguous to exon 50 or exon 52, and comprise the largest subgroup of DMD patients (13%).

Eteplirsen is an antisense RNA therapeutic-targeted with a nucleobase sequence that is complementary to a specific sequence contained within exon 51 of dystrophin pre-mRNA. Hybridization of eteplirsen with the targeted pre-mRNA sequence interferes with formation of the pre-mRNA splicing complex and deletes exon 51 from the mature mRNA. The structure and conformation of eteplirsen allows for sequence-specific base pairing to the complementary sequence contained in exon 51 of dystrophin pre-mRNA as illustrated by [Figure 6](#).

Figure 6: Eteplirsen binding to Dystrophin pre-mRNA via Watson-Crick Base Pairing



Restoration of the Dystrophin Reading Frame Using Exon Skipping

Normal dystrophin mRNA containing all 79 exons will produce normal dystrophin protein. The graphic in [Figure 7](#) depicts a small section of the dystrophin pre-mRNA and mature mRNA, from exon 47 to exon 53. The shape of each exon depicts how codons are split between exons. Rectangular shaped exons start and end with a complete codon. Arrow shaped exons start with a complete codon but end with a split codon, with only the first nucleotide of a codon. The chevron shaped exons start with an incomplete codon, with the second two nucleotides of the codon it splits with the previous, arrow shaped, exon (see [Appendix 17](#) for additional detail).

Figure 7: Depiction of Section of Normal Dystrophin Pre-mRNA



Dystrophin mRNA missing whole exons from the dystrophin gene typically result in DMD. The graphic in Figure 8 illustrates a type of genetic mutation (deletion of exon 50) that is known to result in DMD. Since exon 49 ends in a complete codon and exon 51 begins with the second nucleotide of a codon, the reading frame after exon 49 is shifted, resulting in out-of-frame mRNA reading frame and incorporation of incorrect amino acids downstream from the mutation. The subsequent absence of a functional C-terminal dystroglycan binding domain results in production of an unstable dystrophin protein.

Figure 8: Depiction of section of Abnormal Dystrophin pre-mRNA (example of DMD)



Eteplirsen skips exon 51 to restore the mRNA reading frame. Since exon 49 ends in a complete codon and exon 52 begins with the first nucleotide of a codon, deletion of exon 51 restores the reading frame, resulting in production of an internally-shortened dystrophin protein with an intact dystroglycan binding site, similar to an “in-frame” BMD mutation; Figure 9.

Figure 9: Depiction of Eteplirsen Restoration of “In-frame” reading of pre-mRNA



Source: Adapted from Kole 2012.

3.3. Proposed Indication, Dosing and Administration

The proposed prescribing information for eteplirsen includes the following indication:

Eteplirsen injection is indicated for the treatment of DMD in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping therapy. This indication is approved based on an intermediate endpoint demonstrating delayed disease progression as measured by the 6MWT. Continued clinical benefit will be evaluated through confirmatory trials.

Eteplirsen injection is supplied in single-use, 2- and 10-mL glass vials containing 100 or 500 mg eteplirsen, respectively. The concentrated drug product is provided as a 50 mg/mL sterile, isotonic, phosphate-buffered (pH 7.5) solution without preservatives. Eteplirsen injection is diluted to 100 to 150 mL with normal saline prior to administration via intravenous (IV) infusion.

Eteplirsen at 30 mg/kg will be administered chronically (i.e., lifetime dosing) by once-weekly IV infusions between 35 to 60 minutes in duration.

3.4. Regulatory History and Framework

Framework for Accelerated Approval of a Rare Disease or Condition

There is a new emphasis on broader use of accelerated approval to expedite patients' access to important treatments for serious and life-threatening disease conditions. This was endorsed in the September 2012 President's Council of Advisors on Science and Technology (PCAST) *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation*. The Report noted that "[h]istorically, the use of Accelerated Approval has been primarily used in a limited number of therapeutic areas—principally, HIV/AIDS, cancer, and inhalation anthrax (87 percent of cases)..." As such, the Report concluded that "...the Nation would benefit if the FDA were to expand the use in practice of acceptable indications to other serious or life-threatening diseases" and "...FDA should expand the use in practice of its existing authority for Accelerated Approval."

Meanwhile, the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) codified and expanded FDA's accelerated approval authority. The statute provides that FDA may grant accelerated approval of:

...a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

How to have an effect.

Federal Food, Drug, & Cosmetic Act (FD&C Act) § 506(c)(1)(A).

FDASIA clarified FDA's flexibility in administering the accelerated approval program, especially for rare, serious conditions with a high unmet medical need. The 2012 law makes clear that FDA has always had in its regulations the authority to consider all types of evidence: "The evidence to support that an endpoint is reasonably likely to predict clinical benefit... may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers... or other scientific methods or tools." FD&C Act § 506(c)(1)(B)

In addition, the new law acknowledged that fewer, smaller trials may be the basis for accelerated approval:

...the FDA should be encouraged to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate. *This may result in fewer, smaller, or shorter clinical trials* for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs.

OK relates to surrogates Need a surrogate effect.

FDASIA § 901(a)(1)(C) (emphasis added).

Finally, the accelerated approval pathway means that there will be, at the time of accelerated approval, an acceptable degree of uncertainty about whether the therapy will actually result in the anticipated clinical benefit. This uncertainty about whether the ultimate clinical benefit will be achieved is accounted for by the requirement that a product approved under the accelerated approval program have "appropriate postapproval studies to verify and describe the predicted effect," which are generally referred to as confirmatory postmarketing studies. FD&C Act § 506(c)(2)(A). FDA's regulations explain that at the time of accelerated approval, the "[p]ostmarketing studies would usually be studies already underway." 21 C.F.R. § 314.510.

Accelerated approval is highly relevant to eteplirsen for the treatment of Duchenne Muscular Dystrophy (DMD) because the totality of available evidence from a variety of sources allow, at the time of granting accelerated approval, "experts qualified by scientific training and experience" to conclude that the drug has an effect on either dystrophin (a surrogate endpoint) or 6MWT (an intermediate clinical endpoint) that is reasonably likely to be confirmed on a clinical endpoint in either one of the two planned confirmatory postmarketing studies. FDA described these two potential pathways under accelerated approval in the April 2014 meeting minutes outlined below.

Eteplirsen Regulatory History

The eteplirsen IND was submitted in August 2007 for the treatment of DMD patients with mutations amenable to exon 51 skipping therapy. Orphan Drug and Fast Track designations were also granted for eteplirsen for this indication in October and November 2007, respectively. Based on promising results observed in the Phase 1 proof of concept study (Study 33) and a 12-week dose-ranging study (Study 28) conducted in the United Kingdom from 2007 to 2010, Sarepta conducted a 28-week double-blind, placebo-controlled Phase 2 study (Study 201) in July 2011. In February 2012, an ongoing long-term Phase 2b open-label eteplirsen extension study (Study 202) was initiated where all 12 patients who participated in Study 201 received eteplirsen. Study 202 has now been ongoing for approximately 4 years.

Based on the regulatory framework of FDASIA and after several meetings with the Division of Neurology Products, agreement was reached on the content of an NDA submission, primarily based on the Phase 2b dataset, under the provisions of 21 CFR §314.510 (Subpart H) regulations established for accelerated approval of new drugs for serious or life-threatening illnesses, and confirmatory study design.

Of note, the FDA requirements for Accelerated Approval (AA) are detailed in Table 1. In addition, "the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments need to be taken into account. Post marketing confirmatory trials are required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit." The eteplirsen NDA submission meets the criteria for AA.

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Table 1: Eteplirsen Meets Accelerated Approval Requirements

Characteristics	Accelerated approval Section 506 (c)	Eteplirsen pathway
Disease	Serious and life threatening Severe or rare Lack of alternative treatments	Duchenne Muscular Dystrophy
Surrogate or clinical "intermediate" endpoint	Reasonably likely to predict an effect on irreversible morbidity or mortality (IMM), or other clinical benefit	Intermediate primary endpoint: Six Minute Walk Test (6MWT)
Post-marketing studies	Post-marketing (PM) confirmatory trials required to verify and describe anticipated effect	Two studies agreed upon

If shown

Not issue

FDA Meeting Minutes Received April 2014 (Culmination of 4 meetings held between November 8, 2013 and March 2014)

The FDA provided the following guidance:

- The FDA outlined 2 potential pathways to accelerated approval:
 - “Considering the 201/202 6MWT data as a finding on an “intermediate” clinical endpoint, or”
 - “Using the dystrophin biomarker data as surrogate endpoint(s)”
- For option (1), Sarepta 201/202 6MWT data would need to be compared to a matched historically-controlled DMD population similar to the eteplirsen treated patients; patient-level data for would need to be submitted for both groups. In order to minimize bias, the supportive care, such as steroid use and physical therapy, for both groups would need to be similar.
- The FDA remained “skeptical” about the persuasiveness of the existing biomarker data as it had been analyzed by a single pathologist and therefore potentially open to bias. FDA proposed a collaborative effort to better understand the methods and analyses used for these data, with the goal of applying suitable, consistent, and objective methods for measuring increases in functional dystrophin protein, which would be amenable to independent verification.
- The FDA also proposed obtaining a fourth biopsy and comparing these samples, in blinded fashion, to samples obtained from a group of treatment-naïve patients with exon 51 DMD, as a source of additional biomarker data.

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Confirmatory Studies

To enable accelerated approval, the “FDA envisioned 2 approaches to confirmatory trials:”

- “A historically-controlled trial of eteplirsen, and

2. *A randomized, placebo-controlled trial of another PMO with the same mechanism of action, with demonstration of a correlation between dystrophin production and definitive clinical benefit on the 6MWT or another clinical measure.*”

September 2014: Type B Pre-NDA Meeting

In addition to the previously agreed upon NDA content described above, the FDA required the following additional information to be included in the NDA submission:

- 3-month data from at least 12 to 24 newly exposed patients
- Individual patient-level data for the historical control patients, including rise time or similar timed function tests, baseline factors including steroids, and any ancillary care that affects physical function
- Dystrophin source images, and key analyses
- Study 201/202 Week 168 efficacy data

May 2015: Type C Pre-NDA Follow Up Meeting

In the September 2014 Pre-NDA meeting, FDA considered Sarepta’s proposal for the NDA to be acceptable. FDA also noted the following points:

- Data from the Fourth Biopsy, taken at Week 180, while not required in the initial NDA, was also required to be submitted to the NDA post submission.
- To aid comparison of the Study 201/202 6MWT and NSAA data to historical controls, details of care such as steroid use, other medication use, physical therapy and pulmonary therapy needed to be obtained.
- Independent assessment of the percentage of dystrophin-positive fibers (PDPF) from Studies 201/202 and Study 28
- Review of available historical data regarding dystrophin expression and phenotype in BMD focusing on the natural history of Becker genotypes that would be created by skipping exon 51

Based on the FDA guidance received during the September 2014 and the May 2015 Pre-NDA meetings, the eteplirsen NDA was submitted on June 26, 2015 and filed on August 25, 2015. Priority Review status was also granted, requiring a 6-month review period compared to the standard 10-month review.

In addition, both confirmatory studies (Table 2) will be underway by Q1 of 2016, with the PROMOVI study almost fully enrolled.

Table 2: Confirmatory Studies to Support Eteplirsen Accelerated Approval

Acronym (Protocol No.)	Study Design	Treatment	Duration
PROMOVI (4568-301)	Open-label versus concurrent untreated control	Eteplirsen	96 weeks
ESSENCE (4045-301)	Randomized, double-blind, placebo-controlled	SRP-4045 SRP-4053	48 weeks with planned open label extension

4. NONCLINICAL STUDIES

4.1. Exon Skipping Increases Dystrophin and Improves Function in Dystrophic Animals

The feasibility of ameliorating the DMD phenotype using exon skipping to restore the dystrophin mRNA open reading frame is supported by nonclinical research. Numerous studies in dystrophic animal models of DMD have shown that restoration of dystrophin by exon skipping leads to reliable improvements in muscle strength and function (Sharp 2011; Yokota 2009; Wu 2008; Wu 2011; Barton-Davis 1999; Goyenville 2004; Gregorevic 2006; Yue 2006; Welch 2007; Kawano 2008; Reay 2008; van Putten 2012). A compelling example of this comes from a study in which dystrophin levels following exon skipping (using a PMO) therapy were compared with muscle function in the same tissue. In dystrophic *mdx* mice, tibialis anterior (TA) muscles treated with a mouse-specific PMO maintained ~75% of their maximum force capacity after stress-inducing contractions, whereas untreated contralateral TA muscles maintained only ~25% of their maximum force capacity ($p < 0.05$) (Sharp 2011). In another study, 3 dystrophic *CXMD* dogs received at (2-5 months of age) exon-skipping therapy using a PMO-specific for their genetic mutation once a week for 5 to 7 weeks or every other week for 22 weeks. Following exon-skipping therapy, all 3 dogs demonstrated extensive, body-wide expression of dystrophin in skeletal muscle, as well as maintained or improved ambulation (15 m running test) relative to baseline. In contrast, untreated age-matched *CXMD* dogs showed a marked decrease in ambulation over the course of the study (Yokota 2009).

PMOs were shown to have more exon skipping activity at equimolar concentrations than phosphorothioates in both *mdx* mice and in the humanized DMD (hDMD) mouse model, which expresses the entire human DMD transcript (Heemskirk 2009). In vitro experiments using reverse transcription polymerase chain reaction (RT-PCR) and Western blot (WB) in normal human skeletal muscle cells or muscle cells from DMD patients with different mutations amenable to exon 51 skipping identified eteplirsen as a potent inducer of exon 51 skipping. Eteplirsen-induced exon 51 skipping has been confirmed in vivo in the hDMD mouse model (Arechavala-Gomez 2007).

4.2. Nonclinical Development of Eteplirsen

A comprehensive set of nonclinical pharmacokinetic (PK), safety pharmacology, and toxicity studies has been performed as part of eteplirsen's development.

4.2.1. Nonclinical Pharmacokinetics

Key nonclinical PK study findings include the following:

- An in vivo PK study in *mdx* mice demonstrated an apparent plasma half-life of approximately 6 hours, widespread distribution to skeletal, cardiac, and diaphragm muscles, high concentrations in kidneys and urine, and predominantly renal excretion

- Combined in vitro protein binding, cytochrome P450 enzymes (CYP) or drug transporter interactions, and hepatic microsomal metabolism study results demonstrated a low potential for drug-drug interactions for eteplirsen in humans
 - Low in vitro binding of ¹⁴C-eteplirsen to human plasma proteins (6.1% to 16.5%)
 - No in vitro inhibition of the major human CYP isoenzymes tested (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) at biologically relevant concentrations (i.e., <1 mg/mL)
 - No induction of CYP2B6 or CYP3A4 and minimal induction of CYP1A2 only at high concentrations (>1 mg/mL) in human primary hepatocyte cultures
 - No interactions as either a substrate or inhibitor of key human drug transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, MRP2, and BSEP at biologically relevant concentrations (i.e., <1 mg/mL)

4.2.2. Renal Toxicity of Eteplirsen in Animals

Good Laboratory Practice (GLP) repeat-dose toxicity studies of eteplirsen, administered by IV injection once weekly for 12 weeks in dystrophic (*mdx*) and non-dystrophic mice, for 10 weeks in juvenile rats, and for 12 and 39 weeks in non-human primates (NHPs), demonstrated that the kidney was the main target organ. Renal findings for eteplirsen in mice and NHPs consisted of non-adverse morphological changes of multifocal, renal tubular basophilia/vacuolation, with minimal-to-slight tubular degeneration. These findings were not associated with significant changes in renal-related clinical pathology parameters (e.g., serum creatinine or urea nitrogen, urine chemistries) and the no observed adverse effect level (NOAEL) was the highest dose level tested in these species (960 mg/kg in mice and 320 mg/kg in NHPs). In juvenile rats, renal histopathology findings of marked tubular dilatation, vacuolation, and basophilia were accompanied by minimal to slight necrosis, minimal hemorrhage/interstitial inflammation, increased renal weights, increased serum creatinine/urea nitrogen, and decreased creatinine clearance at the highest dose level tested (900 mg/kg) and were considered adverse. Due to the adverse renal effects at 900 mg/kg, the NOAEL in juvenile rats was 300 mg/kg. Nevertheless, renal effects of eteplirsen in animals were less severe than those reported at lower doses for the phosphorothioate antisense oligonucleotide, drisapersen (Frazier 2014). Eteplirsen plasma exposures assessed in the juvenile rat and NHP toxicity studies were high, increased in a nearly dose-dependent manner, and were 8-fold (juvenile rats) and 28-fold (NHPs) higher than human exposures, based on plasma AUC at the NOAEL versus mean human AUC at 30 mg/kg.

4.2.3. Other Nonclinical Findings for Eteplirsen

Phosphorothioates are known to cause a number of other target organ toxicities in animals, including complement activation and pro-inflammatory effects, coagulopathies, thrombocytopenia, vascular injury, and hepatic Kupffer cell basophilia (Levin 1998; Monteith 1999; Levin 2001; Henry 2008; Frazier 2014; Engelhardt 2015; Frazier 2015). Thorough evaluations of the developing immune system in juvenile rats, which included T cell-dependent antibody responses and immunophenotyping of peripheral blood T- and B-cell subpopulations (total/helper/cytotoxic T-cells, B-cells, and NK cells), demonstrated that eteplirsen had no adverse effect on the immune response. In addition, quantitation of the Bb, C3a, and C5a fragments of the complement

alternative pathway on Day 8 and at Weeks 13 and 39 in the chronic study showed that eteplirsen did not cause complement activation at the highest dose level tested in NHPs (320 mg/kg). Injection site reactions in repeat-dose toxicity studies were infrequent, non-adverse, and showed evidence of reversibility. There was no evidence of eteplirsen-induced thrombocytopenia or vascular injury observed in mice, juvenile rats, or NHPs after repeated high weekly doses of 960 mg/kg, 900 mg/kg, or 320 mg/kg, respectively.

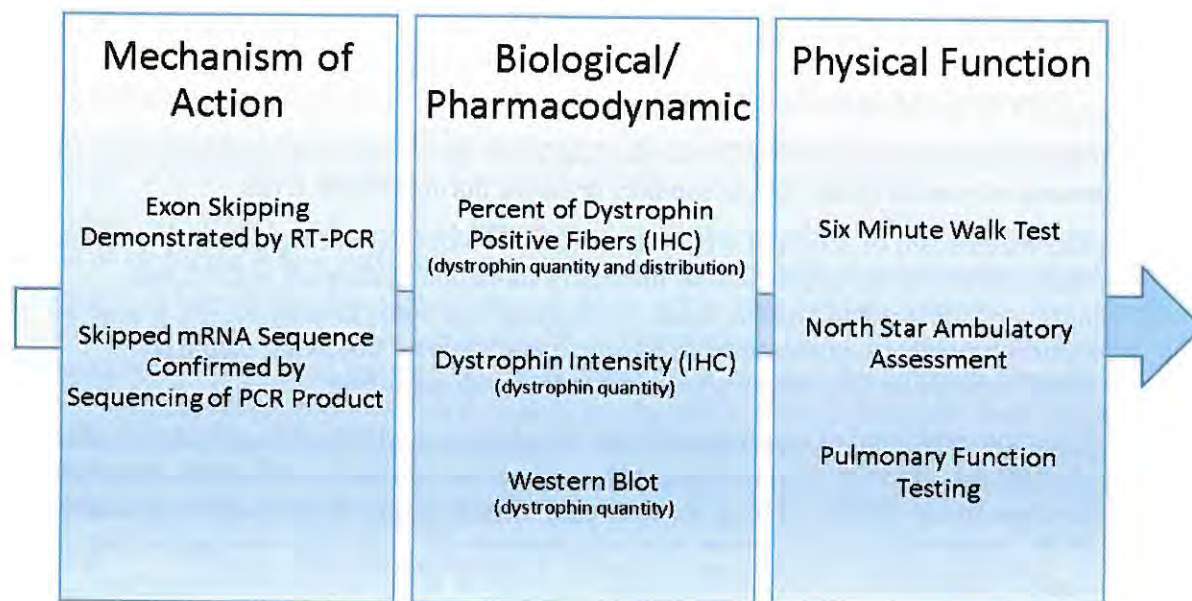
A safety pharmacology study in NHPs showed that single IV injections of eteplirsen at doses up to 320 mg/kg had no adverse effects on cardiovascular, respiratory, renal, hepatic, or global neurological functional assessments. In repeat-dose studies, no morphological changes were observed in the heart, no effects on electrocardiogram parameters, including heart rate (HR) and PR, RR, QT, and QTc intervals, and no effects on coagulation parameters were detected after once-weekly IV injections of eteplirsen in NHPs at doses up to 320 mg/kg for 39 weeks.

No effects were detected on the male reproductive system in mice, juvenile rats, and NHPs in repeat-dose toxicity studies. Eteplirsen did not affect neuromuscular development in juvenile rat pups, including performance in forced swim tests (Cincinnati water maze), grip strength measurements, hind-limb splay, and motor activity, after once-weekly IV injections of doses up to 900 mg/kg. This dose level produced exposures approximately 32-fold higher than human exposures based on plasma AUC. No pathological changes in skeletal muscles or histopathological evidence of hepatic Kupffer cell basophilia were observed in any of the repeat-dose toxicity studies conducted in mice, juvenile rats, or NHPs. Finally, there was no evidence of eteplirsen-associated mutations, chromosomal aberrations, or clastogenic potential in the International Conference on Harmonisation (ICH) standard battery of genotoxicity tests.

6. ETEPLIRSEN CLINICAL STUDIES CONTRIBUTING TO EVALUATION OF EFFICACY

Across the clinical studies the efficacy of eteplirsen has been evaluated by a continuum of study endpoints that reflect the mechanism of action, pharmacodynamics effects and clinical outcomes relevant to DMD.

6.1. Endpoints Evaluating Efficacy in Eteplirsen Clinical Studies



The eteplirsen clinical development program was initiated in pediatric DMD patients with a mutation amenable to exon 51 skipping who received eteplirsen intramuscularly at very low doses in Study 33 in order to demonstrate proof of principle for exon 51 skipping.

- **Proof of Concept Study 33** was the first study, conducted in boys with DMD (primarily non-ambulatory [N = 7]). A single- IM dose of either 0.09 or 0.9 mg/kg was injected into the extensor digitorum brevis muscle of one foot with placebo injected into the other foot. RNA analyses demonstrated that eteplirsen resulted in exon 51 skipping and immunohistochemistry showed production of novel dystrophin.

After demonstrating the mechanism of action and production of dystrophin in Study 33, a dose-ranging study (Study 28) administered eteplirsen at dose levels up to 20 mg/kg.

- **Dose-Ranging Study 28** is a completed 12-week study administering 0.5 to 20 mg/kg of eteplirsen by weekly IV infusion to ambulatory pediatric DMD patients (N = 19). Exon skipping and induction of dystrophin protein expression by eteplirsen was shown with most consistent results observed for the higher dose levels of 10 and 20 mg/kg. No dose limiting toxicities were identified.

Based on these encouraging initial data, a double-blind, placebo-controlled Phase 2 study (Study 201) was designed. Since the maximum tolerated dose had not been reached in Study 28, higher doses of eteplirsen, 30 and 50 mg/kg weekly IV infusion, were selected for Study 201.

Study 202 was an open-label extension study evaluating eteplirsen for a period of over 3 years including 6MWT, NSAA and PFTs.

- **Pivotal Study 201 and its ongoing extension, Study 202** are conducted in ambulatory DMD boys 7 to 13 years of age (N=12) administering 30 or 50 mg/kg by IV infusion. These studies have been ongoing for over 3 years with collection of clinical and biologic outcome data. No dose limiting toxicities were identified.

Key aspects of the studies contributing to evaluation of biologic and functional efficacy are summarized below in [Table 4](#).

Table 4: Clinical Studies Contributing to Pharmacodynamic and Functional Efficacy

Descriptor	Study Number			
	Pivotal		Supportive	
	Study 201	Study 202	Study 28	Study 33
Study Design	Randomized, double-blind, placebo-controlled, multiple-dose, single-center (US) study	Multi-center (US), open-label, multiple-dose extension study	Dose-ranging study Open-label, multiple-dose, (UK)	Proof of concept Single-blind, placebo-controlled, single-dose, investigator-sponsored, (UK)
Dosing Regimen	Eteplirsen 30 or 50 mg/kg/week, or placebo (IV) Weeks 1-24, then eteplirsen 30 or 50 mg/kg Weeks 25-28	Eteplirsen 30 or 50 mg/kg/week (IV)	Eteplirsen 0.5, 1.0, 2.0, 4.0, 10.0 or 20.0 mg/kg/week (IV)	Eteplirsen 0.09 or 0.9 mg IM in the EDB of 1 foot and placebo (IM) in the EDB of the opposite foot
Endpoints	Primary = Change from BL in PDPF at Week 12 (50 mg/kg group and 2 placebo patients), and at Week 24 (30 mg/kg group and 2 placebo patients). Other = 6MWT, Timed 4-step Test, and NSAA; PFTs; Exon skipping (RT-PCR) and dystrophin PDPF and intensity in biopsied muscle	Primary Functional = Change from BL in the 6MWT Primary Biological = Change from BL (of Study 201) to Week 48 in PDPF Other = Exon skipping (RT-PCR) and change from BL in dystrophin intensity, NSAA, PFTs, and Timed 4-Step Test	Primary = safety and tolerability Primary Exploratory = Change from BL to Week 14 in dystrophin PDPF Other = Change from BL to Week 14 in dystrophin intensity and protein levels (Western blot)	Primary = safety Key Secondary = Exon Skipping (RT-PCR); Restoration of dystrophin protein expression and the DAPC
Required Age at Entry (yrs)	7-13		5-15	10-17
Study Status	Completed	Ongoing	Completed	Completed
No. Enrolled	12		19	7
No. Completed	12	NA	18 ^a	7
Study Period	July 2011 – Feb 2012	Feb 2012 – Nov 2014 for Efficacy Aug 2015 for Safety	Jan 2009 – June 2010	Oct 2007 – April 2009
Study Duration	28 Weeks	Week 168 efficacy; Week 208 safety	12 Weeks	Single Dose

Abbreviations: BL=Baseline; yrs=years; EDB=extensor digitorum brevis muscle; IM=intramuscular; IV=intravenous; No.=number; NSAA=North Star Ambulatory Assessment; PDPF=percentage of dystrophin positive fibers; PFT=pulmonary function testing; RT-PCR=reverse transcriptase-polymerase chain reaction; US=United States; UK=United Kingdom; Wk=week.

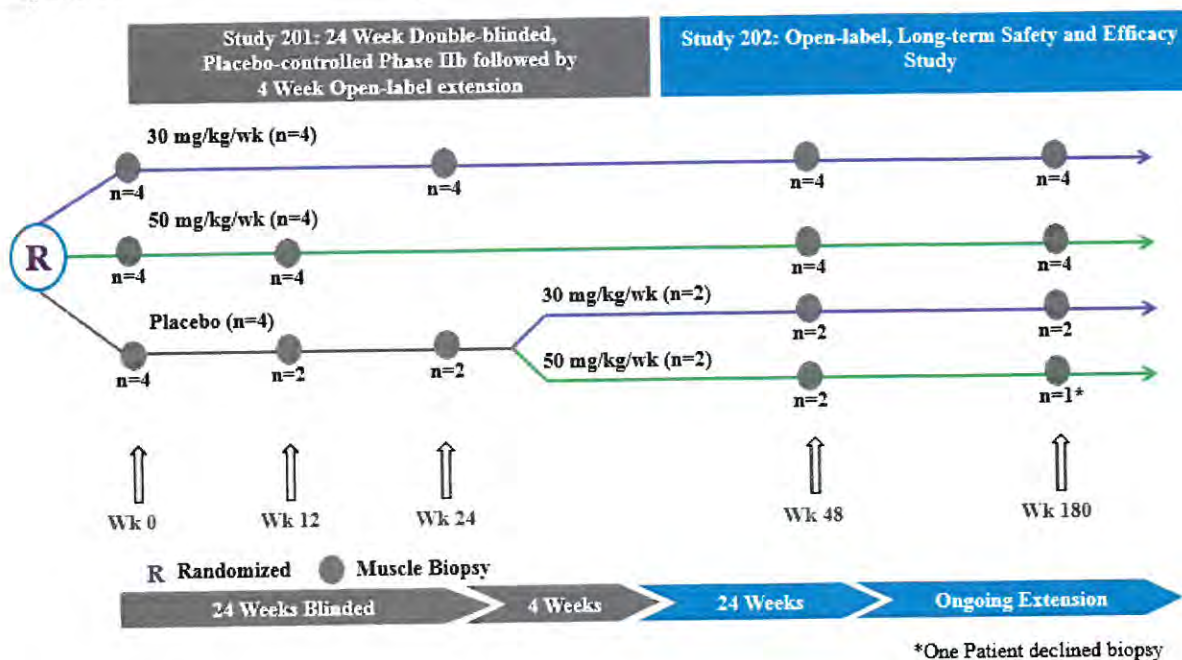
^a One patient in the 4.0 mg/kg/wk group discontinued treatment due to an adverse event.

6.2. Pivotal Studies 201/202

Study 201 is a completed, 28-week double-blind, placebo-controlled study of 12 ambulatory boys with DMD mutations amenable to exon 51 skipping. Elig randomized to receive weekly IV infusions of 30 (N = 4) or 50 mg/kg eteplirs placebo (N = 4) for the first 24 weeks. Afterwards, the 4 patients originally ra placebo, rolled over to open label eteplirsen of 30 mg/kg (N=2) or 50 mg/kg (N=2). Figure 10 presents a schematic for Studies 201/202.

- Following completion of Study 201, all 12 patients continued receiving weekly eteplirsen in the ongoing extension Study 202 for up to 3 years.
- During both studies, muscle biopsies of upper arms were obtained for assessment of exon skipping and dystrophin production for all patients at Baseline and study Weeks 48, and 180. In order to minimize the overall number of muscle biopsies, half of the study patients also underwent biopsies at Week 12 (50 mg/kg) and the other half of patients had an additional muscle biopsy at Week 24 (30 mg/kg).
- Clinical outcomes of 6MWT, NSAA, rise time, pulmonary function tests and other functional measures were performed to assess changes in muscle function over time and have been collected through Week 168 for the 12 patients enrolled in Study 201/202.

Figure 10: Schematic of Study Flow for Pivotal Studies 201/ 202



Inclusion Criteria

Study 201 inclusion criteria were designed to select a homogeneous population of DMD boys that would be expected to experience a predictable decline in 6MWT over the course of the study. Selection of this narrow population was considered the best group to evaluate whether stabilization of function would occur with eteplirsen intervention. Accordingly, the inclusion

criteria specified boys aged 7 to 13 with baseline 6MWT between 180 and 440 meters. The age of 7 years was selected as this was the time-point in the course of DMD when progressive muscle degeneration and loss of function begin to outpace natural growth and maturation such that DMD patients functionally decline. The impact of age and baseline 6MWT on performance on 6MWT are described in the current DMD literature (Henricson 2013a; Pane 2014a; McDonald 2010b; Mazzone 2013; Ricotti 2013; Ricotti 2015).

Steroid use may also influence performance on the 6MWT; (Pane 2014a; Henricson 2013a; McDonald 2010b; McDonald 2013b; Ricotti 2013; Ricotti 2015). DMD clinical trial design guidelines, recommend selection of a population of patients having similar anticipated disease trajectories. (FDA Draft Guidance for Industry: Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment, 2015) Therefore, Study 201 required that patients received a stable dose of steroids for ≥ 24 weeks prior to enrollment. Study 201 Key Inclusion criteria are provided in Table 5. Appendix 2 provides a complete list of Study 201 inclusion and exclusion criteria.

Table 5: Key Entry Criteria for Pivotal Study 201

Population	Male with DMD
	Genetically confirmed deletion mutation amenable to exon 51 skipping
	Aged 7-13 years
	Intact L/R biceps or alternative upper arm muscle group
Disease characteristics	Ambulatory with baseline 6MWT 180-440 meters
	Stable cardiac function with LVEF $>40\%$ on screening echocardiogram
	Stable pulmonary function with FVC $\geq 50\%$ predicted; supplemental oxygen not required
	Stable dose of oral corticosteroids ≥ 24 weeks before study
	No cognitive or behavioral disorder that would impair ability to perform on 6MWT

6.2.1. Study 201/202 Pre-specified Endpoint Results

6.2.1.1. Primary endpoint of Study 201

The primary endpoint of Study 201 was dystrophin production at Weeks 12 and 24. This was achieved at Week 24 for the 30 mg/kg dose group with demonstration of a significant increase of dystrophin in eteplirsen treated patients in comparison to both baseline pre-treatment values and a significant increase relative to placebo treated patients.

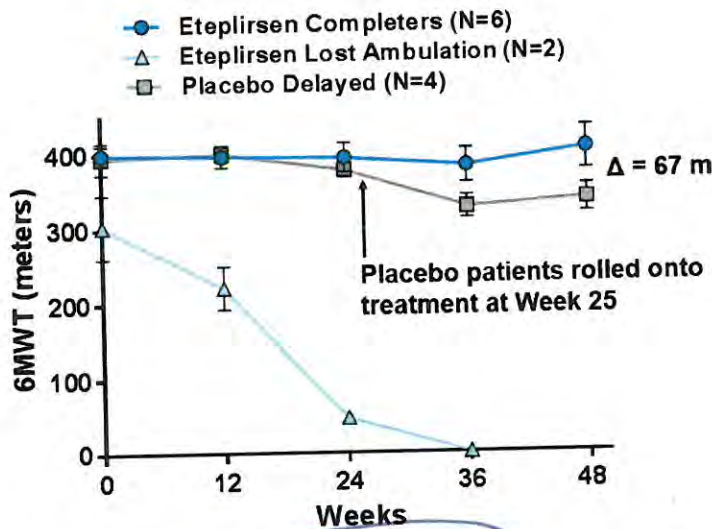
6.2.1.2. Primary endpoint of Study 202

The primary functional endpoint of Study 202 was comparison of Week 48 6MWT results for boys originally randomized to eteplirsen vs placebo separating out boys who were able and unable to complete the 6MWT at Week 48. A co-primary endpoint was Week 48 data for dystrophin which was analyzed for dose selection.

*Surely
Not
Planned*

In the analysis of 6MWT in Study 202, there were 2 eteplirsen treated boys who lost ambulation early in the course of the study. In retrospect, eteplirsen treatment may have been introduced too late in the course of their disease to evaluate benefit on ambulation. These 2 eteplirsen boys had the lowest 6MWT at the time of entry into Study 201 and it may be considered that they were at high risk for loss of ambulation. To evaluate for potential treatment effect of eteplirsen, an analysis of the 6MWT of the eteplirsen boys who maintained ambulation compared to the boys originally randomized to placebo, showed a mean difference of 67 meters at the end of 48 weeks as shown in Figure 11.

Figure 11: Study 201/202: Analysis of 6MWT by Treatment Group and Completion of 6MWT



Not obvious about to lose ambulation. Still > 300 m

Based on these encouraging but limited results, the hypothesis of eteplirsen efficacy was strengthened and it was decided that Study 202 be further extended to continue observation and collection of longitudinal clinical outcomes. However, given the relatively short duration of 24 weeks for the placebo-controlled portion of Study 201, there was an absence of long-term concurrent placebo controlled data. As recommended by the FDA, Sarepta obtained individual patient data from untreated DMD patients enrolled in observational registries who were highly comparable to the eteplirsen treated patients.

The basis of the eteplirsen application is the analysis of the clinical outcomes of 6MWT, Loss of ambulation, NSAA compared to external control cohorts used for comparison of long-term outcomes.

6.2.2. External Control Cohort Used For Comparison of Long Term Efficacy Data

In the absence of long-term, concurrent, placebo-controlled data from Study 201/202, Sarepta obtained individual patient data from untreated DMD patients enrolled in observational registries who were comparable to the eteplirsen-treated patients. The selection process for both registries, as well as individual patients was conducted in a manner to minimize the potential for selection bias. The clinical outcome experience from the external cohorts was used for comparison of 2 clinical efficacy endpoints; the 6MWT and NSAA.

Was 202 a planned study

Sarepta consulted with external DMD experts and reviewed findings from international DMD groups to identify potential registries that could provide individual patient 6MWT data including at least a baseline and post-baseline value for 6MWT. Twelve candidate external DMD registries with clinical outcome data were identified; however, only 2 databases had available, prospectively collected, 6MWT data including a baseline and at least 1 post-baseline value:

- Italian Telethon DMD Registry database (N = 97); Professor Eugenio Mercuri, MD, PhD (Catholic University in Rome); 11 participating tertiary care centers
- Leuven Neuromuscular Reference Center (NMRC) database (N = 89); Professor Nathalie Goemans, MD (University Hospitals in Leuven, Belgium); single site

Registry Characteristics Similar to Eteplirsen Studies 201/202

Although the registries were chosen primarily based on availability of 6MWT outcomes, both registries had characteristics including entry criteria and DMD standards of care comparable to Study 201/202. These registries include the requirement for a genetically confirmed diagnosis of DMD as was the case in Studies 201/202. Both registries followed patients over comparable time periods (2007 – present for the Leuven NMRC and 2008 – present for the Italian Telethon registries) with Studies 201/202 (2011 – present). Finally, Studies 201/202 and both registries excluded patients with known cognitive or behavioral disorders that would be likely to impair compliance with the functional assessments.

In addition, as with Studies 201/202, both registries follow international DMD patient care guidelines (Bushby 2010a, Bushby 2010b) used to set standards for the use of steroids as well as the use of physical therapy and orthotic devices to support continued ambulation.

- Italian Telethon investigators, as well as the principal investigator of the Leuven NMRC, are members of TREAT-NMD, a European organization of neuromuscular experts promote the use of these international treatment guidelines for DMD.
- While guidelines were published in 2010, clinics participating in both registries had been adhering to the standards at the time the registry studies were initiated including the use of steroids.
- The 2 lead physical therapists for the Italian Telethon Registry and Studies 201/202 were part of an international group which trained physical therapists on the 6MWT, further ensuring consistency and standardization of collection of 6MWT data.

Criteria for External Control Cohort was Based on Study 201 Inclusion Criteria

From the combined data set of 186 patients provided by the 2 registries, individuals were identified for inclusion in the external control group(s) using the key prognostic entry criteria for Study 201. Of note, *all patients* who met these criteria were included in the external control cohorts:

- They were required to be ≥ 7 years of age,
- Ambulatory with a baseline and at least 1 post baseline 6MWT result
- Receiving glucocorticoid therapy per treatment guidelines
- Genetically confirmed DMD amenable to exon 51 skipping therapy.

The primary external control group for comparison was comprised of boys with a mutation that was amenable to exon 51 skipping therapy (N=13). A secondary external control group was also identified which included patients with a DMD mutation amenable to any type of exon skipping therapy (N=50). This secondary group provided a larger sized group for comparison, albeit in a population of DMD with a mutation amenable to any kind of exon skipping.

Schematic for Selection of External Control Groups

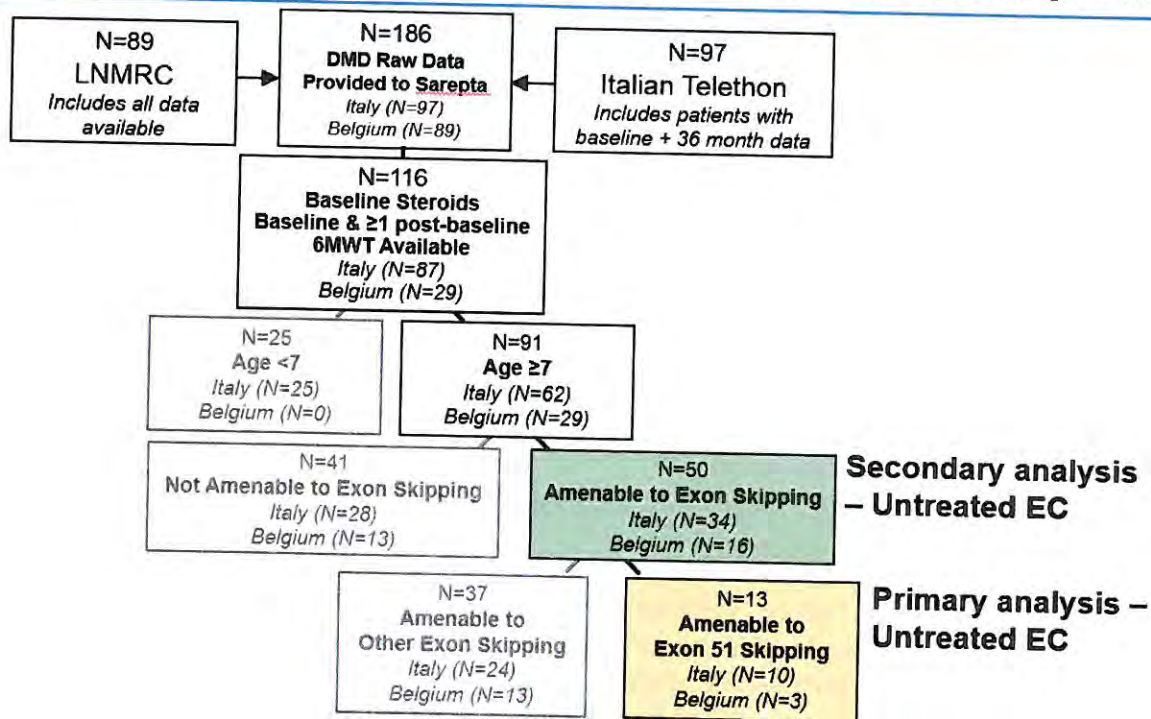
The schematic below (Figure 12) illustrates the application of the selection filters used to identify external control patients, which were based on Study 201 inclusion criteria.

- From the 186 untreated DMD patients included in the registries, 116 received glucocorticoids at Baseline and had Baseline and at least one post-Baseline 6MWT
- 91 of the 116 were ≥ 7 years of age
- 50 of the 91 had DMD genetic mutations amenable to any exon skipping therapy
- 13 of the 50 had DMD specifically amenable to exon 51 skipping therapy

Thus, 2 analysis groups were identified:

- Primary Analysis Group – includes the 13 patients with *DMD* mutations amenable to exon 51 skipping and is the most relevant comparator for the 3-year 6MWT data from Study 201/202 eteplirsen-treated patients. A subset of 10 external control patients from the Italian Telethon registry had longitudinal NSAA data; NSAA data were not provided for patients in the Leuven NMRC.
- Secondary Analysis Group – includes the 50 patients with *DMD* mutations amenable to any exon skipping and thus provides a larger group for comparison of 3 years of 6MWT from Eteplirsen Studies 201/202. A subset of 34 patients from the Italian Telethon registry had longitudinal NSAA data; NSAA data were not provided for patients from the Leuven NMRC.

Figure 12: Selection of External Control Groups for 6MWT and NSAA Comparison



6.3. Comparable Baseline Demographic and Disease Characteristics between Study 201/202 and External Control Cohorts

Study 201/202 had only 24 weeks of randomized placebo-controlled data, and as such use of external control cohorts was necessary in order to compare long-term clinical outcome data. Sarepta recognizes the potential limitations (ICH E 10) of using external control groups. The approach to identification of the external control groups was conducted in a manner to minimize these potential limitations. Table 6 summarizes the potential issues associated with the use of an external control cohort and approaches that Sarepta used in order to address or evaluate the potential for bias.

Table 6: Approaches or Analyses to Address Potential limitations of Use of an External Control Group ICH E10*

Issue	Approach to Address Limitation	Relevant Section in Briefing Document
Inability to control bias in selection of external control	Selected all registries with available baseline and post-baseline 6MWT data, without regard to 6MWT results	Section 6.2.2
	Sensitivity analyses of the 6MWT with covariates of baseline 6MWT and age continue to demonstrate significant benefit for 6MWT for eteplirsen	Section 6.5.1.1
An external control group is often identified retrospectively leading to potential selection bias	Although identification was retrospective, <i>all patients meeting criteria based on inclusion for Study 201/202 were in cohort</i> 7. How many OK	Section 6.2.2 H 50
Difficulty in establishing comparability of eteplirsen and external control groups	High degree of comparability between eteplirsen and EC on baseline characteristics was established	Section 6.3
	High compliance rates with standard of care guidelines for DMD was shown	Section 6.4
Historical control groups have worse outcomes than apparently similar control group in a randomized study	The EC groups had similar or slightly better 6MWT performance compared to the placebo arm of a published randomized drisapersen clinical trial	Section 6.5.1.2
	The EC groups experienced loss of ambulation at an age comparable to published DMD literature	Section 6.5.2

Did they list only at baseline.

* Choice of Control Group and Related Issues in Clinical Trials

Demographic and key Baseline characteristics for the 12 patients treated with eteplirsen in the pivotal 201/202 studies and the primary (exon 51 skipping, N = 13) and secondary (any exon skipping, N = 50) external control groups used for comparison on the 6MWT are presented in Table 7. Demographic and Baseline characteristics for the external control groups used for comparison on the NSAA are not presented as they are a subset of the 6MWT control groups.

Study 201/202 patients were a mean of 9.41 years of age at Baseline, while patients in the primary (N = 13) and secondary (N = 50) external control groups had mean ages of 9.45 and 9.68, respectively. Genetic mutations were similar between Studies 201/202 and those in the primary external group (N=13), with each specific type of genetic mutation observed in Study 201/202 also represented among the boys in the primary external control cohort. Mean baseline height and weight were generally comparable, although patients from the Italian Telethon were slightly taller and heavier. Mean 6MWT scores across the eteplirsen treated and external control groups were within 10 meters of each other and the distribution of patients over the range of Baseline scores for both 6MWT and NSAA was similar (Figure 13).

Importantly, all patients in all groups had been on steroids for at least 6 months prior to Baseline and remained on steroids throughout the study or follow-up period.

The high comparability of the treated pivotal study and untreated control patients across these baseline parameters confirms the validity of the process used for selection of the external controls. Baseline characteristics for the individual patients in Study 201/202 (N = 12) as well as the external control of exon 51 skippable (N = 13) are provided in Appendix 2.

Table 7: Demography and Baseline Characteristics of Eteplirsen Patients in Studies 201/202 vs External Controls

Parameter	Pivotal Study	Untreated External Control Groups	
	Study 201/202 (N = 12)	Primary Analysis Exon 51 Skipping (N = 13)	Secondary Analysis Any Exon Skipping (N = 50)
Male Gender	100%	100%	100%
Age, years	N = 12	N = 13	N = 50
Mean (SD)	9.41 (1.18)	9.45 (1.45)	9.68 (1.52)
Median	9.7	9.0	9.54
Min, Max	7.3, 11	7.3, 11.8	7.0, 13.0
Height, cm	N = 12	N = 10	Not available
Mean (SD)	123.9 (8.37)	131.3 (3.16)	
Median	119	131	
Min, Max	117, 138	126, 136	
Weight, kg	N = 12	N = 10	Not available
Mean (SD)	33.0 (7.29)	35.5 (8.75)	
Median	34.6	32	
Min, Max	23.4, 42	26, 48.0	
Genotype (exon skippable)	N = 12	N = 13	Amenable to any exon skipping ^a
45-50	3	3	
48-50	1	2	
49-50	5	3	
50	1	2	
52	2	3	
Steroid use ≥24 weeks prior to Baseline (% yes)	100%	100%	100%
Steroid use:			
Continuous	11	8	32
Intermittent	1	5	18
Ambulatory (% yes)	100%	100%	100%
6MWT Assessment method	Assessor training and script per modified ATS procedure	Assessor training and script per modified ATS procedure	Assessor training and script per modified ATS procedure
6MWT Distance (m)	N = 12	N = 13	N = 50
Mean (SD)	363.2 (42.19)	357.6 (66.75)	355.7 (87.28)
Median	370	373	356
Min, Max	256, 416	200, 458	100, 558
<i>Comparison of eteplirsen (n = 12) to Italian Telethon Exon 51 Amenable (n = 10) Any Exon (n = 34)</i>			
Total NSAA Score ^c	N = 12	N = 10	N = 34
Mean (SD)	24.9 (4.93)	22.0 (6.27)	22.7 (6.31)
Min, Max	17,31	10,31	10, 32
Rise Time ^d	N=12	N=8	N=28
Mean (SD)	8.2 (7.57)	8.4 (8.99)	8.9 (9.03)
Median	5.5	5.9	5.7
Min, Max	3.1, 30	2.37, 30	2, 30

Abbreviations: 6MWT = Six minute walk test; EC = external control; SD = standard deviation.

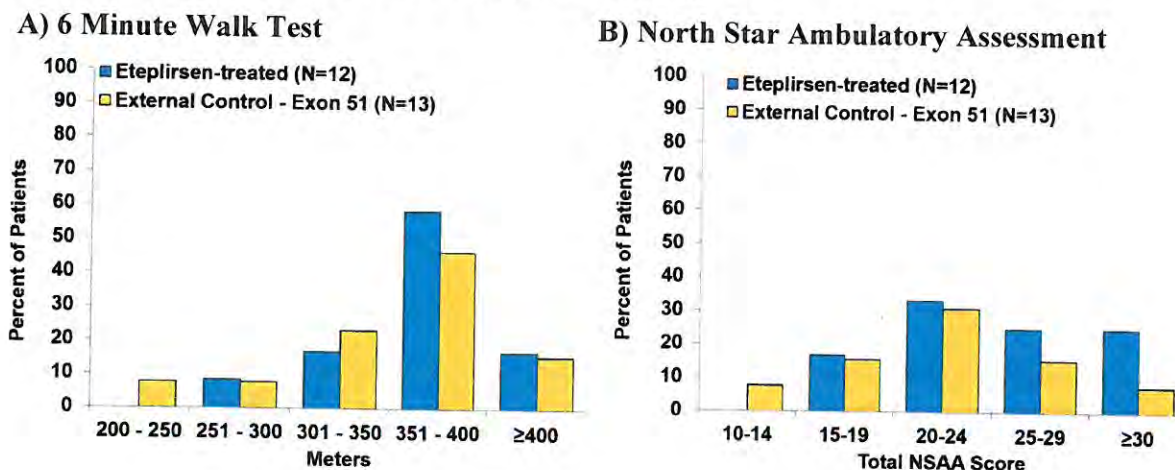
^a Seven of the 50 (14%) had deletion mutations amenable to exon 44 skipping; this genotype may have a milder phenotype compared to other skippable mutations (Pane 2014a).

^b Bushby 2010a; Bushby 2010b

^c NSAA data were only available for patients in the Italian Telethon DMD Registry database.

^d Rise Time data were only available for Italian Telethon Patients. Patients unable to rise without external support were assigned a rise time of 30 seconds (Henricson 2013)

Figure 13: Baseline Distribution of 6MWT and NSAA Scores for Eteplirsen-Treated Patients in 201/202 vs External Controls

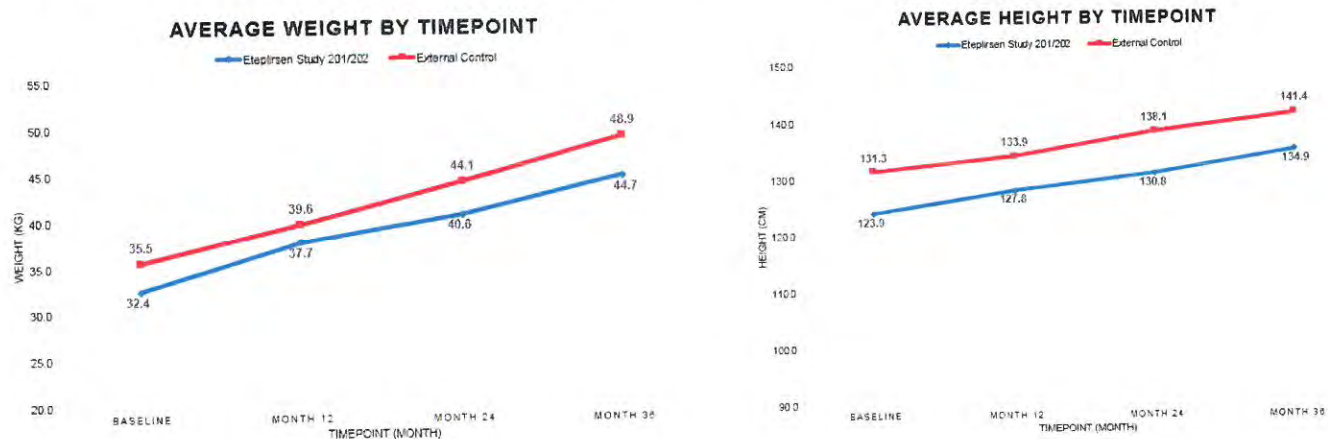


6.4. Longitudinal and Standard of Care Parameters for Studies 201/202 and External Control Patients

In addition to the analysis of baseline parameters of age, 6MWT, NSAA score, height and weight, the trajectory of growth in terms of height and weight are depicted over the course of the 3-year follow-up period by [Figure 14](#).

Patients from both Study 201/202 and the external control cohort received steroids for a period of at least 24 weeks prior to baseline. Furthermore all boys from both Study 201/202 and the external control cohort continued to receive steroids (including deflazacort and prednisolone) through the duration of the 3-year follow-up period. Details regarding the type of glucocorticoid therapy for individual patients are provided in [Appendix 3](#).

Figure 14: Mean Height and Weight over 3-Year Period for Study 201/202 (N = 12) vs. Italian Telethon (N = 10)



Comparison of Study 201/202 patients and the patients from the Italian Telethon Registry, demonstrated that both sets of patients received regular physical therapy and showed high compliance rates with the use of orthoses to maintain lower extremity flexibility.

Most eteplirsen-treated patients as well as those in the Italian study followed home stretching routines in addition to meeting routinely with a trained physical therapist. Patients in the Italian cohort met with a trained physical therapist at least twice and as many as 6 days a week.

In order to maintain ankle flexibility, which is important to ambulation, many boys with DMD wear night splints. The majority of patients in both cohorts wear night splints or, in the case of 2 patients in the Italian cohort, were found not to need them. Details regarding comparison of physical therapy and orthoses are provided by [Table 8](#).

Table 8: Studies 201/202 Comparison of Physical Therapy and Use of Orthoses

		Italian Telethon N = 10	Study 201/202 Eteplirsen N = 12
Physical Therapy	PT Regimen	# of Patients	# of Patients
Home therapy	Stretching with parents/other	6	8
Swimming	1 day/week	5	1
	2-3 days week	0	1
Frequency of appointments with trained physical therapist	4-6 days/week	5	2
	2-3 days/week	5	3
	1 day/week	0	4
	1 day/year	0	1
Use of night splints to maintain ankle flexibility	Use orthoses	8	11
	Orthoses not needed (TA<10°)	2	0
	Orthoses not used	0	1

6.5. Functional Endpoints

6.5.1. Six-Minute Walk Test

Given the importance of ambulatory compromise to the DMD disease process, 6MWT was chosen as the primary endpoint. The 6MWT is an integrated assessment of global muscle function and endurance that also incorporates cardiac and respiratory functions ([ATS 2002](#)) and has been established as accurate, reproducible, simple to administer, and well tolerated in ambulatory patients with DMD ([McDonald 2010a](#)). It is also clinically relevant in DMD as decline in ambulatory capacity, is associated with reductions in DMD patient- and caregiver-reported quality of life ([Bendixen 2012](#); [Bendixen 2014](#); [Magliano 2014](#); [Uzark 2012](#); [Henricson 2013b](#)). Furthermore the 6MWT is an accepted outcome measure for DMD according to the recent FDA draft guidance for industry on developing drugs for DMD ([FDA 2015](#)).

In both the eteplirsen-treated and external control patients, the 6MWT was performed according to published methods modified for DMD patients ([ATS 2002](#); [McDonald 2010a](#)) where patients are asked to walk a pre-set course for 6 minutes during which they receive scripted

encouragement and are followed by a member of the testing staff to ensure patient safety. Furthermore, both lead physical therapists for the eteplirsen study 201/202 and the Italian Telethon have collaborated in an international initiative to train physical therapists on administration of the 6MWT in DMD.

6MWT data for eteplirsen-treated and 2 groups of external control patients (primary exon 51 skipping N = 13 and secondary any exon skipping N = 50) were compared, using the analysis of covariance (ANCOVA) model with group (e.g., genotype [exon skipping amenable vs. non-amenable], age [<7 vs. ≥ 7 years], treatment [eteplirsen vs. untreated]) as a fixed-effect term and Baseline 6MWT as a covariate. Change from Baseline to Years 1, 2, and 3 was also summarized.

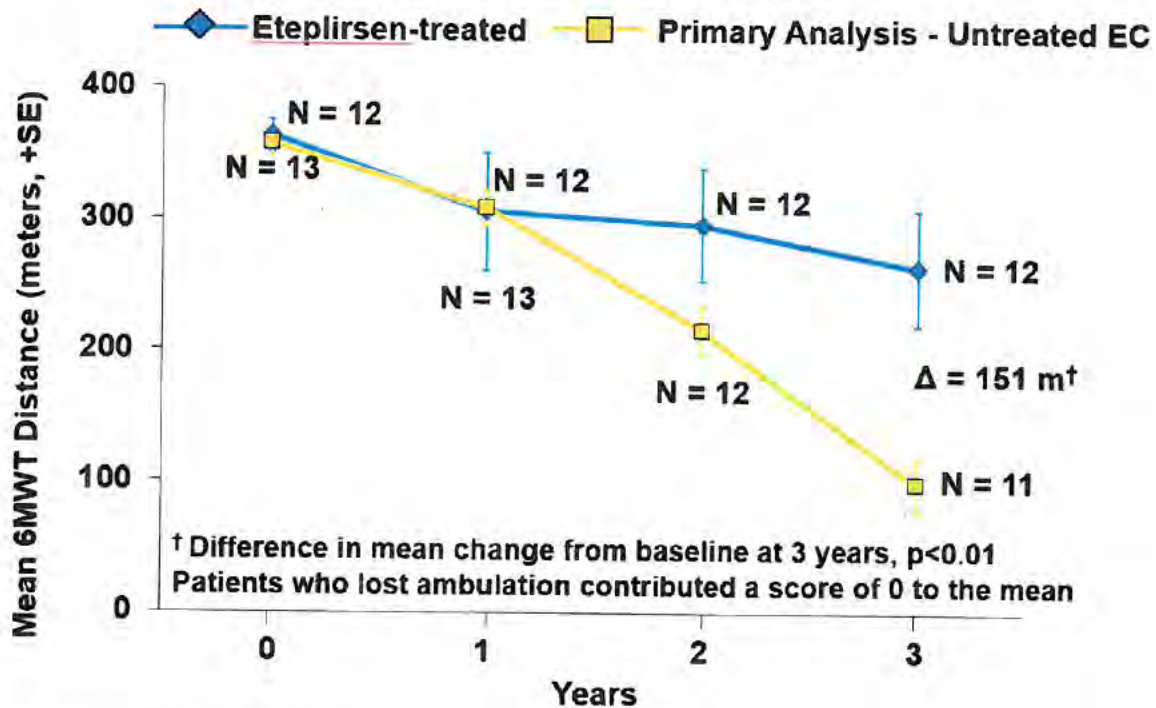
No adjustments were made for multiple comparisons as these analyses were descriptive; p-values, when provided, are nominal and included for guidance purposes only. For eteplirsen-treated patients (N = 12), data for the 30 and 50 mg/kg cohorts (N=8) were pooled along with data for the placebo-to-eteplirsen cohort (N=4) after correcting for the 24-week placebo-period (i.e., by counting Week 24, the last week prior to receiving eteplirsen, as Baseline).

Results for 6MWT of Eteplirsen (N=12) vs External controls amenable to exon 51 (N=13)

Eteplirsen treated patients (N = 12) showed a slower rate of decline in the 6MWT, compared to primary external controls with DMD mutations amenable to exon 51 skipping (N = 13). The 2 patient groups had similar baseline and disease progression trajectories through Year 1 (12 months) supporting the comparability of the groups prior to and during initial stages of treatment with eteplirsen. This is also consistent with pharmacodynamic data that indicates it may take up to 24 weeks to establish significant dystrophin production. However, as the study progresses and the stabilization of ambulation in eteplirsen-treated patients is juxtaposed against the predictable decline of ambulation in untreated external controls, the impact of eteplirsen becomes apparent.

A large treatment effect of 150.8 meters is shown after the course of 3 years. After Year 1, the treated and untreated patients began to diverge, resulting in a 75.1-meter difference in 6MWT decline by Year 2, and a larger, statistically significant ($p < 0.01$) difference of 150.8 meters between the groups by Year 3 (Figure 15).

Figure 15: Mean 6MWT Values over Time in Eteplirsen-Treated Patients (Studies 201/202) vs. Primary External Controls

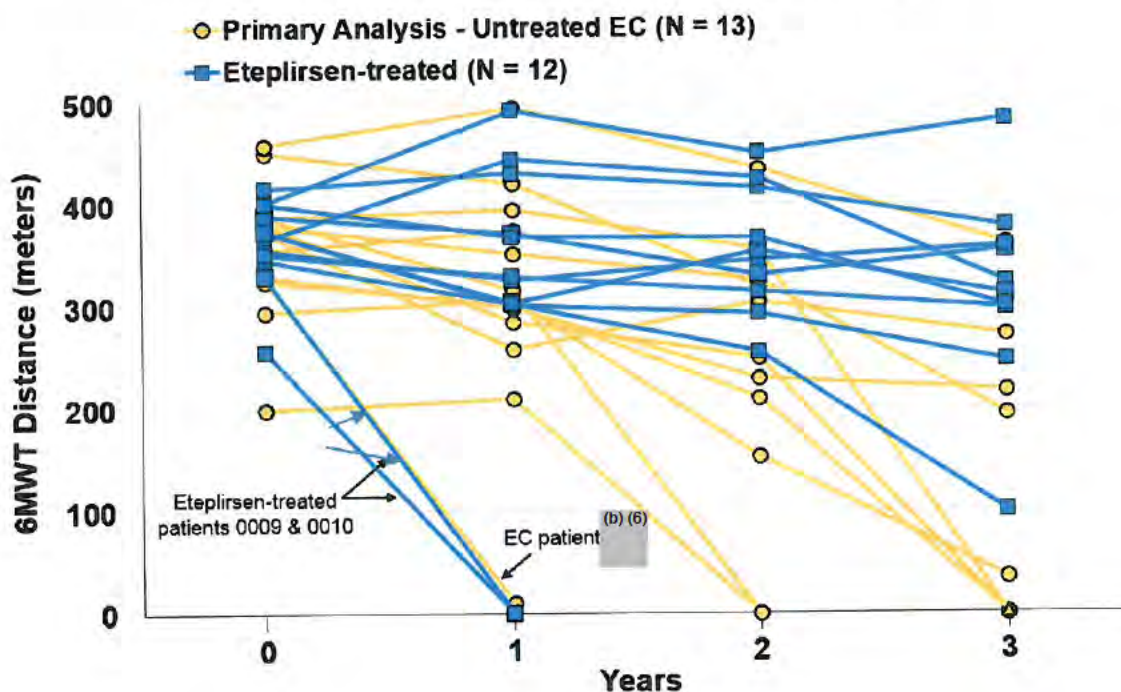


	Baseline	Year 1	Year 2	Year 3
Eteplirsen, n	12	12	12	12
Mean (SD)	363.2 (42.19)	305.8 (155.32)	295.9 (148.98)	263.1 (151.74)
Controls, n	13	13	12	11
Mean (SD)	357.6 (66.75)	309.0 (118.78)	215.4 (148.85)	98.5 (136.28)

In the analysis of individual 6MWT values over time, 2 of the eteplirsen-treated patients (blue lines) lost ambulation relatively early in the study (<48 weeks) compared to 1 of the external control patients (yellow lines). The eteplirsen patients (twin brothers, identified as Patients 009 and 010) had the lowest 6MWT scores at Baseline, hence they may have been at greater risk for loss of ambulation prior to initiation of treatment. The external control patient (identified as Patient ^{(b) (6)}) had a Baseline 6MWT of 327 meters, which was also relatively low.

All boys from either the eteplirsen Study 201/202 or the external control cohort who lost ambulation over the 3 year course were included in the analysis contributing a 6MWT value of "0" meters to the mean (Figure 16).

Figure 16: Individual 6MWT Values over Time in Eteplirsen-Treated Patients (Studies 201/202, N = 12) vs. Primary External Controls

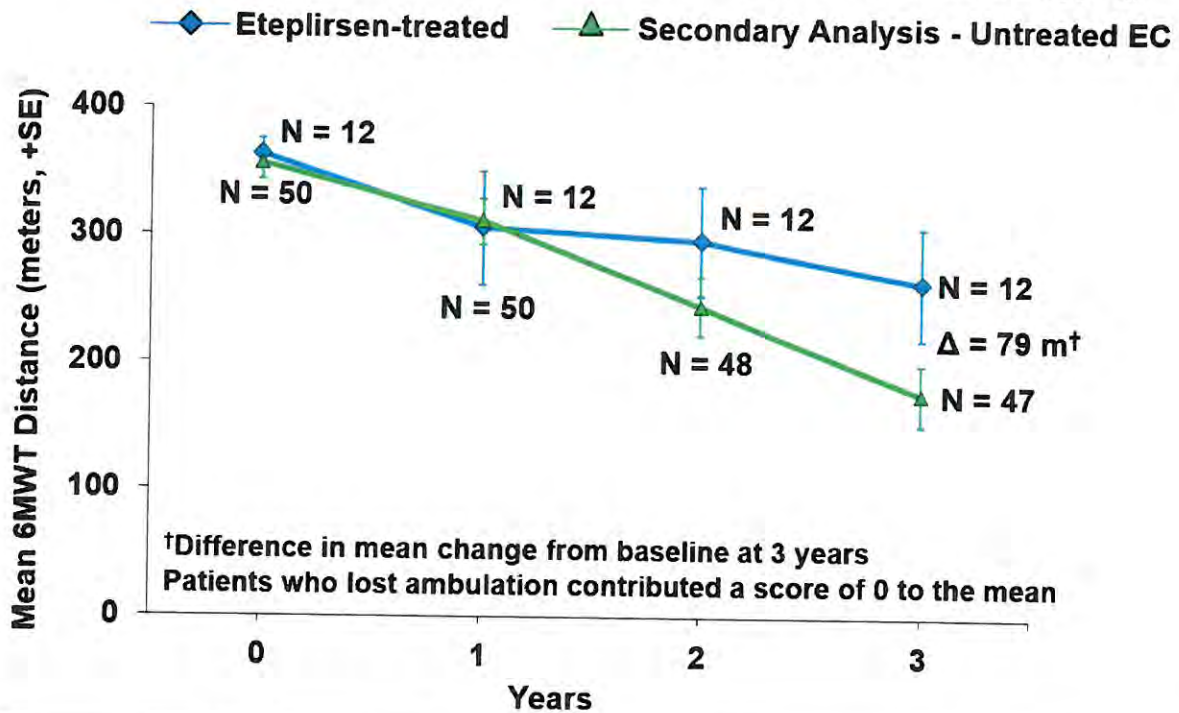


6MWT of Eteplirsen (N=12) vs External controls amenable to any exon skipping 51 (N = 50)

In the analysis between eteplirsen (N = 12) and the external controls amenable to any exon skipping (N = 50), a substantive difference of 79.9 meters on the 6MWT was shown. Although the secondary control was not as well matched as it included a broader population amenable to any exon skipping, this group was larger and provides a more conservative comparison. As shown in Figure 17, the 2 patient groups walked comparable mean distances at Baseline and demonstrated similar disease progression trajectories through Year 1 (12 months). After Year 1, however, they began to diverge, with the eteplirsen-treated patients showing a less severe disease progression, resulting in a clinically relevant difference between the 2 groups of 43.7 and 79.9 meters in 6MWT decline at Years 2 and 3, respectively.

A list of individual 6MWT results for both Study 201/201 patients (N = 12) as well as the external control cohort amenable to exon 51 skipping (N = 13) is provided in Appendix 4.

Figure 17: Mean 6MWT Values over Time in Eteplirsen-Treated Patients (Studies 201/202) vs. Secondary External Controls (Any Exon Skipping)



	Baseline	Year 1	Year 2	Year 3
Eteplirsen, n	12	12	12	12
Mean (SD)	363.2 (42.19)	305.8 (155.32)	295.9 (148.98)	263.1 (151.74)
Controls, n	50	50	48	47
Mean (SD)	355.7 (87.28)	311.3 (125.22)	244.8 (159.50)	175.7 (165.06)

6.5.1.1. Sensitivity Analyses of the Primary Functional Efficacy Endpoint: 6MWT

A series of sensitivity analyses were performed on the 3-year 6MWT data to control for potential confounding factors and evaluate the robustness and validity of the primary efficacy analysis. These sensitivity analyses controlled for potential group imbalances in Baseline 6MWT and age. Additional sensitivity analyses accounted for potential violations of the data's normality assumption and missing data on the 6MWT. As described below and summarized in Table 9, for every analysis performed, the difference between the eteplirsen-treated and untreated external controls in the change from Baseline on the 6MWT remained clinically meaningful and statistically significant. Details for the methodologies of these analyses are provided in Appendix 5.

Table 9: Sensitivity Analysis for 6MWT in Eteplirsen-Treated (N = 12) vs. External Controls Amenable to Exon 51 Skipping (N = 13)

Potential Issue Addressed	Row	Comparison: Change from Baseline in 6MWT in Eteplirsen-Treated (N = 12) vs. Untreated External Controls (N = 13)	LS Mean Difference (meters)	P-Value
Bias Caused by Imbalance in Important Baseline Prognostic Factors	1	ANCOVA with Baseline 6MWT and age as covariates	141	0.0115
Bias Caused by Violation of Normality Assumption	2	ANCOVA with Baseline as a covariate, rank transformation as the outcome for 6MWT	NA ^a	0.0055
	3	ANCOVA with Baseline and age as covariates, rank transformation as the outcome for 6MWT	NA ^a	0.0072
Bias Caused By Missing Data	4	MMRM analysis with Baseline and age as covariates	143	0.0026
	5	MMRM analysis with Baseline and age as covariates and rank transformation as the outcome for 6MWT	NA ^a	0.0091
	6	ANCOVA with Baseline as a covariate and LOCF for missing data	123	0.0221
	7	ANCOVA with Baseline and age as covariates and LOCF for missing data	123	0.0254
	8	ANCOVA with Baseline and age as covariates, LOCF for missing data, rank transformation as outcome for 6MWT	NA ^a	0.0228

Abbreviations: 6MWT = 6 Minute Walk Test; ANCOVA = analysis of covariance; LS = least squares; LOCF = last observation carried forward; MMRM = Mixed Model Repeated Measures; NA = not applicable.

^a Not applicable as the data being analysed are rank-transformed.

An identical series of sensitivity analyses was applied to the comparison of eteplirsen-treated patients (N = 12) to external controls amenable to any exon skipping (N = 50). Although the difference in the change from Baseline on the 6MWT did not reach significance with the pre-specified ANCOVA analysis, the difference between the 2 groups did reach significance (p < 0.05) in 2 analyses:

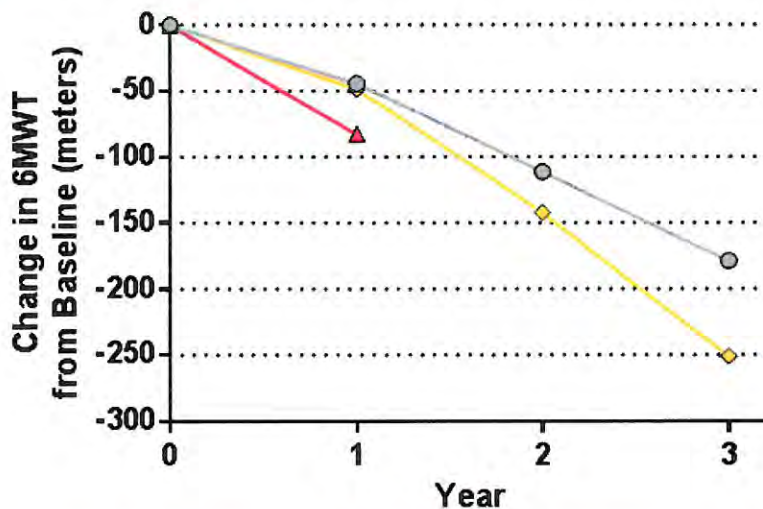
- Sensitivity analysis for the potential for violation of the Normality Assumption using an ANCOVA of rank transformed data with Baseline 6MWT as a covariate.
- Sensitivity analysis for potential for bias due to missing data was addressed using the MMRM analysis with Baseline 6MWT and age as covariates (see [Appendix 6](#)).

6.5.1.2. Decline of 6MWT for External Controls Compared to Published Literature

To evaluate the possibility that the external control had worse outcomes than would have been expected in a cohort of patients from a randomized clinical trial, comparison of the 6MWT for the external control groups to published data from a drisapersen trial was conducted (placebo group N = 32). As shown in Figure 18, both external control groups (exon 51 skipping N = 13 and any exon skipping N = 50) declined at a slower rate than the drisapersen placebo cohort over the course of one year. This supports the conclusion that the 6MWT 150.8 meter difference observed for eteplirsen patients (N = 12) vs the untreated external cohort (N = 13) is attributable to eteplirsen treatment, rather than the chance occurrence of an atypically rapid decline of the external control group.

Figure 18: Eteplirsen-Treated Patients Compared to External Controls and Drisapersen Placebo Cohort

- External Amenable to Skipping Any Exon (≥ 7 , steroid-treated, N=50)
- ◇ External Control Exon 51 Amenable (≥ 7 , steroid-treated, N=13)
- ▲ Drisapersen Placebo (>7 , exon 51 amenable, 85% steroid-treated, N=32)



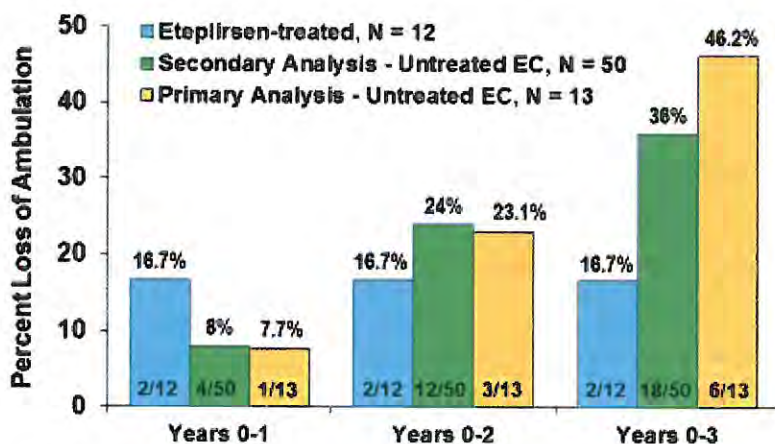
Source: Goemans, et al. Drisapersen Efficacy and Safety in Duchenne Muscular Dystrophy: Results of a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial (Study DMD114044). Late Breaking Oral Presentation, WMS 2013, Asilomar, CA.

6.5.2. Loss of Ambulation

Ambulatory compromise and loss of ambulation are hallmarks of the progressive muscle degeneration characteristic of DMD (Bushby 2010a; Ciafaloni 2009; van Ruiten 2014). Once confined to a wheelchair, other symptoms tend to follow in rapid succession including loss of upper limb function, such that self-care, unsupported sitting, and eating become impaired, severely affecting patient quality of life, as well as that of caregiver and families (Bendixen 2012; Bendixen 2014; Magliano 2014; Uzark 2012). Moreover loss of ambulation is associated with an earlier need for ventilation and premature death (Bushby 2010a; Humbertclaude 2012; Kinali 2007; Van Essen 2004).

Fewer eteplirsen treated boys lost ambulation (defined here as a score of 0 meters on the 6MWT) over the 3-year time period evaluated compared to untreated external control boys (Figure 19). After 3 years, only 2 of 12 (16.7%) eteplirsen-treated patients (i.e., Patients 009 and 010) lost ambulation. In comparison, 6 of 13 (46.2%) external controls amenable to exon 51 skipping lost ambulation, and 18 of 50 (36%) external controls amenable to any exon skipping, lost ambulation over 3 years. A listing of baseline characteristics of the 8 boys who lost ambulation (eteplirsen N = 2 and EC exon 51 N = 6) may be found in Appendix 7.

Figure 19: Cumulative Loss of Ambulation Over 3 Years in Eteplirsen-Treated Patients (Studies 201/202) vs. External Controls



Abbreviations: EC=untreated external control patients.

Loss of ambulation of external controls compared to published literature

To evaluate the possibility that the observed difference in loss of ambulation between eteplirsen and the external controls could be due to an atypical rate of loss of ambulation for external control, a comparison to published data regarding the median age for loss of ambulation (11.2-13.9 years) was conducted (Ricotti 2015; Bello 2015). Based on the literature it would be expected that ~50% of DMD boys would have lost ambulation by the age of ~12.5 years. Since the median age of the external control group was approximately 12.5 years, after 3 years of follow-up, the loss of ambulation rates of 46.2% and 36% which were observed for the external cohorts of exon 51 skipping (N = 13) and the external cohort of any exon skipping (N = 50) appear to be aligned and no worse than published literature. This supports the conclusion that the lower rate for loss of ambulation observed for eteplirsen patients (16.7%) vs the external cohorts is attributable to eteplirsen treatment rather than an atypically rapid loss of ambulation for boys in the external control group.

6.5.3. North Star Ambulatory Assessment

The NSAA is a clinician-reported outcome instrument specifically designed to measure ambulatory function in patients with DMD (Scott 2012). In contrast to the 6MWT, which is a continuous measure, the NSAA is a multiple-item rating scale (17 items) that includes 3 ordered response categories (2, 1, or 0). Items are scored either 2 ('normal' with no obvious modification of activity), 1 (modified method but achieves goal), or 0 (unable to achieve independently). A total 'ambulatory function' composite score is generated by summing items. The 17 items

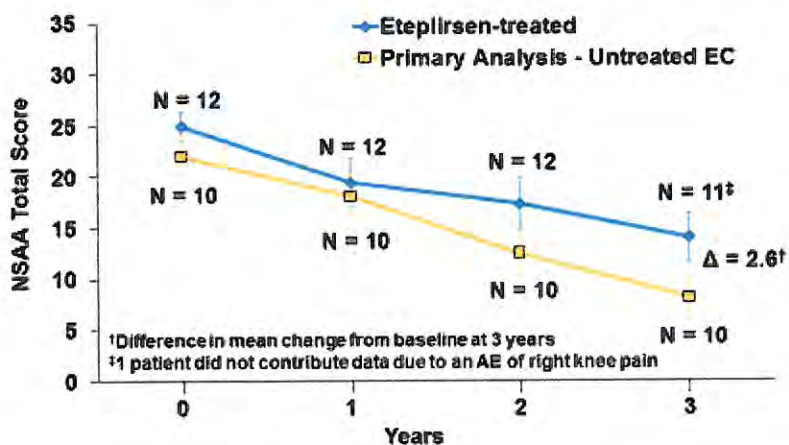
assessed include a 10-meter walk/run, rising from a sit to stand, standing on 1 leg, climbing and descending a step, rising from lying to sitting, rising from the floor, lifting the head, standing on heels, and jumping. The NSAA has undergone detailed psychometric evaluations based on traditional (reliability and validity) and modern (Rasch) methods, and has been included in international DMD clinical trials and natural history studies ([Mazzone 2009](#); [Mazzone 2010](#); [Scott 2012](#); [Mayhew 2011](#)). A listing of the 17 items in the NSAA is provided in [Appendix 8](#).

NSAA data (total scores) from eteplirsen-treated patients in Studies 201/202 were compared with longitudinal data from an external cohort. In both the eteplirsen-treated and external control patients, the NSAA was performed according to published methods ([Mazzone 2009](#)). For eteplirsen-treated patients (N = 12), data for the 30 and 50 mg/kg dose groups were pooled with those for the placebo-to-eteplirsen cohort after correcting for the 24-week placebo-treatment period (i.e., by counting Week 24, the last week before receiving eteplirsen, as Baseline = year 0).

NSAA data from eteplirsen-treated patients in Studies 201/202 were compared with longitudinal data from an external control cohort that included DMD patients amenable to exon 51 skipping (N = 10). As shown in [Figure 20](#), at baseline, eteplirsen-treated patients had a total score of 24.9 compared to a score of 22.0 for the external control group, representing a difference of 2.9. Over the first year, both the eteplirsen treated boys and the EC group declined in function. However, as with the 6MWT, following Year 1, the decline in function for the eteplirsen group became slower. At the end of Year 3, there was a total mean score of 14.0 for the eteplirsen boys compared to a mean score of 8.1 for the external control boys, representing a 5.9 difference in score. Overall the untreated external control had experienced a 3-point decrease relative to eteplirsen treated boys. This is of relevance given that a 3-point decrease in NSAA may represent impairment in 3 activities, or the loss of an entire activity with impairment in another. Moreover, in patients ≥ 7 years of age, NSAA scores below 10 have been associated with a high risk of loss of ambulation within 1 year ([Ricotti 2015](#)).

Below is a figure of the baseline distribution of NSAA between eteplirsen treated boys vs EC boys both at baseline and the end of 3 years. A plot of individual NSAA patient data is provided in [Appendix 4](#).

Figure 20: Mean NSAA Total Scores over Time in Eteplirsen-Treated Patients (Studies 201/202) vs. External Controls Amenable to Exon 51 Skipping



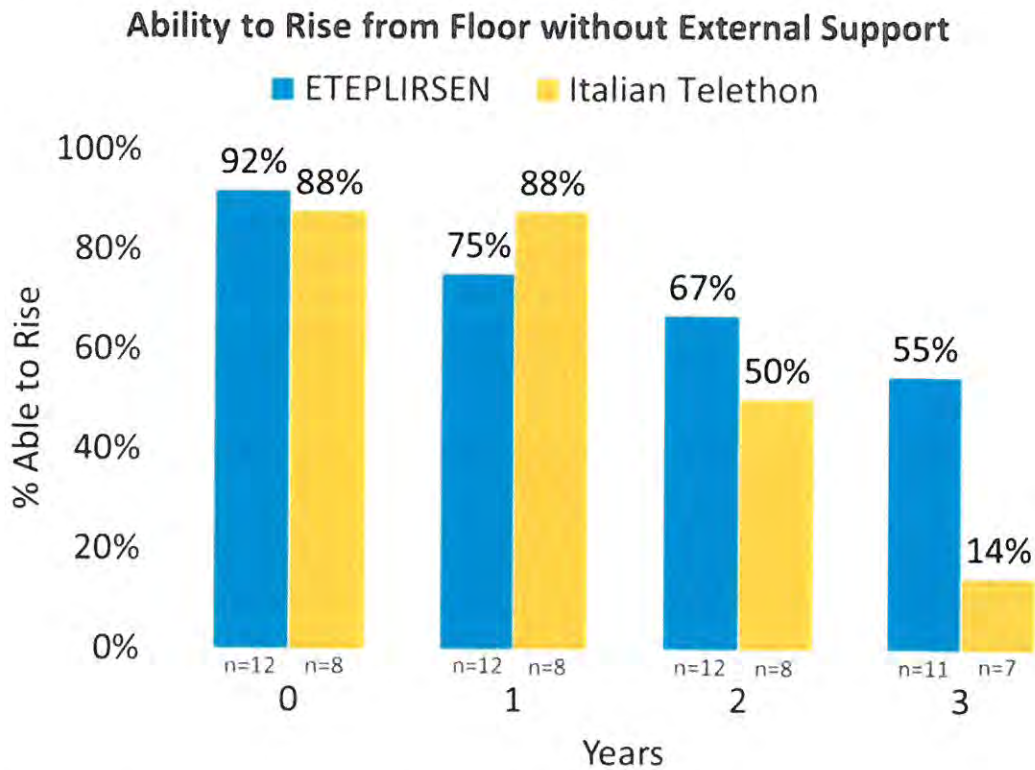
	Baseline	Year 1	Year 2	Year 3
Eteplirsen, n	12	12	12	11
Mean (SD)	24.9 (4.93)	19.4 (7.99)	17.3 (8.55)	14.0 (7.80)
Controls, n	10	10	10	10
Mean (SD)	22.0 (6.27)	18.1 (6.74)	12.5 (6.69)	8.1 (6.92)

6.5.4. Comparison of Rise Time: Eteplirsen Treated (N = 12) vs Italian Telethon (N = 10)

The ability to rise from supine is a critical activity for DMD patients and it is one of the early abilities to be lost in DMD and is predictive of loss of ambulation. Information regarding the ability to rise without external support, was obtained from the Italian Telethon registry.

The proportion of eteplirsen vs Italian Telethon patients who were able to rise at Baseline (Year 0) and Year 1, 2 and 3 was calculated. At Baseline, 92% of eteplirsen treated patients vs 88% of the Italian Telethon patients had the ability to rise independently. However by the end of Year 3, 55% of eteplirsen treated boys had maintained the ability to rise, compared to only 14% of the Italian Telethon patients as illustrated in Figure 21.

Figure 21: Study 201/202 Eteplirsen Treated Patients (N = 12) Vs. Italian Telethon (N = 10) Ability to Rise Without External Support



6.5.5. Pulmonary Function Tests

Respiratory function in DMD is progressively impaired over time as the dystrophic process affects respiratory muscles, including the diaphragm, and leads to significant morbidity and mortality. Respiratory function is measured by pulmonary function testing (PFTs), which includes measurement of lung volume (forced vital capacity, FVC) and the ability to generate pressure during inspiration (maximum inspiratory pressure, MIP) and expiration (maximum expiratory pressure, MEP).

FVC measures integrity of both inspiratory and expiratory muscles, is an excellent measure of respiratory function reserve, and is widely used in DMD to assess respiratory muscle function. Most studies that define the natural history of PFTs in patients with DMD include measurement of FVC, and therefore FVC provides the best available comparator for patients treated with eteplirsen (Mayer 2015; Buyse 2015; Khirani 2014; Henricson 2013; Hahn 1997; McDonald 1995; Miller 2005). MEP and MIP are also used as measures of expiratory and inspiratory muscle function in neuromuscular diseases including DMD (Khirani 2014; Henricson 2013; Hahn 1997). MEP and MIP are indicators of decreased respiratory muscle strength, but are subject to variability given that patients with muscle weakness and especially very young patients may have a reduced ability to perform the test.

Measurements of PFTs such as volume (FVC) or pressure (MEP and MIP) are converted to values relative to normal (% predicted). PFT values in adults decline with age. In children, in

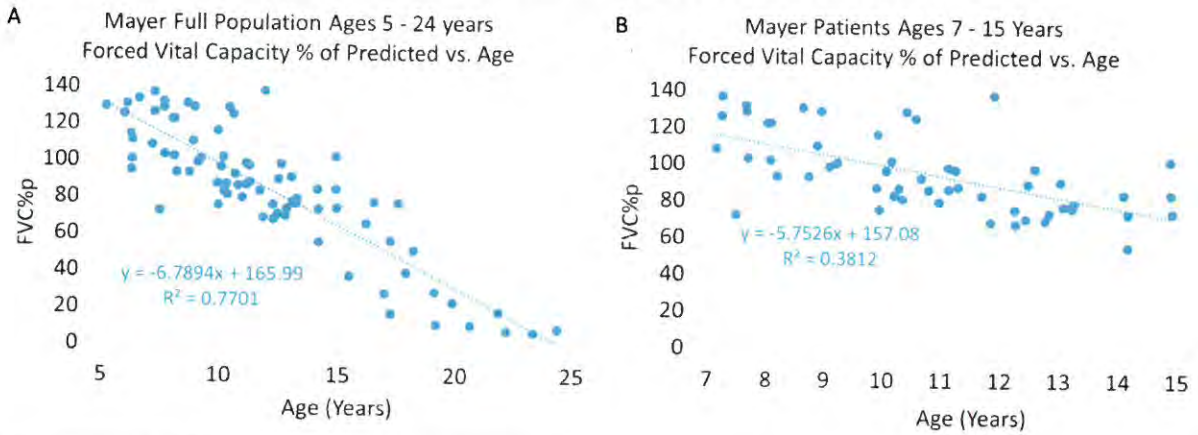
contrast, there is a dramatic increase in PFT parameters over time, which parallels increases in growth and age. Hence, a correction factor accounting for growth/age needs to be incorporated for calculation of predicted values in the pediatric population. The methodology for calculation of predicted FVC values was described by Polgar (Polgar 1971) and corrects based on height. The most widely used correction for predicting MEP and MIP, which adjusts by age (MEP) or weight (MIP), was established by Wilson (Wilson 1984).

A comparison of FVC% predicted for eteplirsen treated patients (N=12) to patient level data from a contemporary, external natural history DMD patient cohort has been conducted. Dr. Mayer et al kindly provided FVC and FVC% predicted data from a subset of the patients that form the basis for their recently published work (Mayer 2015). A dataset of 44 patients with valid data described in the publication was received, of whom 24 were treated with corticosteroids and 14 were non-ambulant. These baseline characteristics were shown by Mayer et al not to impact the rate of decline in FVC% predicted, and therefore, all data received was used in the analyses.

Some proprietary data could not be accessed, however, Sarepta has received assurance that this should not affect the overall analyses. Patient-level data for eteplirsen-treated patients from study 201/202 up to Week 168 was used in the analysis, since all 12 patients had data up to this point. FVC% predicted vs age (in years) was plotted for eteplirsen-treated patients from study 201/202 and for the control patient data from Mayer et al. Simple regression models estimated the slope of the best-fit lines for each group. Given the exploratory nature of these analyses, and the difference in datasets between the more extensive longitudinal analysis in the eteplirsen cohort and the fewer data points per patient in the Mayer cohort, only descriptive statistics are presented.

When all patient level data from Mayer 2015 are plotted relative to age, the linear relationship between age and FVC% predicted in patients with DMD becomes apparent (Figure 22A). Based on regression analysis, the slope in the untreated cohort (N=44) is -6.8, which translates to an overall annual decline in FVC% predicted of 6.8%. This decline is slightly higher than the one published in Mayer et al (Mayer 2015). In order to exclude a potential difference between the overall slope and the slope in the age group of interest for comparison with eteplirsen, i.e. 7-15 years of age, a sensitivity analysis has been performed in a subset of patients in the Mayer population between the ages of 7-15 years old (Figure 22B). The sensitivity analysis showed an overall annual decline of 5.8%. In comparison, the slope in the eteplirsen treated group is -3.2, or approximately half of the annual decline in the similarly aged external control cohort (Figure 23). If only 10-15 year old patients were included, patients from Mayer et al had a slope of -4.7 and eteplirsen treated patients has a slope of -3.3 over 168 weeks. Using only data from 11-15 year old patients, those from Mayer et al had a slope of -3.6 and eteplirsen treated patients has a slope of -1.3 over 168 weeks. Thus the comparison with the external control data favors the eteplirsen treated group regardless of age cut-off.

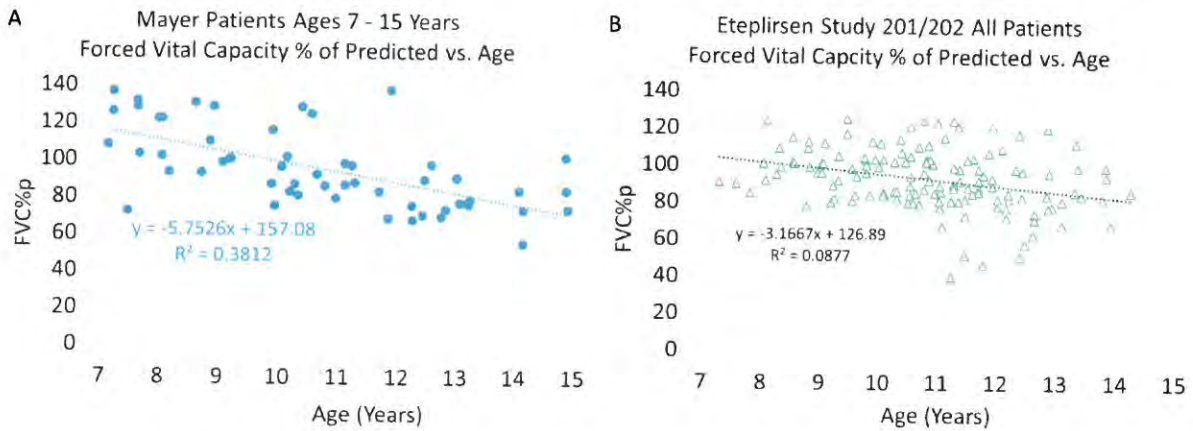
Figure 22: FVC% Predicted: Natural History per Mayer et al by Age Group



	Mayer Full Population (Age 5-24)	Mayer Subset (Age 7-15)
% Annual Decline	6.8%	5.8%

(A) FVC% predicted vs age based on full population (N=44, ages 5-24 years) patient level data from Mayer et al with an annual decrease of FVC% predicted of 6.8%. (B) If patients <7 years and >15 years are excluded (n=33), the resulting annual decrease is 5.8%.

Figure 23: FVC% Predicted: Mayer et al Age Matched Subset Compared to Eteplirsen Treated Patients



	Mayer Subset (Age 7-15)	Eteplirsen Full Population (Age 7-15)
% Annual Decline	5.8%	3.2%

(A) Mayer age matched (Ages 7-15 years) subset, with an annual decline of 5.8%. (B) Eteplirsen treated patients (30 or 50 mg/kg/week IV) from study 201/202: all available on-treatment data plotted vs. age, with an annual decline of 3.2%.

The most recently published dataset on annual decline of FVC% predicted in DMD patients (Khirani 2014) is similar to the data presented above (Mayer 2015), and therefore also supports a beneficial effect of eteplirsen. Findings in other publications have generally provided a higher estimated annual decrease in FVC% predicted than those found by Mayer and Khirani (Miller 2005, McDonald 1995, Hahn 1997, Buyse 2015), and are therefore also supportive.

Measurement of MIP and MEP has been done in patients with DMD, albeit to a lesser extent than FVC, and only 3 relevant scientific publications have been identified (Khirani 2014, Hahn 1997, Henricson 2013). Based on these data, an annual decline of MIP% predicted and MEP% predicted of approximately 3-4% would be expected in patients with DMD during their second decade. The change from baseline over 3 years with eteplirsen treatment (-3.6% for MIP% predicted and -8.4% for MEP% predicted, which translates into an average annual decline of 1% and 2.4%, respectively) appears to be within the same range or lower. However, interpretation of these comparisons is limited by the small number of scientific publications describing these specific assessments in DMD patients over time; the lack of availability of patient level comparator data; and the increased effort dependency compared to FVC for assessment of MIP and MEP, leading to higher variability especially in a pediatric population.

In summary, pulmonary function data from DMD patients who received eteplirsen for approximately 3 years were compared to data from the scientific literature. Analyses of FVC% predicted are strengthened by a comparison to patient level data (Mayer 2015). Using these comparator data, the deterioration of respiratory muscle function as measured by FVC% predicted appears to be slower than expected with eteplirsen treatment. Additionally, MEP% predicted and MIP% predicted may also decline more slowly, though interpretation of this comparison is limited by the aforementioned considerations.

7. PHARMACODYNAMIC RESULTS

7.1. Methods for Assessing Pharmacodynamic Endpoints

Primary Pharmacodynamic/Biological Efficacy Endpoint: Dystrophin Production

Several complementary methods were used to provide a detailed assessment of eteplirsen's effects on exon skipping and dystrophin protein expression, as no single measurement of dystrophin production can provide a complete evaluation of eteplirsen's pharmacodynamic and biological effects. In the eteplirsen clinical program, the evaluation of exon skipping was accomplished by RT-PCR and sequencing of the PCR product. Dystrophin protein production was evaluated by assessment of the percentage of dystrophin positive fibers and dystrophin intensity in histological specimens, and by Western blot.

Overall, in the 4 studies evaluating pharmacodynamics endpoints, there was a high ascertainment rate with all muscle biopsies resulting in evaluable samples. In Studies 201/202, analysis of muscle tissue biopsy samples by IHC was performed according to written procedures in a central laboratory by blinded personnel who were not otherwise involved in the study. Biopsy processing and analysis of samples for Studies 28 and 33 were performed at a separate laboratory. A high-level summary of the methods used to evaluate exon skipping and dystrophin production as well as study specific biopsy schedules are summarized in [Table 10](#).

Table 10: Methods for Evaluation of Pharmacodynamic/Biologic Endpoints by Studies

	Study 33	Study 28	Study 201/202
Anatomic Location of Muscle Biopsy	Extensor digitorum brevis muscle of treated and opposite placebo foot at baseline and Day 14-28	Biceps brachii Biopsy samples at Baseline and Week 14	Biceps brachii (Baseline and Week 24) and deltoid biopsy samples (Week 48 and Week 180)
Mechanism of Action Confirmation			
Detection of internally deleted dystrophin mRNA	RT-PCR assessment of mRNA exon 51 skipping	RT-PCR assessment of mRNA exon 51 skipping	RT-PCR assessment of mRNA exon 51 skipping
Sequencing of mRNA to confirm correct exon skipping	Direct sequencing of RT-PCR product	Direct sequencing of RT-PCR product	Direct sequencing of the RT-PCR product (Week 180 only)
Dystrophin Production and Localization			
Dystrophin protein levels	Western Blot assessment of Dystrophin protein levels with NCL-DYS1 ^a	Western Blot assessment of Dystrophin protein levels with NCL-DYS1 ^a	Western Blot assessment of Dystrophin protein levels with MANDYS106 ^a , NCL-DYS2 ^a and NCL-DYS1 ^a (Week 180 only)
Percent dystrophin-positive muscle fibers	Scoring of digital images for presence of dystrophin-positive muscle fibers following indirect immunofluorescence staining with MANDYS106 ^a	Scoring of digital images for presence of dystrophin-positive muscle fibers following indirect immunofluorescence staining with MANDYS106 ^a	Scoring of digital images for presence of dystrophin-positive muscle fibers following indirect immunofluorescence staining with MANDYS106 ^a , NCL-DYS2 ^a , NCL-DYS3 ^a
Dystrophin Intensity	Assessment of fluorescence signal intensity following indirect immunofluorescence staining with MANDYS106 ^a antibody against dystrophin	Assessment of fluorescence signal intensity following indirect immunofluorescence staining with MANDYS106 ^a antibody against dystrophin	Assessment of fluorescence signal intensity following indirect immunofluorescence staining with MANDYS106 ^a , NCL-DYS2 ^a antibody against dystrophin

^a Dys1: NCL-DYS 1 Clone Dy4/6D3 (Leica); Dys2: NCL-DYS 2 Clone DY8/6C5; MANDYS106: [Nguyen 1992](#).

7.2. Pharmacodynamic/Biological Endpoints

7.2.1. RT-PCR Demonstrates Exon 51 Skipping in Studies 201/202, 28 and 33

All studies used qualitative nested end-point RT-PCR to detect the presence or absence of internally shortened dystrophin mRNA to confirm exon 51 skipping. PCR primers were specific for each patient's known dystrophin mutation, and RT-PCR products were visualized on agarose gels. In addition, the accurate skipping of exon 51 was confirmed by sequencing of the skipped RT-PCR product in Studies 28 and 33, and for the Week 180 biopsy in Studies 201/202. Exon 51 skipping was demonstrated using RT-PCR in all eteplirsen-treated patients evaluated to date (N = 36).

- **Proof of Concept Study 33:** (N = 7) patients were given a single dose of eteplirsen IM 0.9 (N = 5) or 0.09 (N = 2) mg directly into the EDB muscle and a single dose of placebo in the contralateral foot. RT-PCR demonstrated exon 51 skipping in the eteplirsen-treated foot of all patients, although only low-level exon skipping was observed in the 2 patients receiving the low dose of 0.09 mg.
- **Dose-Ranging Study 28:** (N = 17) patients were given 12 weekly IV doses of eteplirsen (0.5-20 mg/kg/week) with muscle biopsies at Baseline and post-treatment Week 14. In this study, exon skipping in post-treatment biopsies was most easily and reliably detected in those patients within the 2 highest dose groups (10 and 20 mg/kg) suggesting a dose-dependent effect of eteplirsen on exon skipping.
- **Pivotal Study 201/202:** (N = 12) tested higher doses of 30 or 50 mg/kg/week with muscle biopsies taken at Baseline and on-treatment Week 12, 24, 48 and 180. Exon skipping was observed for all 12 patients.

Skipping of exon 51 was confirmed with Sanger sequencing (Sanger 1975). Accurate sequences of the flanking DNA at the new exon junction formed by skipping exon 51 were confirmed in all assessed patients from Studies 33 (N = 7), Study 28 (N = 17) and Studies 201/202 (Week 180 biopsies only, N = 11). Observed sequences were consistent with those found in BMD patients with the corresponding in-frame mutation, supporting the hypothesis that eteplirsen results in the production of functional dystrophin protein capable of attenuating the DMD phenotype.

7.2.2. Dystrophin Protein Expression – Percent Dystrophin Positive Fibers

Across studies, the production of dystrophin protein pre- and post-treatment was evaluated using immunohistochemical (IHC) methods. The percentage of dystrophin-positive muscle fibers was determined by a pathologist who counted both the number of dystrophin positive muscle fibers and the total number of muscle fibers allowing the calculation of a percentage of dystrophin-positive muscle fibers. In pivotal studies 201/202, treatment with eteplirsen produced reliable increases in the percentage of dystrophin-positive fibers.

Study 201/202

The primary endpoint in the 24-week placebo-controlled portion of Study 201 was change from baseline in percent dystrophin positive fibers. At Week 25, the placebo patients were rolled over onto open-label treatment and all patients continue to receive treatment in the on-going extension study today.

A key question that Study 201/202 sought to address, was whether dose or duration was more important in the induction of novel dystrophin protein. Accordingly, while all patients had muscle biopsies at baseline, Week 48 and Week 180, in order to minimize the number of required biopsies, the study design varied the biopsy schedule at Week 12 (only 50 mg/kg and 2 placebo patients) and Week 24 (only 30 mg/kg and 2 placebo patients). [Figure 24](#) displays the biopsy schedule by treatment group in Studies 201/202.

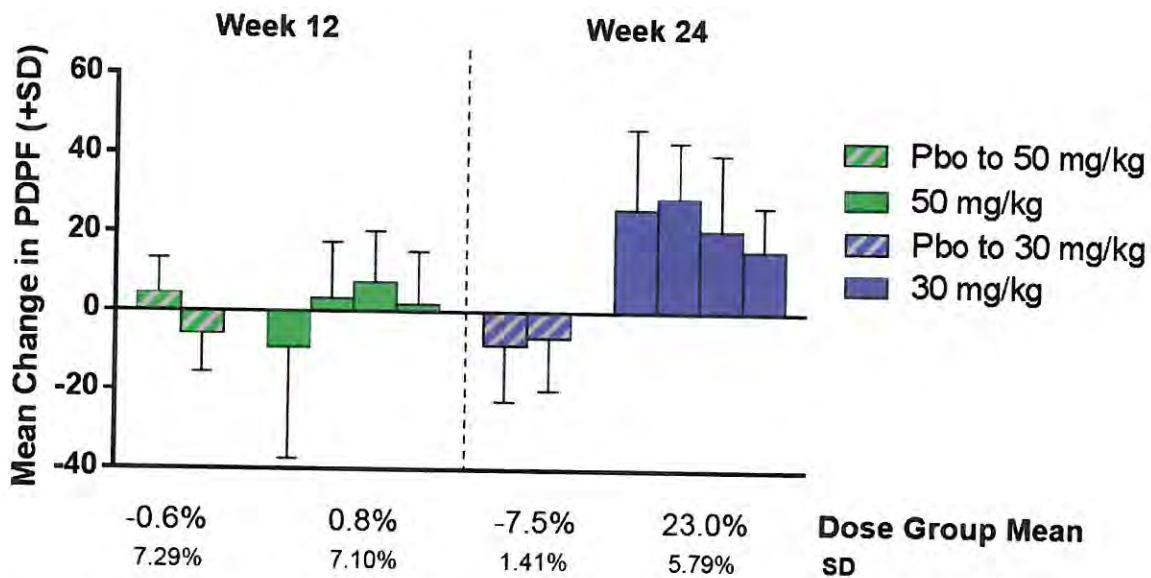
Figure 24: Biopsy Schedule in Study 201/202

Treatment Group	Baseline	Week 12	Week 24	Week 25	Week 48	Week 180
30 mg/kg	√		√	Placebo patients rolled onto treatment	√	√
Placebo	√		√			
50 mg/kg	√	√			√	√*
Placebo	√	√				

*1 patient declined the optional Wk 180 biopsy

Treatment with 50 mg/kg did not demonstrate a significant increase in the amount of mean percentage of dystrophin-positive fibers at Week 12. However, treatment with 30 mg/kg eteplirsen (N = 4) for 24 weeks significantly increased the mean percentage of dystrophin-positive fibers from a baseline of 18.19% to 41.14% resulting in a 22.95% change from baseline ($p \leq 0.004$). This change was also statistically significantly different than the change from baseline observed in the placebo-treated patients ($p \leq 0.002$). Mean change from Baseline in PDPF for each individual patient is shown in Figure 25. Therefore, it was determined that a 12-week treatment duration may not be sufficient to observe significant dystrophin production, whereas significant dystrophin production was shown by Week 24.

Figure 25: Individual Patient Data: Mean Change from Baseline in Percent Dystrophin Positive Fibers (MANDYS106) in Patients Treated with 50 or 30 mg/kg Eteplirsen vs. Placebo at Week 12 and 24, respectively (Study 201)

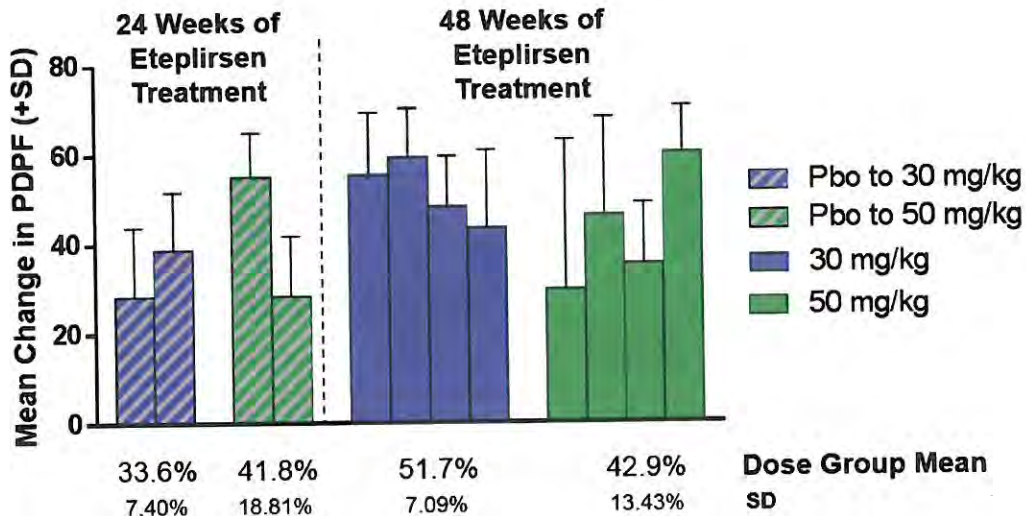


Dose selection of 30 mg/kg based on Week 48 analysis of Studies 201/202

Analysis of mean change in percent dystrophin positive fibers at Week 48 showed that both 30 and 50 mg/kg weekly doses significantly increased the mean percentage of dystrophin-positive fibers compared to Baseline ($p \leq 0.001$, $p \leq 0.008$, respectively), with no significant difference in the magnitude of this change between the 2 dose groups. Statistically significant changes from Baseline were also observed when the dystrophin results at Week 48 were combined for the 4 patients who received placebo for the first 24 weeks ($p \leq 0.009$) and for the 8 patients who received eteplirsen continuously ($p \leq 0.001$). Mean change from Baseline in PDPF for each individual patient is shown in Figure 26.

Given the equivalency of Week 48 mean change in PDPF between 30 or 50 mg/kg, and the need for chronic lifelong administration in a pediatric population, the lower dose of 30-mg/kg dose was selected.

Figure 26: Mean Change from Baseline in Percent Dystrophin Positive Fibers in Patients Treated with 30 vs 50 mg/kg/week Eteplirsen for Week 24 or 48 (Studies 201/202)



Independent Verification of Percent Dystrophin-Positive Fibers

In response to a request by the Agency, the original images used in scoring the percentage of dystrophin-positive fibers in biopsy samples from patients in Studies 201/202 and Study 28 were re-assessed by 3 independent and blinded raters. Per the Agency’s request, the primary endpoint for the image reassessment was the percentage of dystrophin-positive fibers at Week 24 and changes from Baseline. Sarepta engaged 3 trained pathologists (through Flagship Biosciences) to independently identify dystrophin-positive muscle fibers utilizing the same archived digital images obtained from Study 201 and Study 28 used for the original study assessments.

Independent Verification of Study 201/202 Percent Positive Dystrophin Fibers

The mean ratings from the independent pathologists showed the mean percentage of dystrophin-positive fibers for the 4 patients in the 30 mg/kg eteplirsen group increased from 13.63 at Baseline to 27.33 at Week 24, representing a 1.37-fold, statistically significant ($p \leq 0.007$) increase, consistent with the results of the original analysis performed at Nationwide Children’s Hospital in Columbus, OH. Evaluation of inter-rater and intra-rater reliability confirmed that consistency was achieved through training of the independent raters. The inter-rater reliability for the 3 blinded pathologists performing the reassessment was high (interclass correlation coefficient [ICC] = 0.793), as was the intra-rater reliability, with ICCs for each rater ranging from 0.932 to 0.955.

Study 28 Percent Positive Dystrophin Fibers

Once weekly IV infusions of eteplirsen (0.5 to 20 mg/kg) for 12 weeks in Study 28 resulted in a 3-fold increase in the mean percentage of dystrophin-positive fibers, which increased from a mean of 2.2% at Baseline to a mean change from Baseline of 6.5% at Week 14 (biopsies were

taken 2 weeks after the last dose), with the greatest mean increases observed for highest doses (i.e., 10 or 20 mg/kg), although variation across individual results was noted. The original analysis of the percent dystrophin-positive fibers, which was performed at the University College London, was also confirmed by a blinded reassessment of the data by 3 independent pathologists, who noted mean increases from 1.83% at Baseline to 8.19% at Week 14 for 4 patients who received 10 mg/kg/week and mean increases from 2.87% at Baseline to 15.87% at Week 14 for 4 patients who received 20 mg/kg/wk eteplirsen. Although increases in dystrophin were observed as early as 14 weeks in Study 28, this was not consistent across individuals.

Study 33 Percent Positive Dystrophin Fibers

Results from Study 33, in which 7 patients received a single IM dose of 0.09 (N = 2) or 0.9 mg (N = 5) eteplirsen into the EDB muscle of one foot and a single dose of placebo into the EDB of the opposite foot, further support eteplirsen's ability to induce dystrophin production in patients with DMD. In this study, dystrophin-positive fibers were observed in biopsies obtained from the eteplirsen treated feet of the 5 patients who received the higher dose of eteplirsen, 4 of whom were already non-ambulatory at the time of the study. The mean percentage of dystrophin-positive fibers in EDB muscle biopsy specimens from the eteplirsen-treated feet was 59.7% compared with 0% in EDB muscle biopsy specimens from the placebo-treated feet of the same 5 patients. The lower dose of eteplirsen (0.09) did not have a measurable effect on dystrophin production in this study.

7.2.3. Dystrophin Protein Expression – Dystrophin Fiber Intensity

Analysis of dystrophin fiber intensity as measured by an automated software system (Bioquant[®] or MetaMorph[®]) was used as a complementary method to verify the de novo production of dystrophin. In Studies 201/202, 28 and 33, eteplirsen's effect on dystrophin production was examined by measuring the fluorescence staining intensity of dystrophin following indirect immunostaining with primary anti-dystrophin antibodies. In both studies, the mean changes from Baseline in dystrophin fiber intensity were similar in magnitude and direction to the results of the percentage of dystrophin-positive fibers analyses, supporting eteplirsen's ability to increase dystrophin levels in patients with DMD.

Studies 201/202 Dystrophin Intensity

Once weekly treatment with eteplirsen (30 or 50 mg/kg) significantly increased ($p \leq 0.001$) mean dystrophin fiber intensity from 10.57% of normal at Baseline to 25.98% of normal at Week 48 in the 8 patients in Studies 201/202 who received eteplirsen from the start of the study. Eteplirsen also significantly ($p \leq 0.006$) increased mean dystrophin fiber intensity from 8.95% of normal at Baseline to 23.43% of normal at Week 48 in the 4 patients in Studies 201/202 who received placebo from Baseline to Week 24 and eteplirsen from Weeks 24 to 48 (and hence had only received eteplirsen for 24 weeks at the time of the Week 48 biopsy).

Study 28 Dystrophin Intensity

Similarly, in Study 28, once weekly treatment with eteplirsen increased mean dystrophin fiber intensity in the 17 patients with evaluable data from 7.9% of normal at Baseline to 11.5% of normal at Week 14. The results were variable within and across dose groups, but the largest and most consistent increases tended to occur in the 10 and 20 mg/kg/wk eteplirsen groups.

Study 33 Dystrophin Intensity

In Study 33, a single IM dose of 0.9 mg eteplirsen increased the mean dystrophin fiber intensity from 9.4 % in the contralateral saline-injected muscle to 26.4% in the eteplirsen-treated muscle. The lower dose of eteplirsen (0.09 mg) did not have a measurable effect on dystrophin production in this study.

7.2.4. Dystrophin Quantity By Western Blot

Study 33, 28 Western BLOT

Dystrophin expression was also evaluated by Western Blot in Studies 33, 28 and 201/202. In Study 28, the most consistent increase in dystrophin expression from baseline tended to occur in the 10 and 20 mg/kg/wk eteplirsen group. Similarly, the higher dose group in Study 33 showed a more consistent expression above baseline than the lower dose group. Results for Study 201/202 are presented in the Week 180 section below.

7.2.5. Studies 201/202: Week 180 Results For Dystrophin Production

Patients in Studies 201/202 underwent a fourth muscle biopsy after 180 weeks in the study. The primary purpose of this optional biopsy was to evaluate the ability of eteplirsen to sustain dystrophin production during chronic treatment. This biopsy also afforded an opportunity to examine dystrophin production using the optimized method previously described for evaluation of percent dystrophin-positive fibers. In addition, new Western blot methodology was developed in alignment with the NIH-FDA Dystrophin Methodology Workshop (March 2015) and in collaboration with the FDA.

Eleven of the 12 patients provided muscle biopsies at Week 180. As mentioned previously, it is important that biopsy results be compared to pre-treatment or untreated controls in order to evaluate the treatment effect on dystrophin expression. Frozen archived Baseline muscle biopsy tissue from Study 201 was available for re-analyses from only a limited number of patients, resulting in baseline values for only 3 patients for each of the 3 dystrophin parameters. Since baseline tissue was not available for all patients, these samples were supplemented with tissue from untreated control patients amenable to exon 51 skipping in order to provide a total of 9 untreated samples as a comparator group. The additional 6 untreated control samples for each assay were from confirmatory Study 301 (PROMOVI) and were simply the first baseline biopsies collected to have sufficient excess biopsy material available to repurpose for use in the Week 180 analysis. Characteristics for the untreated control patients are summarized in [Appendix 9](#).

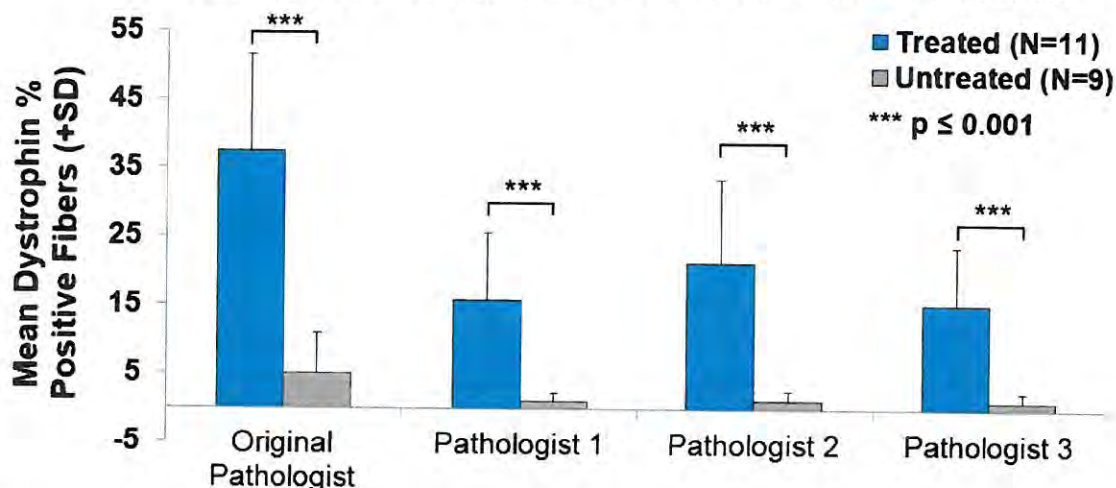
A series of methodologies was utilized including: scoring of digital images for the percentage of dystrophin-positive fibers following indirect immunofluorescence staining; BIOQUANT[®] assessment of dystrophin fiber intensity following indirect immunofluorescence staining; and Western blot assessment of dystrophin protein levels.

Study 201/202 Week 180 Percent Dystrophin-Positive Fibers (PDPF)

As shown in [Figure 27](#), the mean percentage of dystrophin-positive fibers in the eteplirsen-treated patients at Week 180 (37.33%), as determined by a blinded analysis of digital images performed by the expert pathologist at NCH, was 7.4 times greater than that observed in untreated patients (5.04%), a difference that was statistically significant ($p < 0.001$).

Confirmation of this finding (treated PDPF > untreated PDPF) was provided by an independent analysis of identical images conducted by 3 blinded independent pathologists, with mean differences between the eteplirsen-treated patients and the untreated controls ranging from 14.15% to 19.99% for the 3 raters (all p-values <0.001). Refer to [Appendix 10](#) for individual patient PDPF data and [Appendix 12](#) for representative images of dystrophin-positive fibers.

Figure 27: Mean Percentage of Dystrophin-Positive Fibers in Eteplirsen-Treated Patients (Week 180, Studies 201/202) vs. Untreated DMD Controls



	Original Assessment	Reassessment		
	NCH Pathologist	Pathologist 1	Pathologist 2	Pathologist 3
Eteplirsen, mean (SD)	37.33 (14.267)	15.67 (9.846)	21.30 (12.219)	15.20 (8.442)
Untreated, mean (SD)	5.04 (5.85)	1.02 (1.293)	1.31 (1.294)	1.05 (1.371)
Mean Diff. (95% CI)	32.29 (22.15, 42.43)	14.66 (8.01, 21.30)	19.99 (11.75, 28.22)	14.15 (8.44, 19.87)
p-value	p <0.001	p <0.001	p <0.001	p <0.001

Pathologist(s)	Absolute Difference of Mean PDPF (Treated vs. Untreated)	Relative Difference of Mean PDPF (Treated vs. Untreated)	p-value
Multi-rater (3)	16.27%	1,453%	<0.001

Study 201/202 Week 180 Dystrophin Intensity

The IHC images were also evaluated by an automated computer algorithm to assess for dystrophin staining intensity. Generally higher dystrophin staining was observed for individual eteplirsen-treated patients in comparison to untreated control patients, with the overall mean dystrophin fiber intensity in eteplirsen-treated patients at Week 180 (22.61) significantly ($p < 0.001$) greater than that observed in untreated controls (9.41) as shown in [Figure 28](#), [Table 11](#). Results for dystrophin fiber intensity from individual patients are provided in [Appendix 11](#).

Figure 28: Mean Dystrophin Intensity in Eteplirsen-Treated Patients (Week 180, Studies 201/202) vs. Untreated DMD Controls

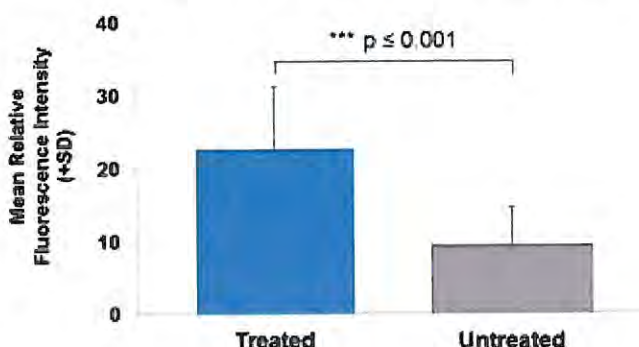


Table 11: Absolute and Relative Differences of Mean Dystrophin Intensity (Week 180, Studies 201/202)

Absolute Difference of Mean Intensity (Treated vs. Untreated)	Relative Difference of Mean Intensity (Treated vs. Untreated)	p-value
13.2%	140%	<0.001

Study 201/202 Week 180 Western Blot

Dystrophin expression was also evaluated using a validated, optimized Western Blot method developed in collaboration with the FDA and in alignment with the FDA-NIH Dystrophin Methodology Workshop (March 2015). This validated method is capable of quantifying dystrophin as low as 0.25% of normal, enabling sensitive robust determination of % normal dystrophin levels.

In Western blot analysis, 9 of 11 biopsied eteplirsen-treated patients had an observable dystrophin band. Comparing these results to biopsies from 9 untreated exon 51 amenable DMD patients, eteplirsen-treated patients demonstrated statistically significant higher mean dystrophin expression levels than untreated patients. The mean dystrophin protein level as assessed by Western blot in eteplirsen-treated patients at Week 180 (0.93) was significantly ($p = 0.007$) greater than that observed in untreated controls (0.08) (Figure 29, Table 12). Results for Western blot analysis from individual patients are provided in Appendix 13.

Figure 29: Mean Percent Normal Dystrophin in Eteplirsen-Treated Patients (Week 180, Studies 201/202) vs. Untreated DMD Controls (Western Blot)

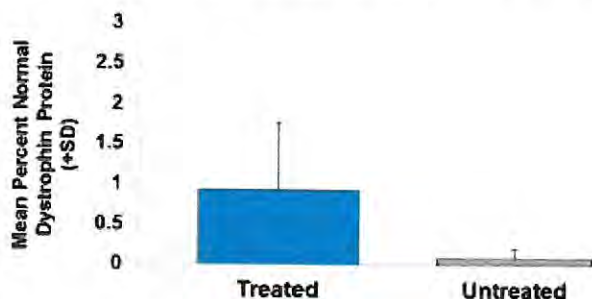


Table 12: Absolute and Relative Differences of Mean Dystrophin by Western Blot (Week 180, Studies 201/202)

Absolute Difference of Means (Treated vs. Untreated)	Relative Difference of Means (Treated vs. Untreated)	p-value
0.85%	104%	<0.007

There is a wide body of literature reporting on dystrophin levels in DMD and BMD. The range of values for Western blot presented in literature sources cannot be directly compared to each other or to the values from eteplirsen studies. Western blot results are not directly comparable due to method variations and most critically, the absence of a universal dystrophin reference standard. This is illustrated by levels of dystrophin across different normal muscle biopsy tissue; samples can vary from as low as 50 % to over 100 % relative to a “normal” reference control (FDA-NIH Dystrophin Methodology Workshop (March 2015) and eteplirsen NDA 206,488). This variability is likely due to variation between individuals, muscle type and/or different regions of a muscle biopsy sample. A uniform, absolute dystrophin standard to enable direct comparison of % normal values between individual assays or laboratories has not been established.

In the Week 180 analysis muscle biopsy samples were measured relative to a single “normal” non BMD/DMD individual’s deltoid muscle biopsy tissue sample in order to enable consistent and accurate quantification and comparison of dystrophin expression in the eteplirsen treated and untreated samples. Western Blot method validation and acceptance standards are detailed in [Appendix 14](#) along with representative gel images.

In summary, the results from the entire set of patient samples from eteplirsen-treated (N = 11) and untreated (N = 9) patients with DMD mutations amenable to exon 51 skipping were concordant across all of the assays ([Table 13](#)), supporting both the robustness of each assay’s underlying methodology as well as the conclusion that long-term treatment of Exon 51 amenable patients with eteplirsen continues to produce sustainable increases in dystrophin muscle tissue.

Table 13: Summary of Week 180, Studies 201/202 Dystrophin Data in Eteplirsen Treated Patients and Untreated DMD Controls

Week 180	Treated (Mean % Dystrophin of Normal)	Untreated (Mean % Dystrophin of Normal)	Difference of Means (Treated vs. Untreated)	Relative Difference of Means	P-value
PDPF (Flagship)	17.39 %	1.12 %	+16.27 %	+1453%	<0.001
Intensity	22.61 %	9.41 %	+13.20 %	+140%	<0.001
Western Blot	0.93 %	0.08 %	+0.85 %	+1063%	<0.007

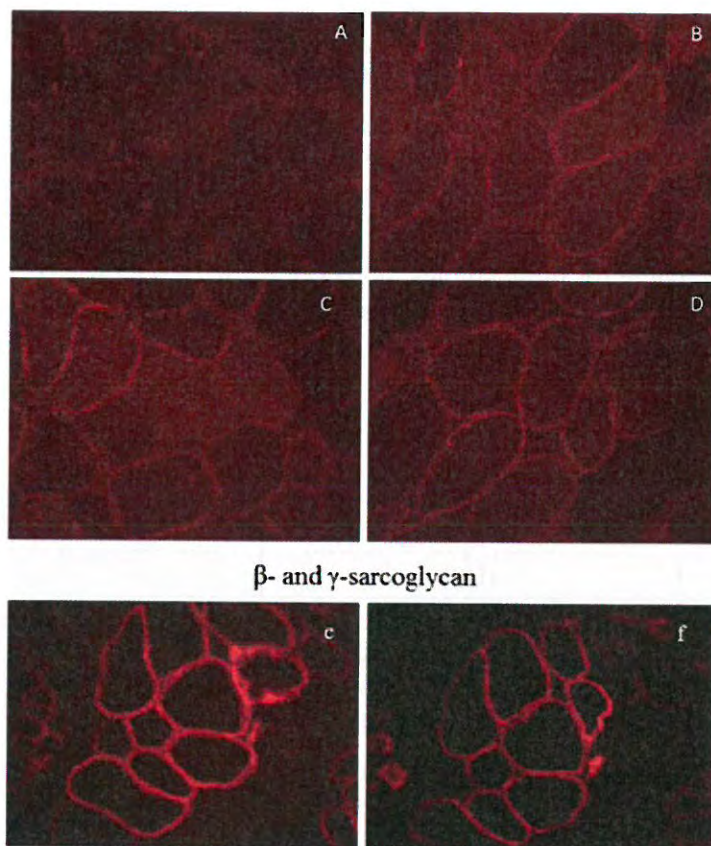
7.2.6. Cellular Localization of Dystrophin, nNOS, and Sarcoglycan Complex Proteins

The functionality of the dystrophin produced by eteplirsen is supported by IHC analysis showing localization of dystrophin with other components of the DAPC, including nitric oxide synthase (nNOS), and α -, β -, and γ -sarcoglycan, at the sarcolemma membrane. The restoration of nNOS to the membrane is especially notable as it is consistently absent in DMD muscle tissue lacking dystrophin.

Figure 30 shows muscle tissue taken from an untreated DMD patient (Panel A), a single DMD patient (Patient 006) after 48 weeks of treatment with eteplirsen in Studies 201/202 (Panels B/D), and normal healthy muscle (Panel C) and stained for nNOS. While no evidence of nNOS binding is evident in muscle taken from the untreated DMD patient (Panel A), there is clear evidence of nNOS staining in both the healthy control tissue (Panel C) and in tissue obtained from the patient treated with eteplirsen for 48 weeks (B and D). Muscle tissue from the same eteplirsen-treated patient (006) positively stained for β -Sarcoglycan (Panel E) and γ -Sarcoglycan (Panel F) confirm restoration of the DAPC complex in this patient.

Similar results, were obtained in Studies 28 and 33 (as published in [Cirak 2011](#) and [Cirak 2012](#)).

Figure 30: Positive Staining for nNOS and Sarcoglycan Complex Proteins in an Eteplirsen-Treated Patient in Studies 201/202



Source: [Mendell 2013](#).

8. ONGOING AND PLANNED STUDIES

8.1. Ongoing Studies Supportive of Safety

Sarepta is also conducting 2 additional studies to further evaluate the safety and efficacy of eteplirsen in younger boys and boys with advanced DMD. Study 203 is an ongoing, 96-week, open-label study to evaluate the safety, efficacy, and tolerability of eteplirsen in DMD patients 4 to 6 years of age; this study includes an untreated control group of DMD patients not amenable to exon 51 skipping. Study 204 is an ongoing, 96-week, open label study of eteplirsen in non-ambulatory patients or unable to walk ≥ 300 meters on the 6MWT.

Efficacy data are not yet available for these studies; however, as of 14 August 2015 (cutoff date for the 120-Day Safety Update) safety data were available for 4 and 24 patients in Studies 203 and 204, respectively. Key aspects of these studies are summarized below.

Table 14: Ongoing Supportive Studies 203 and 204

	Study Number	
	Study 203	Study 204
Study Design	Multi-center, open-label study (US)	Multi-center, open-label study (US)
Dosing Regimen	Eteplirsen 30 mg/kg/week (IV) Includes untreated concurrent control group of DMD patients not amenable to exon 51 skipping	Eteplirsen 30 mg/kg/week (IV)
Endpoints	Primary =Safety and tolerability; Secondary =Change from BL to Wk 48 and Wk 96 in PDPF Exploratory =Dystrophin intensity; Dystrophin protein levels (Western blot); exon 51 skipping (RT PCR); T-cell infiltration; Change from BL to Wk 96 for NSAA, Time to walk 100 meters; PODCI; PK	Primary =Safety and tolerability; Exploratory =Change from BL to Wk 96 in PFTs, PUL Scale, Brooke Score for Arms and Shoulders, 9-hole peg test, ACTIVE, 10-Meter Walk/Run Test, and EK Scale
Required Age at Entry (yrs)	4-6	7-21
Study Status	Ongoing	Ongoing
No. Enrolled	4	24
No. Completed	NA	NA
Study Period	June 2014 –14 Aug 2015 ^a	Nov 2014 –14 Aug 2015 ^a
Planned Study Duration	96 weeks	96 weeks

Abbreviations: ACTIVE = Ability Captured Through Interactive Video Evaluation; BL = Baseline; EK = Egen Klassifikation; IV = intravenous; NSAA = North Star Ambulatory Assessment; PDPF = percentage of dystrophin positive fibers; PK = pharmacokinetics; PFT = pulmonary function testing; PODCI = Pediatric Outcomes Data Collection Instrument; PUL = Performance Upper Limb Scale; RT-PCR = reverse transcriptase-polymerase chain reaction; US = United States; Wk = week.

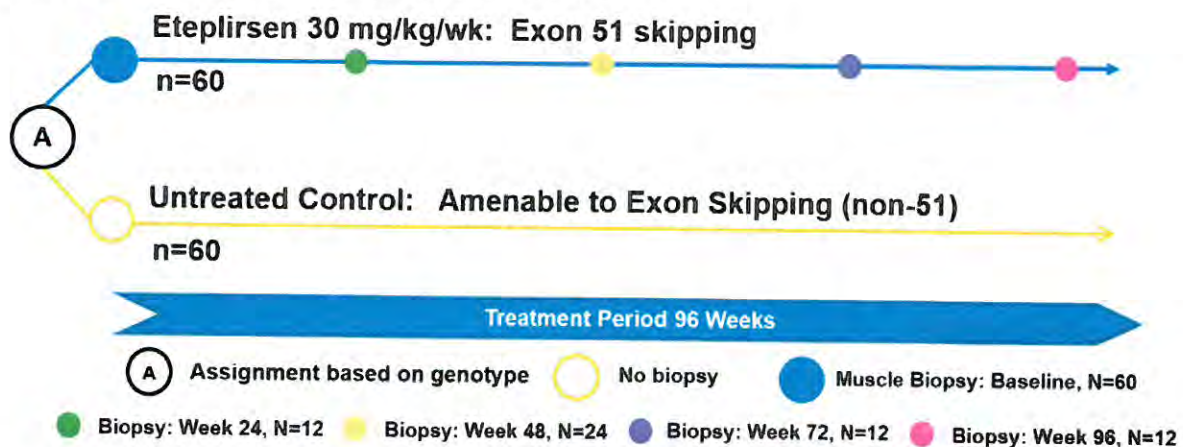
^a Cut-off date for 120 Day Safety Update

8.2. Confirmatory Studies to Support Accelerated Approval

Sarepta will conduct 2 confirmatory studies in accordance with the requirements for Accelerated Approval. Study 4658-301 (also referred to as PROMOVI) will confirm the efficacy of eteplirsen in a population of boys with DMD that is amenable to exon 51 skipping. The second study, 4045-301 (also referred to as ESSENCE) will confirm the efficacy of the PMO platform testing the efficacy of 2 other PMOs in a population of boys that is amenable to exon 45 or 53 skipping.

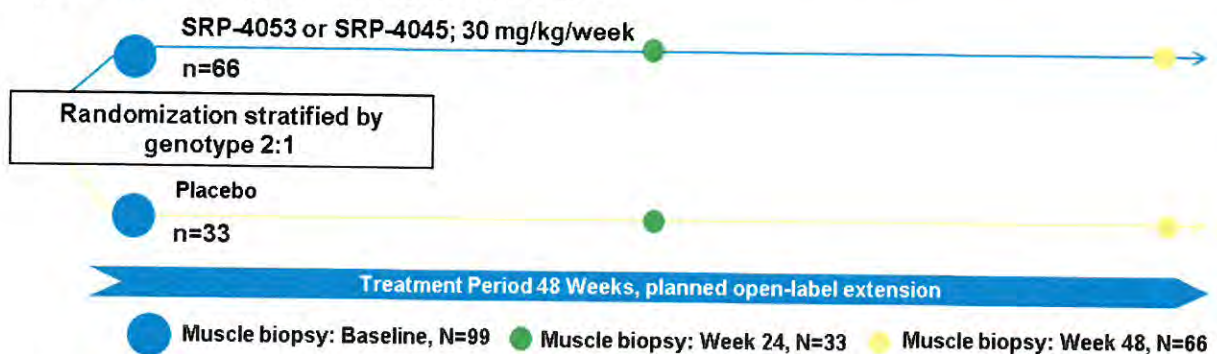
PROMOVI is an ongoing 96-week, open-label study evaluating the effects of eteplirsen in DMD patients amenable to exon 51 skipping in boys 7 to 16 years of age; this study includes an untreated control group of DMD patients with deletion mutations amenable to skipping exons other than 51 (Figure 31).

Figure 31: Study Schematic for PROMOVI



ESSENCE is a planned, double-blind, placebo-controlled study to evaluate the efficacy and safety of 2 other PMOs, SRP-4045 and SRP-4053, in DMD patients amenable to exon 45 and 53 skipping, respectively. This study is expected to begin dosing in Q1 2016 (Figure 32).

Figure 32: Study Schematic for ESSENCE



Efficacy data are not yet available for these studies; however, as of 14 August 2015 (cutoff date for the 120-Day Safety Update) safety data were available for 48 patients from Study 4658-301 (PROMOVI). Key aspects of the confirmatory studies are summarized below in Table 15.

Table 15: Confirmatory Studies: 4658-301 (PROMOVI) and 4045-301 (ESSENCE)

	Study Number	
	4658-301 PROMOVI	4045-301 ESSENCE
Study Design	Multi-center, treatment assigned open-label study of eteplirsen in DMD patients amenable to skipping exon 51 (US) compared to an untreated control group of DMD not amenable to skipping exon 51	Multi-center, randomized double-blind, placebo-controlled study of PMOs for DMD patients amenable to skipping exon 45 or 53 (US) Ratio of 2:1
Dosing Regimen	Eteplirsen 30 mg/kg/week (IV) Includes untreated concurrent control group of DMD patients not amenable to exon 51 skipping	SRP-4045, SRP-4053 (according to genetic mutation) or placebo (IV)
Endpoints	Primary Efficacy =Change from BL to Week 48 on the 6MWT Secondary Efficacy =Change from BL to Wks 24 and 48 in PDPF (treated patients only); Change from BL to Wk 48 in PFT	Primary Efficacy =Change from BL to Wk 48 on the 6MWT Secondary Efficacy =Change from BL to Wk 24 or Wk 48 in PDPF (treated patients only); Change from BL to Wk 48 in PFT
Required Age at Entry (yrs)	7-16	7-16
Study Status	Ongoing	Planned
No. Planned Enrolled	60:60	60:30
No. Enrolled	48 treated/15 untreated	0

Abbreviations: 6MWT = 6 Minute Walk Test; BL = Baseline; IV = intravenous; PDPF = percentage of dystrophin positive fibers; PFT = pulmonary function testing; QMT = quantitative muscle testing; RT-PCR = reverse transcriptase-polymerase chain reaction. SAM = Step Activity Monitor; US = United States; Wk = week.

^a Cut-off date for 120-Day Safety Update.

9. SAFETY EVALUATION

9.1. Methods for Assessing Safety

Across the 7 clinical studies providing safety data, the safety and tolerability of eteplirsen were evaluated using standard safety assessments including review of adverse events (AEs), serious adverse events (SAEs), study or treatment discontinuations; safety laboratory tests (serum chemistry, hematology and coagulation, and urinalysis); electrocardiograms (ECGs); vital signs; and physical examination findings. In addition, echocardiography (ECHO) was performed to further evaluate the clinical course of cardiomyopathy associated with the underlying disease (Spurney 2014). In Studies 201/202, 204, 203 and 301, renal function was closely monitored via serial testing of blood urea, blood creatinine, urine protein, as well as serum cystatin C, due to nonclinical renal findings in kidneys (Section 4.2.2).

9.2. Safety Population

The safety population includes all patients who were randomized / enrolled and received at least 1 dose of study drug (placebo or eteplirsen) or, for untreated control patients from Study 301, all patients who had completed the Week 1 visit. The eteplirsen-treated safety population is shown in Table 16. Eteplirsen is proposed for accelerated approval for the treatment of DMD patients with mutations that are amenable to exon 51 skipping at a dose of 30 mg/kg administered by weekly IV infusion. The safety database provides data from 114 patients from 4-19 years of age at study entry, including 88 patients treated with eteplirsen 30 mg/kg or higher by weekly IV infusion. Twelve (12) patients were treated for up to 208 weeks in Studies 201/202 and 76 patients were treated with eteplirsen 30 mg/kg/wk in Studies 203, 204, and 301 for up to 40 weeks. Although the safety database is not extensive, DMD is a rare disease and the intended patient population is a discrete subpopulation that represents approximately 13% of DMD patients (Aartsma-Rus 2009) which consists of a total of 1,300 to 1,900 patients in the US. As such, the eteplirsen safety database represents approximately 6-9% of the intended US patient population for eteplirsen.

Table 16: Studies Comprising the Eteplirsen Safety Database

Study and Description	Dose (mg/kg)	Route of Administration	Duration of Dosing (weeks)	N
Study 33 ^a (<i>proof of concept</i>)	0.09, 0.9	IM	Single dose	7
Study 28 (<i>dose ranging</i>)	0.5, 1, 2, 4, 10, 20	IV	12	19
Studies 201/202 (<i>placebo-controlled / open-label</i>)	30, 50	IV	184-208	12
Studies 301 (<i>confirmatory</i>), 204 (<i>advanced DMD</i>), and 203 (<i>younger patients</i>)	30	IV	1-40	76
All eteplirsen-treated patients				114

IM = single intramuscular dose; IV = once weekly intravenous infusion.

^a A single intramuscular dose was administered in Study 33.

9.3. Statistical Analysis

Descriptive statistics were used to summarize the safety data. For the purposes of the integrated safety analyses, treatment-emergent adverse events (TEAEs) were defined as any adverse event that began after the start of the first infusion (or injection) of study drug (eteplirsen or placebo) and within ($\leq$) 28 days after the last dose of study medication. Events with missing start dates were considered treatment emergent.

9.4. Exposure to Eteplirsen

A total of 88 patients have received once weekly eteplirsen IV at the proposed clinical dose of 30 mg/kg or higher. Of these, 61 have been treated for $\geq$ 12 weeks. Six patients each at 30 and 50 mg/kg eteplirsen have been treated over 4 years (Table 17).

Mean exposure for patients treated at 30 mg/kg/wk (N = 82) and 50 mg/kg/wk (N = 6) IV is 213.7 and 1394.8 days, respectively. Twelve (12) patients received eteplirsen 30 mg/kg or 50 mg/kg for approximately 4 years in Study 201/202.

Exposure to placebo for the 4 patients who received once weekly IV infusions of placebo for the first 24 weeks of Study 201 was a mean of 162.3 days. Any comparison of adverse event rates between study dose and placebo must take the variation of exposure into account.

Table 17: Extent of Exposure to Study Drug: Integrated Analyses (Safety Population)

	Eteplirsen				
	Placebo (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Days on Study Drug					
N	4	82	6	107	114
Mean	162.3	213.7	1394.8	255.4	239.8
SD	1.26	342.29	87.03	412.93	404.62
Median	162.0	126.5	1449.5	97.0	89.5
Min, Max	161, 164	1, 1451	1282, 1453	1, 1453	1, 1453
Eteplirsen exposure					
	Route	Dose		Patients Exposed (N)	
$\geq$ 1 dose	IM or IV	any		114	
$\geq$ 1 dose	IV	any		107	
$\geq$ 1 dose	IV	$\geq$ 30 mg/kg		88	
$\geq$ 3 months	IV	$\geq$ 30 mg/kg		61	
$\geq$ 6 months	IV	$\geq$ 30 mg/kg		36	
$\geq$ 4 years	IV	$\geq$ 30 mg/kg		12	

Abbreviations: IM = intramuscular; IV = intravenous; max = maximum; min = minimum; SD = standard deviation.

9.5. Treatment-emergent Adverse Events

9.5.1. General Overview of Adverse Events

The majority of patients in each treatment group, including placebo, experienced at least 1 TEAE. TEAEs were reported for 88 (82.2%) patients in the 'eteplirsen IV' group (i.e., all patients receiving eteplirsen IV at any dose, N = 107), and 63 (76.8%) patients in the 30 mg/kg IV group (N = 82).

No deaths or life-threatening events occurred during the eteplirsen clinical studies (see [Section 9.5.4](#)). Two (2) patients experienced a treatment-emergent SAE; none of the SAEs were considered related to treatment. One (1) patient discontinued treatment with eteplirsen due to a TEAE ([Section 9.5.5](#)).

Five (5) patients (4.7%) in the 'eteplirsen IV' group (3 of whom received 30 mg/kg IV) and 1 patient in the untreated group experienced severe TEAEs ([Section 9.5.6](#)). TEAEs that were considered related to study drug occurred in 35 (32.7%) patients in the 'eteplirsen IV' group, 18 (22.0%) patients in the 30 mg/kg group, and in 1 patient (25.0%) in the placebo group ([Section 9.5.7](#)).

The limited numbers of adverse events that were severe, serious, or resulted in discontinuation were observed across dose groups with no suggestion of a dose effect.

9.5.2. Adverse Events in the Placebo-Controlled Period of Study 201

Safety data in patients who received 30 or 50 mg/kg/wk eteplirsen or placebo (N = 4 per group) over a 24-week period are available from Study 201.

All patients experienced at least 1 TEAE during the 24-week placebo-controlled period of the study. Review of all TEAEs by system organ class (SOC) did not show any increases in the frequency of events within any SOC in eteplirsen-treated patients versus placebo-treated patients or with increasing dose of eteplirsen.

There were 19 TEAEs that occurred in ≥ 2 patients as presented below in [Table 18](#). A table of all TEAEs occurring in the placebo-controlled period of Study 201 is provided in [Appendix 15](#).

Table 18: Treatment-emergent Adverse Events Occurring in ≥ 2 Patients during the 24-Week Placebo-controlled Period of Study 201

System Organ Classification Preferred Term	Eteplirsen			
	Placebo N = 4 n (%)	30 mg/kg IV N = 4 n (%)	50 mg/kg IV N = 4 n (%)	All Eteplirsen N = 8 n (%)
Number of Subjects With a TEAE	4	4	4	8
Injury, poisoning & procedural complications				
Procedural pain	3 (75.0%)	1 (25.0%)	3 (75.0%)	4 (50.0%)
Fall	1 (25.0%)	1 (25.0%)	0	1 (12.5%)
Incision site pain	1 (25.0%)	1 (25.0%)	0	1 (12.5%)
Respiratory, thoracic & mediastinal disorders				
Oropharyngeal pain	3 (75.0%)	3 (75.0%)	0	3 (37.5%)
Cough	2 (50.0%)	1 (25.0%)	1 (25.0%)	2 (25.0%)
Nasal congestion	2 (50.0%)	1 (25.0%)	0	1 (12.5%)
Musculoskeletal & connective tissue disorders				
Pain in extremity	3 (75.0%)	0	1 (25.0%)	1 (12.5%)
Back pain	2 (50.0%)	1 (25.0%)	0	1 (12.5%)
Nervous system disorders				
Balance disorder	0	1 (25.0%)	2 (50.0%)	3 (37.5%)
Headache	2 (50.0%)	1 (25.0%)	0	1 (12.5%)
General disorders & administration site conditions				
Pyrexia	2 (50%)	1 (25.0%)	0	1 (12.5%)
Metabolism & nutrition disorders				
Hypokalaemia	2 (50.0%)	2 (50.0%)	2 (50.0%)	4 (50.0%)
Gastrointestinal disorders				
Vomiting	0	1 (25.0%)	2 (50.0%)	3 (37.5%)
Abdominal pain	2 (50.0%)	0	0	0
Diarrhoea	1 (25.0%)	0	1 (25.0%)	1 (12.5%)
Nausea	1 (25.0%)	0	1 (25.0%)	1 (12.5%)
Infections & infestations				
Rhinitis	1 (25.0%)	0	1 (25.0%)	1 (12.5%)

Table 18: Treatment-emergent Adverse Events Occurring in ≥ 2 Patients during the 24-Week Placebo-controlled Period of Study 201

System Organ Classification Preferred Term	Placebo N = 4 n (%)	Eteplirsen		
		30 mg/kg IV N = 4 n (%)	50 mg/kg IV N = 4 n (%)	All Eteplirsen N = 8 n (%)
Vascular disorders				
Haematoma	1 (25.0%)	1 (25.0%)	1 (25.0%)	2 (25.0%)
Skin & subcutaneous tissue disorders				
Dermatitis contact	0	2 (50.0%)	0	2 (25.0%)

Abbreviations: IV = intravenous; TEAE = treatment-emergent adverse event.

Note: Patients were counted once in each body system and preferred term.

9.5.3. Adverse Events in the Integrated Safety Analysis

Common adverse events, defined as TEAEs reported in $\geq 10\%$ of all eteplirsen-treated patients, are summarized in [Table 19](#) and all adverse events that occurred in eteplirsen-treated patients are summarized in [Appendix 16](#).

The most commonly experienced TEAEs were consistent with the underlying diagnosis of DMD, steroid treatment, and/or the pediatric nature of the patient population and included headache (27 patients; 23.7%); back pain and vomiting (24 patients each; 21.1%); cough (18 patients, 15.8%); pain in extremity (17 patients; 14.9%); procedural pain (16 patients; 14.0%); upper respiratory infection (15 patients; 13.2% each); arthralgia, contusion, excoriation, oropharyngeal pain, and nasopharyngitis (14 patients each, 12.3%); and nasal congestion (13 patients; 11.4%). Of these, the following occurred more frequently in patients who received 30 or 50 mg/kg eteplirsen IV than in patients who received placebo: headache, vomiting, cough, procedural pain, upper respiratory tract infection, arthralgia, contusion, excoriation, nasopharyngitis and nasal congestion, however this needs to be interpreted in the context of the shorter exposure period for placebo treated patients. The majority of these common TEAEs were mild in severity, considered not related to study drug, and resolved during continued treatment with study drug.

Table 19: Treatment-emergent Adverse Events Observed in ≥10% of ‘All Eteplirsen’ Patients by System Organ Classification and Preferred Term: Integrated Analyses (Safety Population)

System Organ Classification Preferred Term	Eteplirsen								
	Placebo (N = 4)	0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Number of Patients With a TEAE Occurring in ≥10% of Patients While on Eteplirsen	4 (100%)	0	11 (100%)	3 (75.0%)	2 (50.0%)	47 (57.3%)	6 (100%)	69 (64.5%)	69 (60.5%)
Musculoskeletal and connective tissue disorders									
Back pain	2 (50.0%)	0	3 (27.3%)	1 (25.0%)	0	17 (20.7%)	3 (50.0%)	24 (22.4%)	24 (21.1%)
Pain in extremity	3 (75.0%)	0	2 (18.2%)	1 (25.0%)	0	10 (12.2%)	4 (66.7%)	17 (15.9%)	17 (14.9%)
Arthralgia	0	0	3 (27.3%)	0	0	8 (9.8%)	3 (50.0%)	14 (13.1%)	14 (12.3%)
Injury, poisoning and procedural complications									
Procedural pain	3 (75.0%)	0	2 (18.2%)	0	0	8 (9.8%)	6 (100%)	16 (15.0%)	16 (14.0%)
Contusion	0	0	1 (9.1%)	0	0	10 (12.2%)	3 (50.0%)	14 (13.1%)	14 (12.3%)
Excoriation	0	0	0	0	1 (25.0%)	11 (13.4%)	2 (33.3%)	14 (13.1%)	14 (12.3%)
Respiratory, thoracic and mediastinal disorders									
Cough	2 (50.0%)	0	2 (18.2%)	0	0	12 (14.6%)	4 (66.7%)	18 (16.8%)	18 (15.8%)
Oropharyngeal pain	3 (75.0%)	0	0	0	0	10 (12.2%)	4 (66.7%)	14 (13.1%)	14 (12.3%)
Nasal congestion	1 (25.0%)	0	0	0	0	11 (13.4%)	2 (33.3%)	13 (12.1%)	13 (11.4%)
Nervous system disorders									
Headache	2 (50.0%)	0	5 (45.5%)	2 (50.0%)	1 (25.0%)	14 (17.1%)	5 (83.3%)	27 (25.2%)	27 (23.7%)
Gastrointestinal disorders									
Vomiting	0	0	2 (18.2%)	1 (25.0%)	0	18 (22.0%)	3 (50.0%)	24 (22.4%)	24 (21.1%)

Table 19: Treatment-emergent Adverse Events Observed in ≥10% of ‘All Eteplirsen’ Patients by System Organ Classification and Preferred Term: Integrated Analyses (Safety Population)

System Organ Classification Preferred Term	Placebo (N = 4)	0.09 & 0.9 mg IM (N = 7)	Eteplirsen						
			≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Infections and infestations									
Upper respiratory tract infection	0	0	3 (27.3%)	2 (50.0%)	1 (25.0%)	5 (6.1%)	4 (66.7%)	15 (14.0%)	15 (13.2%)
Nasopharyngitis	1 (25.0%)	0	0	0	0	10 (12.2%)	4 (66.7%)	14 (13.1%)	14 (12.3%)

Abbreviations: IM = intramuscular; IV = intravenous; TEAE = treatment-emergent adverse event.

Note: AEs are coded using MedDRA V14.0. AEs were attributed to the treatment being received at start of AE. TEAEs are those starting during or after the first infusion of study drug (or week 1 for untreated patients) or within 28 days after the last infusion (or last visit for untreated patients). Patients who experience a coded event more than once are only counted once per treatment received.

9.5.4. Deaths and Other Serious Adverse Events

There have been no deaths and no life-threatening SAEs with an overall exposure of 72 patient years.

Two (2) treatment-emergent SAEs (one event each of moderate vomiting and severe femur fracture) have been reported in the eteplirsen clinical development program. These were considered as unrelated to study drug. A brief narrative summary for each of these is provided below.

In addition, 4 SAEs that did not occur on eteplirsen have also been reported: 1 'treatment emergent' event that occurred in an untreated patient in Study 301 (lymphadenitis viral); 2 events (ankle fracture, wound infection) that occurred more than 28 days after the patient had discontinued study medication; and 1 event (postoperative oxygen saturation decreased due to emesis) that occurred prior to treatment in a post-operative setting.

Patient 201/202-01-009 (eteplirsen 30 mg/kg)

*Femur Fracture (fracture of right distal femur)
Severe, unrelated*

Patient 201/202-01-009 was a 9-year-old boy with DMD enrolled in Studies 201/202 in the 30 mg/kg IV group. On (b) (6) (Study Day 608), he sustained a fracture of the right distal femur after falling out of his wheelchair when his mother made a sudden stop in their van. He had taken off his seatbelt. He was taken to the emergency room where an X-ray confirmed he had suffered a closed stable femoral fracture; a cast was applied. He received versed, opioids, fentanyl, and ibuprofen for pain relief. Approximately 2 months later, the patient recovered from this event.

Patient 28-01-107 (eteplirsen 2 mg/kg)

*Vomiting (post-operative nausea and vomiting)
Moderate, Unrelated*

Patient 28-01-107 was a 10-year-old boy diagnosed with DMD and enrolled in Study 28. He received 12 doses of once weekly eteplirsen 2.0 mg/kg IV beginning on (b) (6)

On (b) (6) 2 days after the last dose of study drug, he was admitted to the hospital for the protocol-specified muscle biopsy to be performed under general anesthesia. Per standard procedure prior to general anaesthesia, the patient fasted the night before surgery. Initially following the procedure, he made a good recovery and was given liquid and a light diet that evening; however, later that evening (at approximately 20:00 hours), he developed nausea and vomiting. On physical examination, his vital signs were normal and he looked well. Laboratory results from that day were consistent with his underlying DMD condition and were considered unremarkable. His sodium, chloride, and potassium levels were within the normal range. The following day (b) (6), the event of vomiting was considered resolved and he was discharged. The Investigator attributed the event to the prolonged fasting (12 hours) prior to general anesthesia.

9.5.5. Adverse Events Leading to Drug or Study Discontinuation

One (1) patient, a 10-year-old boy with DMD enrolled in Study 28, discontinued treatment due to a TEAE (cardiomyopathy).

Patient 28-02-202 (eteplirsen 4 mg/kg)

Cardiomyopathy (Cardiomyopathy [left ventricular dysfunction])

Severe, Possibly related

Patient 28-02-202, a 10-year-old boy in the 4 mg/kg IV dose group, had 3 reported TEAEs of mild tachycardia and 1 TEAE of sinus tachycardia on Days 1, 8, 24 and 36, with heart rate up to 127 beats per minute. An echocardiogram was performed and revealed decreased fractional shortening of 22% (ejection fraction [EF] of 40% to 45%). The investigator reported this finding as an adverse event of cardiomyopathy (described as 'cardiomyopathy [left ventricular dysfunction]') that was possibly related to eteplirsen and led to study drug discontinuation on Day 47 (after 7 doses of eteplirsen 4 mg/kg IV). Retrospective review of echocardiograms obtained prior to study entry showed evidence for pre-existing cardiomyopathy per the investigator's report. Moreover, subsequent re-evaluation of all study echocardiograms of this patient by an independent cardiologist (without the cardiologist being provided clinical details of the adverse event) determined normal left ventricular ejection fraction (>55%) on all study echocardiograms.

Given the possibility of presence of left ventricular dysfunction prior to study treatment, and inconsistency with respect to independent interpretation of the echocardiographic data, a relationship between study drug and this event is difficult to establish. Further discussion of cardiac function, including the diagnosis and prevalence of cardiomyopathy in the DMD population, is provided in the section on adverse events of special interest ([Section 9.5.8.1](#)).

9.5.6. Severe Adverse Events

The majority of TEAEs across all treatment groups were mild or moderate in intensity, as assessed by the Investigator. A total of 5 eteplirsen-treated patients (4.4%) experienced 8 severe TEAEs, including incision site haemorrhage, haemorrhoids, back pain, cardiomyopathy, nasal congestion, balance disorder, bone pain, and femur fracture. With the exception of cardiomyopathy ([Section 9.5.5](#)), which was considered by the investigator to be possibly related to treatment, all other severe events were considered unrelated to study drug. In addition, one untreated patient experienced one event of lymphadenitis viral that was considered severe in intensity and that met the criteria for seriousness.

9.5.7. Treatment-Related Adverse Events

TEAEs assessed by the investigator to be possibly, probably, or definitely related to study treatment were considered treatment-related. Overall, treatment-related TEAEs were reported in 36 (31.6%) patients in the 'all eteplirsen' treatment group and in 1 (25%) patient in the placebo group. In the 'all eteplirsen' group, the most frequent treatment-related TEAEs were headache (8 patients, 7.0%), proteinuria (4 patients, 3.5%), and dizziness, fatigue, vomiting, and tachycardia (each in 3 patients, 2.6%). One (1) patient was reported to have a treatment-related TEAE of nausea while receiving placebo. Treatment-related TEAEs occurred across dose groups with no indication of a dose effect.

Treatment-related TEAEs were reported in 21 (23.9%) of the 88 patients who received eteplirsen at either 30 or 50 mg/kg IV weekly, the treatment groups that represent the greatest exposure to eteplirsen. Of these, proteinuria, protein urine present, thrombosis in device, vomiting, and flushing were reported in >1 patient; these TEAEs are discussed in more detail in [Section 9.5.8](#), Adverse Events of Special Interest.

9.5.8. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for the eteplirsen program included potential safety related findings based on manifestations of the underlying DMD disease (cardiac function), nonclinical observations with eteplirsen (renal function, see [Section 9.5.8.2](#)), AEs associated with other RNA analogs (renal and hepatic function, coagulopathy and infusion site reactions), and general precautions with administration of a compound in clinical development (infusion related reactions, hypersensitivity, severe cutaneous reactions, leukopenia and neutropenia).

The inclusion of adverse events associated with other RNA analogs in Adverse Events of Special Interest for eteplirsen, a phosphorodiamidate morpholino oligomer, is a conservative approach, since the non-clinical toxicity data for eteplirsen did not show a signal except for renal findings at the highest dose administered ([Section 4.2.2](#)). Other RNA analogs, specifically phosphorothioate oligonucleotide therapeutics have been associated with renal toxicity, including increases in proteinuria, α 1 microglobulin, and KIM 1 ([McGowan 2012](#), [Goemans 2011](#)); elevated levels of transaminases and hepatic steatosis ([McGowan 2012](#)); thrombocytopenia and other coagulation related adverse events ([Goemans 2014](#)); and injection site reactions ([Voit 2014](#), [McGowan 2012](#)).

To identify potential AESIs, search criteria for specific MedDRA preferred terms were developed. In addition, medical review of all TEAEs, as well as relevant laboratory, vital sign, ECG and echocardiogram results was performed.

9.5.8.1. Cardiac Function

In addition to progressive muscle weakness and wasting, manifestations of DMD typically include cardiac symptoms. While cardiac function is generally normal during early childhood, they progressively worsen over time, and patients typically die from cardiac or respiratory failure ([Brooke 1989](#), [Eagle 2002](#)).

Boys with DMD have a resting heart rate that is consistently higher than normal even when cardiac function remains normal. Although elevation in resting heart rate in this patient population is likely multifactorial, it is associated with increased risk of cardiomyopathy ([Thomas 2012](#)), which is usually diagnosed after the age of 10 years as dilated cardiomyopathy with reduced left ventricular ejection fraction in boys with DMD. While cardiomyopathy rarely manifests clinically in the early teens in DMD patients, the prevalence of cardiomyopathy as measured by a left ventricular ejection fraction of <55% has been estimated at 27% overall. Cardiomyopathy shows an increasing prevalence with age and disease progression, with 10% to 20% of patients affected between 6 and 13 years of age and over 60% of patients $\geq$ 18 years affected ([Spurney 2014](#)). A long latency between initial abnormal cardiac findings in laboratory assessments and clinically manifest cardiomyopathy exists, and the pathology includes myocyte atrophy, hypertrophy and fibrosis.

In the ‘all eteplirsen’ group, 6 patients (5.3%) had a total of 12 reported events potentially indicative of a cardiac disorder. None of the events was serious, and the majority of events were assessed by the investigator as mild in intensity (9/12) and as possibly related (7/12) to eteplirsen (Table 20).

The observed TEAEs included cardiomyopathy, congestive cardiomyopathy, pericardial fibrosis, tachycardia, and sinus tachycardia, and were distributed across dose groups with no suggestion of a dose effect. One (1) 10-year-old patient (28-02-202) with mild events of tachycardia and sinus tachycardia prematurely discontinued treatment in Study 28 due to an event of cardiomyopathy; this event was described above in Section 9.5.5. The other event of cardiomyopathy was reported in a 13-year-old patient 27 days after a single low dose of eteplirsen 0.09 mg IM. An event of pericardial fibrosis was identified by routine cardiac MRI as part of DMD natural history surveillance at the study site and was considered to be related to the underlying disease of DMD:

Patient 204-206-104 (eteplirsen 30 mg/kg)

Pericardial fibrosis

Mild, not related

Patient 204-206-104 was a 14-year-old with advanced DMD who experienced mild, asymptomatic pericardial fibrosis on Day 120, after receiving 18 eteplirsen doses. The finding was identified by routine cardiac MRI as part of DMD natural history surveillance at the study site. The event is ongoing and the patient remains asymptomatic. The Investigator assessed causality of the event as unrelated to study drug or study procedures, and definitely related to the underlying disease of DMD. The patient’s cardiologist started him on spironolactone. No action was taken with study drug administration and the patient remained in the study through the D120 data cutoff.

Table 20: Cardiac Function TEAEs

Patient ID	Age (yr)	Dose (mg/kg)	Preferred Term	Treatment Related	Severity	Outcome
204-206-104	14	30	Pericardial fibrosis	No	Mild	Not recovered
201/202-01-006	10	30	Tachycardia	No	Moderate	Not recovered
			Tachycardia (worsening)	No	Moderate	Recovered
			Tachycardia	No	Mild	Recovered
28-02-205	10	20	Tachycardia	Possibly	Mild	Not recovered
28-02-207	9	20	Tachycardia	Possibly	Mild	Not recovered
28-02-202	10	4	Cardiomyopathy	Possibly	Severe	Not recovered
			Sinus tachycardia × 3	Possibly	Mild	Recovered
			Tachycardia	Possibly	Mild	Recovered
33-01-002	13	0.09 ^a	Congestive cardiomyopathy	No	Mild	Unknown

^a Patient 33-01-002 received a single 0.09-mg intramuscular dose of eteplirsen.

In addition, 3 patients had 5 reported events of tachycardia and sinus tachycardia.

To further evaluate the cardiac clinical course of patients with DMD, predefined criteria were established for abnormal changes for QTcF; there were no patients who met predefined criteria for QTcF. Of the predefined criteria for abnormal ECG results, only the criterion for abnormal HR (HR >120 bpm) was met. A total of 7 patients (1 in ≤4 mg/kg, 2 in 20 mg/kg, and 4 in 30 mg/kg) met this criterion; 3 of these patients had reported TEAEs of tachycardia or sinus tachycardia (Table 20). The remaining 4 patients had a single occurrence of HR >120 bpm with no reported cardiac events associated with elevated heart rate. It should be noted that 4 additional patients also experienced heart rates above 120 bpm prior to treatment initiation.

In addition, serial echocardiograms were conducted in Studies 201/202. None of the patients in the safety population had left ventricular ejection fraction results that met the criteria for a predefined abnormal change. Longitudinal analysis of the left ventricular ejection fraction as assessed at the annual milestone visits in Studies 201/202 is provided in Table 21 below. In this table, the Week 24 assessment was used as baseline in patients originally randomized to placebo to ensure that only the period on eteplirsen treatment is represented. These data characterize the stability of LVEF in patients treated with eteplirsen over 4 years.

Table 21: Left Ventricular Ejection Fraction over Time in Studies 201/202

Timepoint	Patients Treated with Eteplirsen at 30 or 50 mg/kg IV (N = 12)		
	n	Median LVEF	Min, Max LVEF
Baseline	12	61.5	50, 74
Year 1	11	66.0	52, 71
Year 2	12	62.5	54, 67
Year 3	12	65.0	53, 71
Year 4	8 ¹	62.0	55, 76

Abbreviations: LVEF = left ventricular ejection fraction; max = maximum; min = minimum

¹ At the time of the data cut for the Day 120 Safety Update, the 4 patients initially on placebo had not been on eteplirsen treatment for 4 years.

The occurrence of tachycardia, cardiomyopathy and cardiac fibrosis observed during clinical trials with eteplirsen was not related to study dose or duration of administration, is not unexpected in the DMD population enrolled, and appears consistent with the underlying disease.

9.5.8.2. Renal Function

The primary elimination pathway for eteplirsen is renal, and the kidney was identified as the primary target organ for toxicity in nonclinical toxicology studies. In addition, other RNA analogs, specifically phosphorothioate oligonucleotides, have been associated with renal toxicity, including increases in proteinuria, α1 microglobulin, and KIM 1 (McGowan 2012, Goemans 2011).

However, it should be noted that renal dysfunction is a common complication in advanced stages of DMD, and DMD patients have additional risk factors, including dehydration, for renal dysfunction (Bratt 2015). While serum creatinine levels are typically a fairly reliable indicator of

kidney function, this is not the case in patients with more advanced DMD whose basal creatinine levels tend to be low or low normal due to decreased muscle mass (Viollet 2009); therefore, elevations that would typically be seen in patients with renal dysfunction would not necessarily be observed in patients with DMD. Thus, serum cystatin C may provide a better measure of renal function than creatinine.

In the ‘all eteplirsen’ group, 16 patients (14.0%) had a total of 21 TEAEs potentially representative of renal toxicity. One (1) patient in the placebo group had an event of proteinuria and one patient in the 30 mg/kg treatment group had an event of proteinuria prior to treatment initiation. None of the events were serious, and all were assessed by the investigator as mild in intensity. The majority of events were transient and spontaneously resolved with ongoing study drug administration. Nine (9) patients (7.9%) had 9 TEAEs that were reported by the investigator as treatment related (Table 22).

Table 22: Treatment-related TEAEs Potentially Indicative of Renal Toxicity

Patient ID	Age (yr)	Dose (mg/kg)	Preferred Term	Treatment Related	Severity	Outcome
201/202-01-004	8	50	Hypercalciuria	Possibly	Mild	Not recovered
201/202-01-015	9	50	Proteinuria	Possibly	Mild	Recovered
204-202-101	13	30	Protein urine present	Possibly	Mild	Recovered
204-202-104	11	30	Protein urine present	Possibly	Mild	Recovered
204-233-105	17	30	Blood urine present	Possibly	Mild	Not recovered
301-213-001	12	30	Urine analysis abnormal	Possibly	Mild	Recovered
301-218-004	9	30	Proteinuria	Possibly	Mild	Recovered
301-234-001	12	30	Proteinuria	Possibly	Mild	Recovered
201/202-01-006	10	30	Proteinuria	Possibly	Mild	Recovered

Proteinuria/urine protein present were the most common reported adverse events; these events were transient or sporadic, spontaneously resolved with ongoing treatment, and were not associated with increasing renal laboratory values, with the exception of 1 patient who had evidence of transient renal laboratory abnormalities in the setting of dehydration (Patient 201/202-01-003, 50 mg/kg IV). No other concurrent indicators of renal toxicity were reported. Only 1 event of proteinuria (Patient 204-202-101, 30 mg/kg IV) led to interruption of study drug. This patient resumed treatment after missing 1 dose without further TEAEs or abnormal laboratory findings.

Adverse Events of Proteinuria / Protein Urine Present

In the ‘all eteplirsen’ group, of the 16 patients with reported renal events, 11 patients (9.6%) had reported TEAEs of either proteinuria (10 TEAEs) or protein urine present (2 TEAEs). Of these 12 events, 6 (50.0%) were considered possibly related to treatment. In addition, 1 event of proteinuria was reported in 1 patient who was receiving placebo. All events were mild with no

consistent pattern of time to onset (onset ranged from Day 1 to Day 785), and all patients continued treatment uninterrupted with 1 exception (1 dose of study medication was withheld as a precautionary measure for Patient 204-202-101).

In 10 of the 11 patients, the events were isolated with no increases in serum BUN, serum cystatin C, or urine KIM 1, had no accompanying symptoms of renal disease, were generally mild, transient, and resolved in subsequent assessments. The case of proteinuria with associated changes in laboratory values is briefly summarized below.

Patient 201/202-01-003 (eteplirsen 50 mg/kg)

*Blood creatinine increased, Blood urea increased, Dehydration, Proteinuria
Mild, Not related*

Patient 201/202-01-003 (50 mg/kg IV), who was 7 years of age at baseline, experienced blood creatinine increased, blood urea nitrogen increased and proteinuria at Week 60, with concurrent abnormal laboratory findings of creatinine 102.5 $\mu\text{mol/L}$, blood urea nitrogen (BUN) 14.6 mmol/L, and trace urine protein at the time of the observed laboratory abnormalities. Of note, the serum cystatin C and urine KIM 1 values at the time of the TEAEs were normal. Both BUN and creatinine abnormalities had resolved by the time of re-testing 11 days later and remained normal with continued eteplirsen treatment through data cutoff at Week 208. Subsequent urinalysis was sporadically positive for trace or 1+ protein. The investigator interpreted this event in the context of dehydration, noting that this patient had a history of dehydration on several occasions, and a TEAE of dehydration was recorded. The patient remained in the study and continued to receive study drug through data cutoff at Week 208.

In addition, a value of 2+ urine protein on dipstick, corresponding to ≥ 100 mg/dL and < 300 mg/dL, was predefined as the criterion for a markedly abnormal value; 5 treated patients had a post-treatment 2+ urine protein value that was not recorded as an AE. In all cases, the finding was a single occurrence that spontaneously resolved with ongoing treatment. It should be noted that 2+ urine protein values were also recorded prior to treatment.

Additional renal TEAEs included dehydration, chromaturia, crystalluria, hypercalciuria, blood creatinine increased, blood urea increased, blood urine present, and urine analysis abnormal; with the exception of dehydration, which was reported in 2 patients, these events were reported in only 1 patient (per event).

Laboratory observations of protein in urine (Study 201/202)

To assess whether or not elevations in urine protein were increasing over time with eteplirsen, a longitudinal analysis of positive ($\geq 1+$ by dipstick, corresponding to ≥ 30 mg/dL and < 100 mg/dL) urine protein findings over time in Studies 201/202 was performed. Over the 4-year period, a total of 721 urinalysis assessments were performed in the 12 patients. Overall, 702 ($>97\%$) of the assessments were normal, and no increase in the occurrence of urine protein was observed over time, suggesting no cumulative effect (Table 23).

Table 23: Instances of Urine Protein $\geq 1+$ Over Time in Studies 201/202 (based on urinalysis by dipstick assay)

Timepoint	Instances of protein in urine $\geq 1+$	Number of Assessments
Placebo and Prior to dosing	2	68
Week 0-48	3	183
Week 48-96	6	150
Week 96-144	5	152
Week 144-Week 208 (data cutoff)	3	168

Laboratory Observations of Serum Creatinine and Cystatin C

In patients with DMD, creatinine levels tend to be low or low normal due to decreased muscle mass. Serum cystatin C is less dependent on muscle mass and therefore, may provide a better measure of renal function. Thus, serum cystatin C levels were evaluated in the eteplirsen clinical program as an additional biomarker of kidney function.

One patient (201/202 01 003), described above, had a creatinine value that met predefined criteria for an increase over baseline of $\geq 35 \mu\text{mol/L}$ and a clinically noteworthy treatment-emergent value. No other patient treated with eteplirsen met the criterion for abnormal change, and no other patient had a creatinine value above the ULN while on eteplirsen treatment. Patient 201/202 01 003 was discussed above.

Two (2) patients (1 in the 30 mg/kg IV dose group and 1 untreated) had a shift from normal to high for serum cystatin C. Concurrent BUN and creatinine values were normal, urine protein was negative, and cystatin C levels returned to normal at the next assessment for both patients.

Adverse events of Myoglobinuria

There were 4 AEs of myoglobinuria reported in eteplirsen studies. All of the myoglobinuria events were reported in Study 33, after a single intramuscular (IM) dose, in the 0.9mg/kg IM arm. The myoglobinuria was reported on the day that study drug was administered for 3 of the 4 subjects, and was reported on the day of the post-treatment biopsy for the remaining subject (on Day 29). The myoglobinuria events were self-limited and resolved, without treatment. Due to the temporal relationship between the administration of general anesthesia and the onset of myoglobinuria, the general anaesthesia may have contributed to the onset of these events; however, it is more likely that direct injury to muscle following the IM injection or the muscle biopsy caused the observed myoglobinuria. Myoglobinuria events were not observed in subsequent eteplirsen studies.

In summary, protein in urine was observed not only during treatment with eteplirsen, but also in patients prior to dosing. In addition, there was a lack of concurrent elevation of other markers of renal function, including BUN, creatinine, and cystatin C, (with the exception of one event of increased BUN and creatinine as described above) and spontaneous resolution was observed with ongoing eteplirsen dosing. The data suggest that protein in urine may occur in the background population. Additional renal events were isolated, mild in intensity, and the majority resolved

with ongoing treatment. Thus, the data generated to date do not suggest an association between renal dysfunction and eteplirsen at this time.

9.5.8.3. Hepatic Function

There were no treatment emergent adverse events representative of a potential drug-induced hepatotoxicity.

Laboratory Observations of Liver Function Tests

Traditional criteria to assess liver function may have limited applicability in the DMD population, because high transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] up to approximately $22 \times$ ULN) are generally observed in these patients due to leakage of the enzymes from degenerating muscle fibers (McMillan 2011). Therefore, abnormal change criteria in the eteplirsen clinical development program were defined as $\geq 2 \times$ baseline for ALT and $\geq 3 \times$ baseline for AST.

Three (3) patients in the 30 mg/kg IV dose group, met the predefined abnormal criterion of $\geq 2 \times$ baseline for ALT. No patients in the untreated or the 50 mg/kg IV dose group met this criterion. In all 3 instances, the patient had no increase in bilirubin or GGT and a pre-treatment ALT value that was higher than the on treatment value designated as meeting the predefined abnormal criterion. The abnormal ALT values on-treatment were, therefore, considered consistent with fluctuations in ALT that may be seen with the underlying DMD.

Two (2) patients in the 30 mg/kg IV dose group had elevated AST levels that met the predefined abnormal change criterion of $\geq 3 \times$ baseline. In one case, the patient also had recorded pre-treatment ALT and AST values that were higher than the on-treatment values that met the abnormal criteria. In both cases, AST decreased with ongoing study drug, and both patients were asymptomatic. No changes were made to study drug administration, and the patients continued in the study.

In addition, 1 patient in the 30 mg/kg IV group met the predefined criterion of $\geq 1.5 \times$ ULN for bilirubin. This patients had elevated bilirubin levels prior to study drug administration that were higher than on study values. No action was taken with study drug, and the patient continues to be followed.

Overall, there were no adverse events suggestive of hepatic effect of eteplirsen, and the observed transaminase levels appeared consistent with the underlying disease.

9.5.8.4. Coagulopathy

In the 'all eteplirsen' group, 21 patients (18.4%) had a total of 42 TEAEs which were reviewed to evaluate whether they were potentially indicative of a coagulation disorder. None of the events were serious, and the majority were reported by the investigator as mild in intensity and unrelated to eteplirsen. There were no discontinuations or changes to study treatment due to any of these events, and at the time of data cutoff, all events had resolved. Three (3) patients (2.6%) had 5 TEAEs that were reported by the investigator as treatment related and/or as moderate or severe in intensity (Table 24). Four (4) events involved the Port a Cath device; in each case, there were no abnormal platelet, prothrombin time (PT), international normalized ratio (INR), or activated partial thromboplastin time (aPTT) values. Therefore, the sponsor considers these events to be not related to study drug, but rather to the Port-a-Cath device. For the event of

platelet anisocytosis, there were no concurrent events indicative of a bleeding disorder, and platelet counts, aPTT, PT, and INR were normal around the time of the reported event.

Table 24: Treatment-related and/or Moderate or Severe TEAEs Potentially Indicative of Coagulopathy

Patient ID	Age (yr)	Dose (mg/kg)	Preferred Term	Treatment Related	Severity	Outcome
201/202-01-009	9	30	Thrombosis in device	Possibly	Moderate	Recovered
201/202-01-010	9	30	Thrombosis in device	Possibly	Moderate	Recovered
			Thrombosis in device	Possibly	Moderate	Recovered
			Device occlusion	Possibly	Moderate	Recovered
28-01-108	10	4	Platelet anisocytosis	Possibly	Mild	Recovered

Other unrelated events included infusion and injection site haematoma, prolonged aPTT, ecchymosis, thrombosis in device, catheter site haematoma, device occlusion, and petechiae.

Ten (10) patients had more than 1 adverse event potentially indicative of coagulopathy. Most of the events for the 10 patients with multiple AEs in this category were consistent with catheter site hematomas or device thrombosis. Two (2) of the 10 patients experienced events of prolonged aPTT and ecchymosis. One (1) of the 2 patients, had an elevated aPTT measurement from a normal baseline test (baseline 25.7 seconds) ranging from 36.0-53.3 seconds (normal range 23.6-32.5 seconds) on Study Days 52-95, and concurrent ecchymosis on Study Days 67-97. This patient had another asymptomatic episode of aPTT elevation (35.2 seconds) on Study Day 162-177 without an associated AE. The second patient experienced bilateral lower limb ecchymosis of 3-day duration (Study Days 501-504) 11 months prior to the onset of aPTT elevation ranging from 43.0-48.0 seconds (baseline 30.0 seconds) on Study Days 918-936. All of the events of aPTT and ecchymosis experienced by the two patients above were of mild severity and resolved without treatment.

Overall review of the events potentially related to coagulopathy suggested no consistent pattern of eteplirsen drug effect.

9.5.8.5. Infusion Site Reactions

Patients receiving eteplirsen were monitored closely for events related to potential infusion site reactions. In the analysis of infusion site reactions focus was on the eteplirsen IV group, as the route of administration for eteplirsen is IV. The 7 patients who received a single low dose of intramuscular eteplirsen in Study 33 are not included in this analysis.

In the 'eteplirsen IV' group, 24 patients (22.4%) had a total of 55 TEAEs which were reviewed to evaluate whether they were potentially representative of infusion site reactions. None of the events were serious, and the majority were assessed by the investigator as mild in intensity and unrelated to eteplirsen. At the time of data cutoff, the majority of events had resolved without changes to treatment administration. Two (2) patients (1.9%) each had 1 TEAE that was reported by the investigator as treatment-related and/or as moderate or severe in intensity (Table 25). The event that was considered to be possibly related resolved the same day and the patient had no

other reported infusion site reactions; and the event of moderate intensity was described as pain post-operative to port placement.

Table 25: Treatment-related and/or Moderate or Severe TEAEs Potentially Indicative of an Infusion Site Reaction

Patient ID	Age (yr)	Dose (mg/kg)	Preferred Term	Treatment Related	Severity	Outcome
204-233-102	8	30	Catheter site pain	Possibly	Mild	Recovered
201/202-01-010	9	30	Catheter site pain	No	Moderate	Recovered

Additional mild and unrelated events included catheter or infusion site haematoma (21 events in 9 patients); catheter, infusion or injection site pain (15 events in 11 patients); pyrexia (5 events in 4 patients); infusion site extravasation (4 events in 4 patients); application or infusion site erythema or rash (4 events in 3 patients); catheter site hemorrhage, inflammation, and related reaction (1 event each in 1 patient each); and infusion site swelling (1 event in 1 patient). Four (4) patients (3.7%) had their infusion interrupted as the result of a mild, unrelated TEAE of either extravasation (n = 3) or infusion site pain (n = 1).

Overall, the majority of events were mild (98.2%) and considered unrelated to eteplirsen (98.2%) and were generally reflective of the types of events due to catheter placement rather than due to a direct effect of eteplirsen.

9.5.8.6. Hypersensitivity

In the ‘all eteplirsen’ group, 27 patients (23.7%) had a total of 43 TEAEs which were reviewed to evaluate whether they were potentially representative of hypersensitivity, and 1 untreated patient (6.7%) had 1 event (mild rash). All of the events were reported as non-serious and recovered/resolved, and the majority of events in the ‘all eteplirsen’ group were mild (41/43, 95.3%) and considered by the investigator to be unrelated to study treatment (38/43, 88.4%). Study drug administration was interrupted for 2 events.

Six (6) patients (5.3%) had 7 TEAEs that were reported by the investigator as treatment related and/or as moderate or severe in intensity (Table 26). All of the events that were considered by the investigator as treatment related were mild in intensity and resolved with ongoing eteplirsen treatment; and the investigator provided an alternate etiology (‘possible reaction to Ametop plastic’) for 1 event (drug eruption) despite having recorded it as possibly related to treatment.

Table 26: Treatment-related and/or Moderate or Severe TEAEs Potentially Indicative of Hypersensitivity

Patient ID	Age (yr)	Dose (mg/kg)	Preferred Term	Treatment Related	Severity	Outcome
201/202-01-004	9	50	Erythema	Possibly	Mild	Recovered
			Erythema	Possibly	Mild	Recovered
201/202-01-005	8	50	Alopecia	No	Moderate	Recovered
301-218-001	10	30	Flushing	Definitely	Mild	Recovered
301-239-001	13	30	Flushing	Possibly	Mild	Recovered
201/202-01-002	9	30	Dermatitis contact	No	Moderate	Recovered
28-02-207	9	20	Drug eruption	Possibly	Mild	Recovered

Both events of flushing occurred on Day 1 (first infusion), resolved the same day, and did not recur despite continued dosing with eteplirsen. One (1) patient experienced 2 events of erythema (Days 974 and 988) that each occurred within 1 hour of drug infusion, resolved the same day, and did not recur despite continued dosing with eteplirsen.

There were also mild and unrelated events of rash, rash papular, rash pruritic, pruritus, erythema, urticaria, urticaria thermal, flushing, feeling hot, dermatitis contact, papule, seasonal allergy, hypersensitivity ('worsening of seasonal allergies'), lip swelling, and swelling.

Overall, no trends or patterns in these events were observed. The time to onset from last dose ranged from 44 minutes to 7 days; the number of doses prior to event onset ranged from 1 to 199; and event duration ranged from 15 minutes (dermatitis contact) to 50 days (feeling hot). Given the resolution and lack of recurrence for most events despite continued treatment, these events appear to be reflective of the background population rather than due to study drug treatment. The 2 events, mild erythema and flushing, that occurred on the day of study drug infusion may represent potential adverse drug reactions with eteplirsen.

9.5.8.7. Infusion-related Reactions

The 7 patients who received a single low dose of intramuscular eteplirsen in Study 33 were excluded from this analysis, because IV infusion is the proposed route of administration.

In the 'eteplirsen IV' group, 30 patients (28.0%) had a total of 55 TEAEs which were reviewed to evaluate whether they were potentially representative of an infusion-related reaction, and 3 events occurred in 2 patients while receiving placebo. The majority of events in the 'eteplirsen IV' group were non-serious (54/55, 98.2%), mild in intensity (51/55, 92.7%), and unrelated to study treatment (49/55, 89.1%). None of the events required a change in treatment administration, and as of the data cutoff date, 54 of the 55 events had resolved.

Nausea and/or Vomiting

Although nausea and vomiting are relatively non-specific events and may occur in a pediatric population, these events were medically reviewed to assess whether they potentially represented a type of infusion related reaction. The overall frequency of nausea and vomiting were comparable across dose groups and not suggestive of a dose effect, ranging from 4.9 to 50.0% in

the active groups and 0 to 25.0% in the placebo group. Seven (7) patients in the 'eteplirsen IV' group experienced events that were moderate in intensity and/or related (possibly or definitely) to eteplirsen according to the investigator. The time to onset for these 7 events was variable with only 1 patient experiencing intermittent nausea on a day of study drug infusion. All 7 patients continued to receive study drug, and nausea or vomiting did not recur except in 2 patients. Overall, events of nausea and vomiting were not considered to represent infusion related reactions.

Pyrexia

A total 5 events of pyrexia occurred in 4 patients in the 'eteplirsen IV' group and 2 events occurred in 2 patients in the placebo group. All of the events were assessed by the investigator as mild in intensity and unrelated to study drug. The time to onset from last dose for the events of pyrexia ranged from 10 hours to 5 days; the number of doses prior to event onset ranged from 4 to 194; and event duration ranged from 30 minutes to 6 days with 4 of the 5 events resolving within 1 day of onset. Only 1 patient, a 9-year-old boy, experienced a recurrence of pyrexia (after dose 13 and dose 124). No trends or patterns were observed. Given the resolution and lack of recurrence for most patients despite continued treatment, and the observation of pyrexia in 2 placebo patients, it may be concluded that these events are reflective of the background population.

However, there was one case of "mild temperature elevation" coincident with study drug infusion which the investigator considered related to study drug, and this event is therefore considered a potential adverse drug reaction. " (Patient 28-01-110 [10 mg/kg IV]) was described as a mild temperature elevation to 37.9°C after infusion of eteplirsen; this event resolved the same day, and the investigator did consider this event to be possibly related to study drug and this event is considered a potential adverse drug reaction.

Pruritus

Two (2) events of pruritus occurred in 2 patients in the 'eteplirsen IV' group. Both events were assessed by the investigator as mild in intensity and unrelated to study drug, and no changes were made to study treatment administration. Patient 204-201-103 (30 mg/kg IV) had a reported TEAE of pruritus from Day 106 to Day 112, and Patient 201/202-01-003 (50 mg/kg IV) had a reported TEAE of pruritus on Day 275 that resolved the same day.

Overall, non-specific symptoms of potential infusion-related reactions such as nausea and vomiting occurred in the eteplirsen-treated population at a relatively low rate, and also occurred prior to treatment or in the placebo group. Although some events have been noted on days of infusion, there was no consistent pattern of recurrence with subsequent infusions. These events were typically mild in intensity and similar across treatment groups. On review of events of pyrexia, there were no trends or patterns observed to suggest an association with study drug, as this event was also seen in the placebo group and all of the events resolved despite continued treatment. There was one case of "mild temperature elevation" coincident with infusion of eteplirsen, which the investigator considered related to study drug. This event is, therefore, considered a potential adverse drug reaction.

9.5.8.8. Severe Cutaneous Reactions

In the 'all eteplirsen' group, 2 patients (1.8%) had a total of 2 TEAEs (one event of mild skin erosion resulting from an accident and one event of mild dermatitis bullous that resolved without intervention within 7 days). Neither event was serious; both resolved with no change to study treatment, both were reported by the investigator as mild in intensity and unrelated to study drug.

These events were mild and self-limited without sequelae. Both had alternative etiologies, including traumatic injury and post-biopsy complication. The events were not consistent with severe cutaneous reaction.

9.5.8.9. Leukopenia/Neutropenia

In the 'all eteplirsen' group, 1 patient (0.9%) had 3 TEAEs that were potentially representative of leukopenia and/or neutropenia. The patient had 2 events of lymphocyte count decreased, both of which were considered by the investigator to be unrelated to treatment and mild in intensity, and 1 event of white blood cell count decreased that was mild and possibly related to treatment. All 3 events resolved with no action taken.

Given the clinical characteristics and spontaneous resolution of these events with ongoing eteplirsen treatment, there is no indication of leukocyte or neutrophil toxicity associated with eteplirsen.

9.6. Clinical Laboratory Evaluations

Laboratory parameters including hepatic tests (i.e., ALT, AST, bilirubin, alkaline phosphatase, GGT), renal function tests (i.e., BUN, creatinine), along with hematologic parameters (i.e., hemoglobin, platelet counts, leukocytes, and leukocyte differential count) and parameters related to coagulation (aPTT and PT) were reviewed. These results were discussed above in relationship to AESIs.

Overall, review of serum chemistry data did not identify safety concerns or any consistent patterns of effect that were indicative of hepatic or renal toxicity. Likewise, review of coagulation and hematologic parameters did not identify any consistent effects suggestive of a coagulation disorder or hematologic toxicity. Markedly elevated transaminase levels that decrease over time were observed and are consistent with results expected in patients with DMD.

In addition, other chemistry laboratory parameters (glucose, albumin, potassium, and creatine phosphokinase) and immunogenicity assessments were also reviewed. Increases in glucose and decreases in potassium values were observed; however, these are considered reflective of the use of corticosteroids in the study population.

Creatine kinase (CK) and immunogenicity results are presented below.

9.6.1. Creatine Kinase

Patients with DMD have grossly elevated CK values due to leakage of the enzyme from degenerating muscle fibers (Zatz 1991). Early in the disease, CK levels are usually 50 to 300 × ULN (normal range 37 to 430 U/L) as muscles degenerate, and over time, the levels tend to decrease as muscle is lost.

Overall, CK values were elevated at baseline and last observation. A total of 20 patients who received eteplirsen at 30 mg/kg or higher met the predefined criterion of $\geq 2 \times$ baseline for an abnormal change in CK value. However, in 10 of the 20 patients (30 mg/kg or higher), there was a recorded pre-treatment CK value that was higher than the reported on-treatment abnormality, and among the 20 patients, medical review determined that only 1 patient (301-210-004) had concurrent mild muscle related event (back pain lasting 5 hours), with no other reported myalgia or musculoskeletal pain. In addition, 1 untreated patient and 2 patients receiving placebo also had an increase in CK that was $\geq 2 \times$ baseline. Therefore, these abnormal CK values are considered representative of fluctuations in CK laboratory values that occur during the clinical course of DMD.

9.6.2. Immunogenicity

The potential for eteplirsen to cause immunotoxicity by complement activation was assessed in repeat-dose studies in juvenile rats, which included assays for T-cell dependent antibody response and blood immunophenotyping, and in non-human primates in complement activation assays. No biologically meaningful effects of eteplirsen on the immune system were detected in these studies.

Consistent with these findings, mean CD3, CD4 and CD8 lymphocyte counts (detected by IHC) decreased or remained stable from baseline to Week 48 in eteplirsen-treated patients in Studies 201/202, indicating a lack of immunogenicity of the newly formed dystrophin. Furthermore, there were no meaningful differences among the treatment groups in the number of interferon-gamma-induced spot-forming colonies on enzyme-linked immunosorbent spot assay (ELISPOT) from baseline through Week 48, indicating the newly expressed dystrophin in eteplirsen-treated patients did not elicit a T-cell response.

Similarly, in supportive Study 28, none of the patients had detectable levels of anti-dystrophin antibody following treatment and most of the patients in the 10 mg/kg and 20 mg/kg dose groups showed decreases in CD3, CD4 and CD8 counts. Finally, there were no clinically significant changes in immunoglobulins (IgA, IgG, or IgM) or in CD4 or CD8 counts following a single IM injection of eteplirsen in Study 33.

9.7. Therapeutic Class Effects

Even though eteplirsen being a PMO is an RNA analog, it has significant, distinct chemical and biological properties that are not seen in other RNA analogues such as phosphorothioates. The difference in the nonclinical toxicity profile between phosphorothioate-based oligonucleotides, which are negatively charged, and eteplirsen is thought to be attributed to the uncharged nature of eteplirsen's phosphorodiamidate linkages that minimize protein binding and thus off-target effects.

Other RNA analogs, specifically those with phosphorothioate linkages, which are negatively charged, have been associated with renal toxicity, including increases in proteinuria (McGowan 2012; Goemans 2011). Elevated levels of transaminases, as well as an SAE of hepatic steatosis, have been observed in the context of treatment with a 2'-O-methoxyethyl (2'OME) phosphorothioate antisense oligonucleotide, mipomersen (McGowan 2012). SAEs of thrombocytopenia, as well as TEAEs related to coagulation, were observed in clinical trials of another phosphorothioate antisense oligonucleotide, drisapersen (Goemans 2014). Injection site

reactions comprised the most common TEAEs observed in clinical trials with both of these oligonucleotides, which share the common structural element of negatively-charged phosphorothioate linkages (Voit 2014, McGowan 2012).

These toxicities are dose limiting for phosphorothioate-based oligonucleotides in the clinical setting and are consistent with the nonclinical toxicity profile of phosphorothioate-based oligonucleotides (Levin 1998; Monteith 1999; Levin 2001; Henry 2008; Frazier 2014).

The safety data for eteplirsen in the clinical setting, including in 88 patients for an overall exposure of 72 patient years at the clinical dose of 30 mg/kg or higher for up to 4 years, did not suggest a signal for the above-mentioned toxicities. These clinical data for eteplirsen are consistent with the nonclinical toxicity data, which showed only non-adverse renal findings at the highest doses administered to mice and NHPs and adverse renal findings, but no other toxicities, at the highest dose level in juvenile rats (Section 4.2.2).

Unlike phosphorothioates, PMOs thus may be less likely to be associated with off-target and serum protein binding, and immune activation. Eteplirsen thus has a chemical and biological profile that is distinct from phosphorothioates.

9.8. Safety in Special Populations

9.8.1. Intrinsic Factors

The safety profile of eteplirsen was evaluated in subgroups of patients in terms of specific age groupings, BMI, race, duration since DMD diagnosis, and ambulatory status. Due to the overall small number of patients (N = 107 in the 'eteplirsen IV' group) in safety dataset, interpretation of findings is limited when the dataset is split across subgroups; in addition, interpretation is further confounded by the low number of serious, severe, and 'uncommon' TEAEs (i.e., those occurring in <10% of patients).

The overall incidence for TEAEs was 82.2% for the 'eteplirsen IV' group and was comparable across patient subgroups of age, BMI, duration since DMD diagnosis and ambulatory status. The majority of patients were between ≥ 6 and <12 years of age, and all of the very few severe or serious adverse events occurred in ambulatory children aged ≥ 6 to <12 years.

Common adverse events observed in at least 10% of patients were also evaluated by patient subgroups. The frequency of these events was generally comparable across subgroups for age, ambulatory status, and duration since diagnosis except for lower frequency rates observed in the older age groups and children with non-ambulatory status.

9.8.2. Pregnancy, Lactation, Geriatric Use

DMD is an X-linked genetic disease occurring in boys. Female carriers are, apart from extremely rare exceptions, asymptomatic. Therefore, eteplirsen has not been studied in pregnant and/or lactating women. In nonclinical testing, no evidence of eteplirsen-associated mutations, chromosomal aberrations, or clastogenic potential was observed in the ICH standard battery of genotoxicity tests. Geriatric patients have not been studied, because DMD is universally fatal during early adulthood.

10. SUMMARY OF RESULTS

10.1. Summary of Efficacy Results

Eteplirsen's ability to reliably induce the production of functional dystrophin in patients with DMD significantly slows the progression of this devastating disease as demonstrated by the following findings in eteplirsen-treated patients:

Biological Endpoints

- Confirmation of exon 51 skipping in all eteplirsen-treated patients with post-treatment biopsies (n = 36)
- De novo dystrophin production was demonstrated by Week 24 in Study 201 based on significant increases in the percent dystrophin positive fibers and intensity; these results were confirmed by independent, blinded pathologists
- Sustained dystrophin production was demonstrated by comparison of Study 201/202 Week 180 biopsy results to untreated controls. Utilizing methods agreed upon by FDA, significant increases in 3 complementary parameters (percent dystrophin positive fibers, dystrophin intensity, and Western Blot) were demonstrated.
- Correct localization of dystrophin at the sarcolemma, as well as localization of nNOS, and components of the DAPC at the sarcolemma, supporting the functionality of the newly expressed dystrophin protein

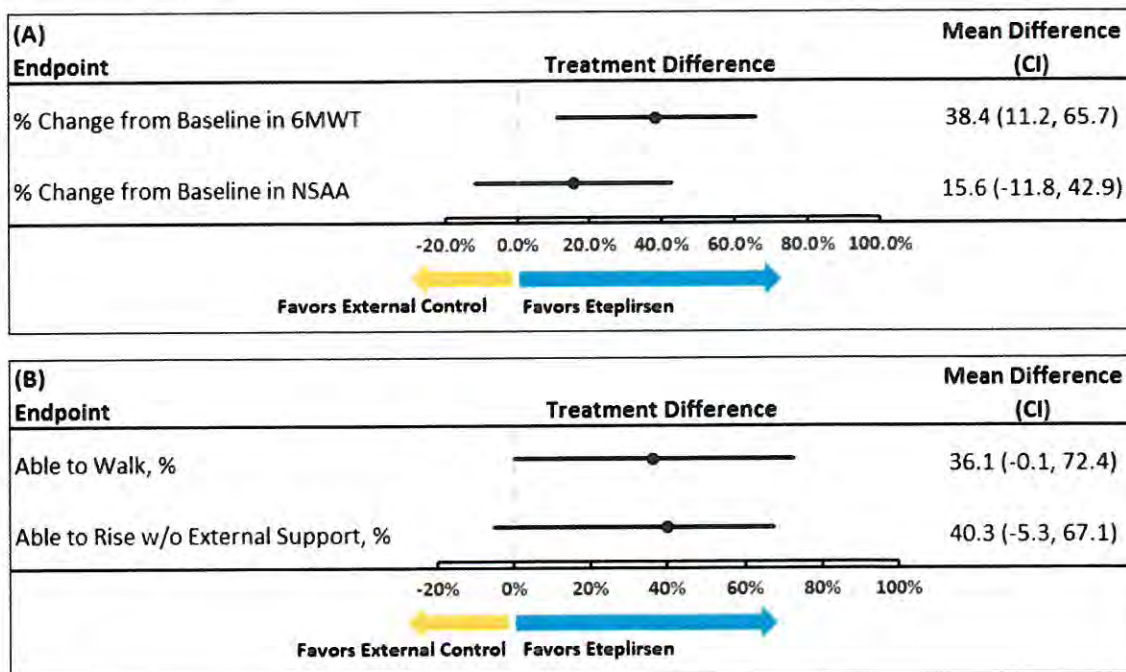
Primary Clinical Endpoint of 6MWT

- A significant reduction in the rate of decline for eteplirsen treated boys (N = 12) of 150.8 meters when compared to the external control group of exon 51 skippable (N = 13). Reduction in the rate of decline in 6MWT reflects amelioration of disease in terms of ambulation, endurance, and muscle function
 - Large magnitude of effect is clinically relevant (treatment effect of 150.8 meters); p<0.01
 - Substantive reduction in the rate of decline (78.7 meters) even when compared to the larger, but less well matched group of any exon skipping (N = 50)
- Temporal pattern for 6MWT in both analyses is divergence of trajectories after Year 1
 - Consistent with significant dystrophin production shown at Week 24
 - Sufficient time is required for decline of comparator in order to demonstrate eteplirsen stabilization of 6MWT

Supportive Endpoints Consistently Favor Eteplirsen vs External Controls

Analyses of supportive endpoints including the percent change from baseline in NSAA total score (Figure 33 Panel A) and preservation of function including the ability to walk and the ability to rise from supine (Figure 33 Panel B) are all directionally consistent with the results of the primary 6MWT. The analysis of mean adjusted treatment differences are directionally consistent and favor eteplirsen treated patients.

Figure 33: Treatment Difference on Multiple Endpoints at Year 3: Study 201/201 Eteplirsen Treated Patients vs External Controls Amenable to Exon 51 Skipping



- **Loss of Ambulation:** Fewer eteplirsen treated boys lost ambulation over the course of 3 years (2/12; (16.7%) compared to 6 of 13 (46.2%) for external controls amenable to exon 51 skipping (N=13). The mean difference of 36.1% represents the larger proportion of eteplirsen treated boys maintaining the ability to walk.
- **NSAA Score:** A smaller decline in NSAA total scores over 3 years for eteplirsen boys (N = 12) compared to untreated external controls (N = 10) of 3 points representing loss or impairment of fewer abilities. In analysis of the difference in percent change from baseline the eteplirsen treated patients declined 15.6% less than the external control patients.
- **Ability to Rise from Supine without External Support:** More eteplirsen treated boys were able to rise from supine without external support (6/11; 55%) compared to the external control boys from the Italian Telethon cohort (1/7; 14%). The mean difference of effect is 40.3%.

Additionally comparisons of eteplirsen FVC% predicted to external patient level data provided by Mayer et al, confirmed the slower decline for eteplirsen treated patients compared to untreated DMD patients in a similar age group.

- **Pulmonary Function Tests:** Eteplirsen treated boys had slower deterioration of respiratory muscle function as measured by FVC% predicted (annual decrease of 3.2%) when compared to a cohort of patients in the 7-15 year age group (annual decrease of 5.8%). Additionally, based on review of published literature MEP% predicted and

MIP% predicted may also decline more slowly with eteplirsen treatment, though the comparison is limited.

In summary, eteplirsen has been shown to slow the progression of DMD as measured by the 6MWT in DMD patients amenable to dystrophin exon 51 skipping over 3 years. This is supported by additional clinical measures, which are directionally consistent, including loss of ambulation NSAA and pulmonary function. The consistency of results across these endpoints supports the conclusion that eteplirsen is an effective treatment for DMD patients with genetic mutations amenable to exon 51 skipping therapy.

10.2. Summary of Safety Results

Exposure and Demography

The overall safety analysis dataset includes a total of 114 eteplirsen-treated patients; 107 patients received once weekly IV infusions of eteplirsen at doses ranging from 0.5 to 50 mg/kg and 7 received a single IM dose of 0.09 mg or 0.9 mg eteplirsen. 88 patients received eteplirsen at either the proposed dose (30 mg/kg, N = 82) or higher (50 mg/kg, N = 6), including 61 patients who received the proposed dose or higher for at least 3 months. Collectively, these data represent over 72 patient-years of safety experience at the proposed once weekly dose of 30 mg/kg or higher. A safety database of this size is not unprecedented in the rare disease setting and the accelerated approval pathway which is reserved for serious and rare diseases with a high unmet medical need.

Treatment-emergent Adverse Events

The most common ($\geq 10\%$ of patients) TEAEs occurring more frequently in patients treated with eteplirsen at either 30 or 50 mg/kg IV than in patients who received placebo were: headache, arthralgia, vomiting, upper respiratory tract infection, nasopharyngitis, cough, nasal congestion, contusion, excoriation and procedural pain. The majority of these common TEAEs were mild in severity, considered unrelated to study drug, and resolved during continued treatment with study drug.

No deaths or life-threatening events occurred during the eteplirsen clinical studies, and only 2 patients (1.8%) experienced a treatment-emergent SAE, both of which were unrelated to eteplirsen. Five (5) patients (4.4%) on eteplirsen and 1 patient in the untreated group experienced severe TEAEs, and 1 patient (0.9%) discontinued treatment prematurely due to a TEAE.

Adverse Events of Special Interest

TEAEs of special interest for the eteplirsen clinical program included medical topics that were selected based on: potential safety-related findings observed in nonclinical toxicity studies of eteplirsen (renal function), AEs associated with other RNA analogs (renal and hepatic function, coagulopathy and infusion site reactions), and general precautions with administration of a compound in clinical development (infusion-related reactions, hypersensitivity, severe cutaneous reactions, leukopenia and neutropenia). Inclusion of adverse events associated with other RNA analogs in Adverse Events of Special Interest for eteplirsen, is a conservative approach, since eteplirsen is structurally dissimilar and the nonclinical toxicity data for eteplirsen did not show a signal except for renal findings at high doses.

Renal function

Twenty-one (21) TEAEs potentially representative of renal toxicity were reported in 16 patients (14.0%) in the 'all eteplirsen' group, and an event of proteinuria was reported in both a placebo patient and a 30 mg/kg patient prior to treatment initiation. All of the events were mild; the majority were transient and spontaneously resolved with ongoing study drug administration. Proteinuria/urine protein present were the most common events observed; these events were transient or sporadic, spontaneously resolved with ongoing treatment, and were not associated with increasing renal laboratory values, with the exception of 1 patient who had adverse events of increased BUN and increased creatinine in the setting of dehydration.

Review of renal adverse events and laboratory parameters identified no pattern of drug effect.

Cardiac function:

Twelve (12) TEAEs potentially indicative of a cardiac disorder were reported in 6 patients in the 'all eteplirsen' group. These events included tachycardia and cardiomyopathy which are known to occur in the background population. None of the events were serious, and the majority were assessed by the investigator as mild in intensity and as possibly related to eteplirsen with the exception of a severe case of cardiomyopathy, which resulted in study drug discontinuation.

Echocardiogram data in the ongoing Study 201/202 did not suggest any pattern of decline in left ventricular ejection fraction for the 12 patients on eteplirsen at 30 or 50 mg/kg/wk for 4 years.

Based on the known prevalence (27%) of cardiomyopathy in patients with DMD, it is difficult to establish a causal association with drug therapy.

Hepatic function:

There have been no reported adverse events suggestive of drug-induced hepatotoxicity.

Coagulopathy: Forty-two (42) TEAEs potentially indicative of a coagulation disorder were reported in 21 patients (18.4%) in the 'all eteplirsen' group. None of the events were serious, and the majority were reported by the investigator as mild in intensity and not related to eteplirsen. Overall review of the events potentially related to coagulopathy suggested no consistent pattern of eteplirsen drug effect.

Infusion site reactions: Fifty-five (55) infusion site reactions were reported in 24 patients (22.4%) in the 'eteplirsen IV' group with over 3900 infusion (event rate <1.5%). Events of catheter-related pain, hematoma, or infusion site extravasation occurred during clinical studies of eteplirsen, but were generally reflective of the types of events due to catheter placement rather than due to a direct effect of eteplirsen. These events were all transient, mostly mild in severity, and consistent with catheter-related complications, which does not suggest an association with eteplirsen.

Infusion related reactions: Fifty-five (55) TEAEs were reported in 30 patients (28.0%) in the 'all eteplirsen IV' dose group and 3 events were reported in 2 placebo patients (50.0%). Non-specific symptoms of potential infusion-related reactions such as nausea and vomiting occurred in the eteplirsen-treated population at a relatively low rate, and also occurred prior to treatment or in the placebo group. Although some events have been noted on days of infusion, there was no consistent pattern of recurrence with subsequent infusions. There was one case of "mild temperature elevation" (coded to the Preferred Term "Infusion related reaction") coincident with

infusion of eteplirsen, which the investigator considered possibly related to study drug. This event is, therefore, being considered a potential adverse drug reaction.

Hypersensitivity: A total of 43 TEAEs potentially representative of hypersensitivity were reported in 27 patients (23.7%) in the 'all eteplirsen' group. None of the events were serious, and the majority were reported by the investigator as mild in intensity and not related to eteplirsen. There have been reports of mild and unrelated rash, contact dermatitis, papule, urticaria and pruritus coincident with eteplirsen treatment. There were no trends or patterns in time to onset from last dose, the number of doses prior to event, or event. Given the resolution and lack of recurrence for most events with continued treatment it may be concluded that these events are reflective of the background population rather than due to study drug treatment. There have been mild events of erythema and flushing occurring on days of study drug infusion, which may represent potential adverse drug reactions with eteplirsen.

Severe cutaneous reactions

Two (2) TEAEs potentially indicative of a severe cutaneous reaction were reported in 2 patients (1.8%) in the 'all eteplirsen' group. These events were mild and self-limited without sequelae. Both had alternative etiologies, including traumatic injury and post-biopsy complication. The events were not consistent with severe cutaneous reaction.

Leukopenia and neutropenia

The potential for leukopenia/ neutropenia was evaluated by review of TEAE data as well as pertinent laboratory parameters. TEAEs of mild leukopenia and lymphopenia were reported for a single patient. Both the leukocyte and lymphocyte counts subsequently normalized with ongoing eteplirsen treatment. There were no reported TAEs of neutropenia. Across all patients, evaluation of leukocytes, neutrophils, and lymphocytes identified no consistent pattern suggestive of drug effect.

Safety will continuously be evaluated in the post-marketed setting including spontaneous adverse event reports, reports from ongoing clinical studies and other sources. In addition a planned longitudinal observational safety registry in DMD patients will collect safety assessments including adverse events of special interest.

In summary, eteplirsen has been shown to be well tolerated, with low rates of serious or severe adverse effects, and the most common events are likely characteristic of the background population. The following common events occurred more frequently in patients who received 30 or 50 mg/kg eteplirsen IV than in patients who received placebo: headache, vomiting, cough, procedural pain, upper respiratory tract infection, arthralgia, contusion, excoriation, nasopharyngitis and nasal congestion. Due to their temporal occurrence relative to eteplirsen administration, the following events will be categorized as ADRs: erythema, flushing, and mild temperature elevation.

11. BENEFITS AND RISKS CONCLUSIONS

11.1. Medical Need

Duchenne muscular dystrophy is a rare, degenerative neuromuscular disease caused by mutations in the *DMD* gene leading to progressive muscle degeneration and ultimately death by early adulthood (Brooke 1989; Eagle 2002; Kohler 2009).

There are no approved therapies for DMD in the US. Although glucocorticoids may be used, their modest effects on delaying disease progression are accompanied by significant side effects. (Beenakker 2005; Biggar 2006; Pradhan 2006; Manzur 2009; Schram 2013; Henricson 2013a). Therefore, there remains a high unmet medical need for an effective therapy for these patients.

11.2. Benefits of Eteplirsen

Eteplirsen is a disease-modifying PMO therapeutic for DMD patients with mutations that are amenable to skipping exon 51. Clinical trials have demonstrated that, in this specific DMD population, eteplirsen treatment induced dystrophin expression resulting in the following sustained clinical benefits:

- Eteplirsen treated patients demonstrated significantly better performance on the 6MWT versus an untreated external control cohort bearing exon 51 skippable mutations, with a clinically meaningful 151-meter advantage after 3 years of therapy
- Fewer eteplirsen-treated patients lost ambulation over the course of 3 years compared to untreated external controls; 2 of 12 (16.7%) eteplirsen-treated patients lost ambulation, compared with 6 of 13 (46.2%) external controls with *DMD* mutations amenable to exon 51 skipping.
- Treatment with eteplirsen resulted in a slower rate of decline on the NSAA total score compared to untreated external control patients over 3 years; this was consistent with results for the 6MWT
- Eteplirsen treated patients experienced relative pulmonary function stability (annual decline of 3.2% on FVC% predicted) compared to an external cohort of patient level data provided by Mayer et al (annual decline of 5.8% on FVC% predicted)

11.3. Risks of Eteplirsen

Clinical trials have evaluated safety in a total of 114 patients with DMD, 88 of whom received a dose of ≥ 30 mg/kg.

- The favorable tolerability of eteplirsen is demonstrated by low rates of treatment emergent SAEs (N = 2, 1.8%), severe AEs (N = 5, 4.4%), and AEs resulting in study drug discontinuation (N = 1, 0.9%).
- The most common ($\geq 10\%$ of patients) TEAEs occurring more frequently in patients treated with eteplirsen at the clinical dose of 30 mg/kg or higher than in patients treated with placebo were: headache, vomiting, cough, procedural pain, upper respiratory infection, arthralgia, contusion, excoriation, nasopharyngitis, and nasal congestion.

- In addition, due to their temporal relationship to eteplirsen administration, the following events are also categorized as ADRs: erythema, flushing, and mild temperature elevation.
- Adverse events of special interest in the following medical categories were not considered related to eteplirsen treatment (i.e. renal toxicity, hepatotoxicity, cardiac-related events, coagulopathy, severe cutaneous reactions, and leukopenia)

11.4. Benefit:Risk Conclusions

The favorable benefit:risk profile of eteplirsen is demonstrated by the totality of evidence showing that weekly administration of eteplirsen is well-tolerated, and is an effective treatment in patients with DMD who are amenable to exon 51 skipping therapy. Specifically, eteplirsen slows the rate of decline in ambulation, endurance, and muscle function as measured by the 6MWT over a 3-year treatment period compared to external control data. Sarepta is committed to the completion of confirmatory trials that will not only aim to verify the clinical benefit of eteplirsen using the 6MWT (intermediate endpoint for accelerated approval), but will also provide an evolving understanding of the safety profile.

The benefits of eteplirsen are demonstrated by a significant difference in the 6MWT of 151 meters compared to external control and a reduction in the number of boys with a loss of ambulation (17% for eteplirsen compared to 46% for the external control cohort of exon 51 skippable patients). Given the highly comparable nature of the eteplirsen patients to the external control including Baseline age, 6MWT distance and longitudinal use of steroids, this difference can only be reasonably attributed to the beneficial intervention of eteplirsen. Moreover, additional clinical assessments using the NSAA and PFTs are supportive of the beneficial clinical effect of eteplirsen as well. In addition, to the demonstrated clinical benefit, the biologic endpoints confirm the predicted mechanism of action and that de novo dystrophin production occurs when boys are treated with eteplirsen.

Significantly, this clinical benefit is accompanied by a safety profile that indicates that eteplirsen is well tolerated with no apparent signal of safety risks. Although the safety dataset of 114 patients may not detect rare events and therefore carries the potential risk of uncertainty in characterization of such events, this needs to be weighed against the certainty of relentless disease progression and premature death for boys with DMD without treatment.

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APPENDIX 1. KEY FDA REGULATORY INTERACTIONS REGARDING ETEPLIRSEN

Date	Summary of Key Regulatory Activity
02 Aug 2007	AVI BioPharma (AVI) submits an initial IND for eteplirsen.
23 Oct2007	FDA grants orphan drug designation to eteplirsen for the treatment of DMD
27 Nov 2007	FDA designates the investigation of eteplirsen for DMD a Fast Track development program
25 Apr 2011	AVI submits a new proposed clinical protocol for study 4658-us-201, a randomized, double-blind, placebo-controlled, 24-week study of eteplirsen with two arms: • 50 mg/kg eteplirsen IV and matched placebo with a 12-week on-treatment biopsy time point • 30 mg/kg eteplirsen IV and matched placebo with a 24-week on-treatment biopsy time point
14 Jun 2011	A Type B End-of-Phase I meeting is held between the FDA and AVI. Key issues discussed at this meeting are: • Surrogate endpoints: FDA states that a statistically significant finding on a clinically meaningful functional outcome would be needed to support an efficacy claim for eteplirsen, and that findings on biomarkers and exploratory functional endpoints could only be supportive • Extension study: FDA agrees that an open-label rollover study, 4658-us-202, may initiate at the end of study 201 • Juvenile toxicology study: FDA makes various recommendations for the design of a 10-week repeat-dose toxicology study of eteplirsen in juvenile rats, including an assessment of immune function • FDA agrees that analysis of complement activation in the 9-month repeat dose cynomolgus monkey study will suffice to assess complement activation in NHPs
12 Jul 2012	AVI BioPharma changes its name to Sarepta Therapeutics

Date	Summary of Key Regulatory Activity
13 Mar 2013	A Type B End-of-Phase 2 meeting held between FDA and Sarepta. Key issues discussed at this meeting are: • Accelerated approval: FDA considers the study 201/202 dataset through Week 48 of the combined studies to be inadequate to support accelerated approval for the following reasons: ○ No difference observed in the 6MWT in study 201 based on the ITT analysis ○ 6MWT results in study 202 are uninterpretable due to the uncontrolled, open-label study design, and the effort-dependent nature of the 6MWT ○ Inadequate characterization of the quantity of dystrophin in treated patients, due to the lack of western blot data ○ Dystrophin as assessed by IHC appears of lesser quantity than in BMD ○ “No good correlation” observed between the dystrophin and 6MWT results in 201/202 FDA concludes that Sarepta should submit further information to support the use of dystrophin as a surrogate, as well as a discussion of all clinical functional outcomes assessed in eteplirsen studies, in order to determine whether it will consider filing an NDA for accelerated approval • Confirmatory study design: Sarepta proposes study 4658-301 (named PROMOVI), an open-label study of eteplirsen in exon 51 skipping amenable DMD patients, versus a concurrent untreated cohort of DMD patients with exon deletions not amenable to skipping exon 51, as a confirmatory study to support accelerated approval of eteplirsen. FDA indicates that placebo control is seemingly necessary to provide interpretable data of an effect on the 6MWT beyond the known variability range of DMD. • Safety population: FDA requires that additional exposed patients beyond the existing 38 in order to conclude that the drug has an acceptable risk/benefit profile.
23 Jul 2013	A Type C guidance meeting is held between the FDA and Sarepta as a follow-up to the March 2013 EOP2 meeting. • FDA states that based on additional information submitted on dystrophin and clinical outcomes; “We are now open to considering an NDA based on these data for filing”. FDA also makes the following general recommendations: • Creation of a proposed charter for dystrophin quantification methods to be used in future biopsies • Independent confirmation of the dystrophin-positive fiber results from study 201/202 • Collaborative development of a protocol for either a western blot or dot blot method to quantify total protein • Obtaining and analyzing a fourth biopsy from patients in study 201/202 • Obtaining additional safety data

Date	Summary of Key Regulatory Activity
08 Nov 2013	A Type C guidance meeting is held between the FDA and Sarepta to discuss the design of PROMOVI, and determine whether it will be placebo-controlled or open label. • In preliminary comments received November 6th, FDA states that the negative reports of the large Phase 3 drisapersen study and Phase 2 PTC124 study, two drugs also thought to act by increasing dystrophin, “raises considerable doubt about the biomarker (dystrophin), and consequently, its ability to reasonably likely predict clinical benefit”. Taken in combination with perceived difficulties in interpretation of the 6MWT results from studies 201/202, FDA “currently consider an NDA filing for eteplirsen as premature” • FDA also stated that “further biopsies should be delayed until a “validated assay to quantify dystrophin becomes available.” • Sarepta’s presentation for this meeting focuses on the chemical differences eteplirsen and drisapersen (i.e. the backbone and sequence), the lack of publicly available evidence that drisapersen adequately induces either exon skipping or de novo dystrophin expression, and the superiority of eteplirsen over drisapersen reported in vivo (Heemskerk 2009).
15 Nov 2013	A teleconference is held between the FDA and Sarepta to continue the discussion from the November 8th Type C meeting regarding the design of PROMOVI. • Sarepta discusses the projected difficulty of enrolling a 120-patient placebo-controlled study of eteplirsen in the United States. • FDA concludes that it may be open to the open-label design of PROMOVI if analysis of DMD natural history data were to reveal subgroups with high degrees of predictability of decline on the 6MWT.
13 Dec 2013	FDA requests the methodology and protocols used for the dystrophin-positive fiber, dystrophin intensity, western blot, and RT-PCR assays in study 201/202
19 Dec 2013	A Type A guidance meeting is held between the FDA and Sarepta to continue discussion on the design of PROMOVI, including presentation of the study 201/202 Week 96 6MWT data. • FDA requests that Sarepta contact the sponsors of the Italian Telethon and Belgian DMD natural history databases and request that their raw be provided to the FDA for analysis. • FDA also recommends that Sarepta develop a plan to assess the immunogenicity of eteplirsen. • FDA concludes that it is not prepared to take a position on the open label design of the proposed confirmatory trial, nor resume a position on the feasibility of filing an NDA for eteplirsen based on the current dataset.

Date	Summary of Key Regulatory Activity
07 Feb 2014	An ad hoc teleconference is held between the FDA and Sarepta. The FDA requests all of the biomarker images and data listings from study 201/202 for review: • Dystrophin-positive fibers by IHC • Fluorescent intensity of dystrophin by BIOQUANT • Total protein by western blot • Exon skipping by RT-PCR
20 Feb 2014	Sarepta completes submission of all of the requested biomarker data
19 Mar 2014	A guidance meeting is held between the FDA and Sarepta. • FDA states that it is open to filing an NDA for eteplirsen for consideration under accelerated approval • FDA proposed a potential approach of two confirmatory studies, an open-label study of eteplirsen and a randomized, double-blind, placebo-controlled trial of another exon skipping PMO • In order for FDA reviewers to better understand the dystrophin-positive fiber methodology, FDA reviewers will visit the laboratory where the dystrophin assessments in study 201/202 were conducted. FDA adds the following remaining reservations regarding the 201/202 dataset, which it states will be NDA review issues: • The 6MWT analysis is based on a modified ITT population, excluding the two patients who became non-ambulant during study 201 • The supportive care given to 201/202 patients versus patients in a historically-controlled population • Potential bias in administration of the 6MWT during the open-label study 202
21 Mar 2014	In accordance with verbal agreement at the March 19th meeting, Sarepta sends correspondence to FDA outlining a new proposed clinical development plan for eteplirsen, including: • the open-label confirmatory study PROMOV1, • a safety study of eteplirsen in DMD patients with advanced disease (4658-204), • a safety study of eteplirsen in 4- to 6-year-olds (4658-203), • a randomized, placebo-controlled confirmatory study of SRP-4045 and SRP-4053 in a pooled population of DMD patients amenable to skipping exons 45 and 53 (protocol 4045-301, named ESSENCE) • Sarepta also commits to collaborating with FDA in development of bioassay methods for analysis of dystrophin in future biopsies.

Date	Summary of Key Regulatory Activity
15 Apr 2014	FDA sends an advice letter verifying that an NDA for eteplirsen should be fileable based on the available dataset, and identifies additional data needed to support the efficacy and safety of eteplirsen. FDA proposes two potential pathways to accelerated approval: • Considering the 6MWT data from 201/202 as a finding on an intermediate clinical endpoint • Considering quantification of dystrophin in muscle biopsies via a number of modalities as a surrogate endpoint FDA identifies two confirmatory trials to verify clinical benefit and urges Sarepta to initiate both studies as soon as possible: • A historically-controlled study of eteplirsen (PROMOVI) • A randomized, placebo-controlled study of another PMO with a similar mechanism of action, directed at a different exon (ESSENCE) FDA makes the following requirements for NDA filing: • Obtain and submit patient-level historical control data, establishing that treatment modalities were similar to the 201/202 patients • Submitting additional patient exposure data beyond the existing 38 patients FDA remains “skeptical” of the existing biomarker data and provides the following recommendations: • A collaborative effort between the FDA and Sarepta to develop a better understanding of the methods and analyses used for generation of the existing biomarker data and aid the development of suitable, consistent, and objective methods for collection and analysis of additional biomarker data • A fourth biopsy of patients in study 202, with the samples compared in a blinded fashion to samples obtained from treatment-naïve patients with exon 51 skipping amenable DMD • Extending the duration of PROMOVI open-label confirmatory trial beyond 48 weeks
09 May 2014	Protocol 4658-301, entitled “<i>An Open-Label Multi-center, 48-Week Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in DMD</i>” (PROMOVI) is submitted to the IND to initiate the first confirmatory trial.
03 Jul 2014	Protocol 4658-204, entitled “<i>An Open-Label Multi-center Study to evaluate the Safety and Tolerability of Eteplirsen in patients with Advanced Stage DMD</i>” is submitted to the IND to initiate the study.
29 Jul 2014	FDA sends an advice letter requesting that Sarepta arrange for reassessment of the raw IHC images for determination of dystrophin-positive fibers from studies 201/202 and 28 by three independent experts, including assessment of the inter- and intra-operator reliability

Date	Summary of Key Regulatory Activity
18 Sep 2014	A Type B Pre-NDA meeting is held between FDA and Sarepta. FDA states that in addition to the available data, the following supplementary data are required to be included in the initial NDA submission in order to accept (file) the application for review: • 3-month safety data from at least 12 to 24 newly exposed patients • Results of the University of Florida MRI natural history study • Patient-level historical control data on clinical endpoints, including timed tests, baseline factors, and ancillary care • Blinded reassessment of dystrophin-positive fiber data from studies 201/202 and 28 by 3 independent pathologists • Week 168 efficacy data from study 201/202 • Presentation and analysis of the historical data available regarding dystrophin expression in BMD, including correlation between protein level and phenotype
15 Oct 2014	FDA and Sarepta hold an ad hoc teleconference to discuss a design for the blinded reassessment of IHC images from study 201/202
28 Oct 2014	FDA sends correspondence regarding on Sarepta's proposed protocol for reassessment of IHC images from study 201/202, including comments that: • Quantification of protein level, which is not provided by the dystrophin-positive fiber assay, will be a "key" NDA review consideration • The primary statistical endpoint of the reassessment should be the baseline samples versus Weeks 12 and 24, as the Week 48 biopsy was taken from a different muscle type (deltoid vs. biceps) and processed in a separate batch, either of which could introduce confounding factors
14 Nov 2014	FDA agrees to Sarepta's revised protocol for reassessment of IHC images from study 201/202

Date	Summary of Key Regulatory Activity
18 Nov 2014	A Type A guidance meeting is held between the FDA and Sarepta to discuss and agree on the design of the second proposed confirmatory study to support accelerated approval of eteplirsen. FDA and Sarepta agree to the following design aspects: • Randomized, double-blind, placebo control • A pooled study of SRP-4045 and SRP-4053 at a 30 mg/kg/week dose each • A patient population aged 7 to 16 years with a baseline 6MWT distance 300 to 450 meters and receiving a stable dose of oral corticosteroids • A primary endpoint of the 6MWT • Secondary endpoints of PFTs, dystrophin-positive fibers, protein level by western blot, the NSAA, and timed function tests • A 48-week duration • A total sample size of 99 patients, allocated to placebo or treatment in a 2:1 ratio
23 Jan 2015	Protocol 4658-203, entitled "<i>An Open-Label Multi-center Study to evaluate the Safety, Efficacy and Tolerability of Eteplirsen in Early-Stage DMD</i>" is submitted to the IND to initiate the study.
30 Mar 2015	FDA agrees that analysis of the Week 180 fourth biopsy tissue samples from study 202 may proceed with the assay protocols for western blot, dystrophin-positive fibers, dystrophin intensity, and RT-PCR submitted by Sarepta
19 May 2015	A Type C Pre-NDA meeting is held between FDA and Sarepta, as a follow-up to the September 18th Pre-NDA meeting. FDA states that Sarepta's proposed outline of the NDA is "<i>generally acceptable</i>" and requests submission of the following data to the NDA as soon as possible: • Week 192 efficacy data from study 201/202 • Week 180 fourth biopsy data • FDA accepts that Sarepta was unable to obtain patient-level PFT natural history data from the Cooperative International Neuromuscular Research Group (CINRG), but requests that Sarepta continue efforts to obtain these data. • Sarepta states that they will submit the NDA as a rolling submission.
20 May 2015	Sarepta initiates the rolling NDA submission by providing the chemistry, manufacturing and control (CMC) and nonclinical portions of the NDA
26 Jun 2015	Sarepta submits the clinical portion of the NDA, completing the rolling NDA submission

Date	Summary of Key Regulatory Activity
25 Aug 2015	FDA accepts (files) the NDA for review and grants priority review designation, setting the user fee goal date of 26 February 2016

APPENDIX 2. INCLUSION AND EXCLUSION CRITERIA STUDY STUDY 201/202

Inclusion Criteria Study 201

Patients had to meet all of the following criteria to be eligible for this study:

1. Be a male with DMD and have an out-of-frame deletion(s) that may be corrected by skipping exon 51 [e.g., deletions of exons 45-50, 47-50, 48-50, 49-50, 50, 52, 52-63], as confirmed in a Clinical Laboratory Improvement Act (CLIA)-accredited laboratory by any peer-reviewed and published methodology that evaluates all exons (including, but not limited to, multiplex ligation-dependent probe, comparative genomic hybridization, and single condition amplification/internal primer analysis).
2. Be between the ages of 7 and 13 years, inclusive.
3. Have stable cardiac function and stable pulmonary function (forced vital capacity [FVC] $\geq$ 50% of predicted and not require supplemental oxygen) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
4. Be receiving treatment with oral corticosteroids and have been on a stable dose for at least 24 weeks before study entry. Patients may be allowed to take other (except RNA antisense or gene therapy) medication, including angiotensin-converting enzyme [ACE] inhibitors, β -blockers, losartan potassium, and coenzyme Q, as long as they have been on a stable dose of the medication for 24 weeks before the screening visit (Visit 1) and the dose will remain constant throughout the study.
5. Have intact right and left biceps muscles or an alternative upper arm muscle group.
6. Achieve an average distance within 200 and 400 meters $\pm$ 10% (i.e. within 180 and 440 meters) while walking independently over 6 minutes.
7. Have a left ventricular ejection fraction (LVEF) of $>$ 40% based on the ECHO that is obtained at the screening visit (Visit 1). A patient who has abnormal ECHO findings but who has an LVEF of $>$ 40% may be enrolled in the study at the Investigator's discretion; however, the patient must have been receiving stable doses of ACE inhibitors or β -blockers for at least 24 weeks before study entry.
8. Have a parent(s) or legal guardian(s) who is able to understand and comply with the all of the study procedure requirements.
9. Be willing to provide informed assent and have a parent(s) or legal guardian(s) who is willing to provide written informed consent for the patient to participate in the study.

Exclusion Criteria Study 201

Patients who met any of the following criteria were excluded from this study:

1. Use of any pharmacologic treatment, other than corticosteroids, that might have an effect on muscle strength or function within 12 weeks before study entry (e.g., growth hormone, anabolic steroids).
2. Previous treatment with the experimental agents eteplirsen, BMN-195, or PRO051.
3. Previous treatment with any other experimental agents or participation in any other DMD interventional clinical study within 12 weeks before entry into this study; including use of the shock training system or "STS," or planned use during this study.
4. Surgery within 3 months before study entry or planned surgery at any time during this study.
5. Presence of other clinically significant illness at the time of study entry, including significant renal dysfunction (as measured by urinary cystatin C, KIM-1, or urinary total protein), or average heart rate during screening Holter monitoring in excess of 110 bpm (unless subsequently treated and confirmed controlled and stable on a β -blocker) or QTc >450 ms.
6. Use of any aminoglycoside antibiotic within 12 weeks before the screening visit (Visit 1) or need for use of an aminoglycoside antibiotic during the study (unless discussed and agreed with the Principal Investigator and Medical Monitor).
7. Prior or ongoing medical condition that, in the Investigator's opinion, could adversely affect the safety of the patient or that makes it unlikely that the course of treatment or follow-up would be completed or could impair the assessment of study results.

Inclusion Criteria Study 202

In order to be considered eligible, all of the following criteria must have been met:

1. The patient and/or their parent/legal guardian are willing and able to provide signed informed consent.
2. The patient has successfully completed 28 weeks of treatment in Study 4658-us-201.
3. The patient has a parent(s) or legal guardian(s) who is able to understand and comply with all of the study procedure requirements.

Exclusion Criteria Study 202

Patients who met any one of the following criteria were ineligible for participation in the study:

1. The patient has a prior or ongoing medical condition that, in the Investigator's opinion, could adversely affect the safety of the patient or make it unlikely that the course of treatment or follow-up would be completed or impair the assessment of study results.

APPENDIX 3. BASELINE CHARACTERISTICS OF STUDY 201/202 ETEPLIRSEN TREATED (N = 12) VS. EXTERNAL CONTROL COHORT (N = 13)

SOURCE	SUBJ.	Deleted Exon(s)	AGE (YRS)	HEIGHT (CM)	WEIGHT (KG)	6MWT (M)	NSAA (TOTAL SCORE)	STEROID, DOSE, & REGIMEN (Dose: mg or mg/kg†)		
Eteplirsen Study 201/202	2	48-50	9.03	117	24.8	416	28	DFZ	18	Continuous
	3	49-50	7.29	118	23.7	366	31	DFZ	18	Continuous
	4	45-50	8.79	117	27.4	389	27	DFZ	24	Continuous
	5	50	8.01	117	23.5	374	23	DFZ	21	Continuous
	6	52	10.53	131	35.1	355	17	DFZ	21	Continuous
	7	49-50	8.02	120	40.9	374	30	PRD	20	Continuous
	8	49-50	10.49	117	35	346	23	DFZ	22.5	Continuous
	9	45-50	9.79	138	39.8	330	21	PRD	25	Continuous
	10	45-50	9.79	136	39.7	256	17	PRD	25	Continuous
	12	49-50	10.95	133	38.3	351	27	PRD	75	Intermittent
	13	49-50	10.58	126	34.2	400	24	DFZ	22.5	Continuous
	15	52	9.6	117	26.8	401	31	DFZ	15	Continuous
	LNMRC	(b) (6) 50	11.8	UNK	UNK	327	UNK	DFZ or Equiv	UNK	Continuous
		52	11.5	UNK	UNK	451	UNK	DFZ or Equiv	UNK	Continuous
		45-50	8.6	UNK	UNK	355	UNK	DFZ or Equiv	UNK	Continuous
Italian Telethon	48-50	11.5	133	47	200	10	DFZ	0.8	Continuous	
	Ex 50	8.6	135	48	380	31	DFZ	0.9	Intermittent	
	52	9	130	28	373	24	PRD	0.75	Intermittent	
	45-50	8.83	136	42	329	24	DFZ	0.9	Continuous	
	49-50	9.3	131	44	295	15	DFZ	0.9	Intermittent	
	49-50	8	131	33	380	23	DFZ	0.8	Continuous	
	45-50	7.33	131	26	325	29	DLT	17.5	Continuous	
	52	10.2	126	27.1	458	25	DFZ	0.9	Continuous	
	48-50	10.1	133	31	388	20	PRD	0.75	Intermittent	
	49-50	8.1	127	39	388	19	PRD	0.75	Intermittent	

Abbreviations: DFZ = Deflazacort; PRD = Prednisone; DLT = Deltacortene; UNK = Unknown

Note in the table of baseline characteristics, rows for patients with loss of ambulation during 3 years of follow-up are shaded.

APPENDIX 4. LONGITUDINAL RESULTS FOR 6MWT, NSAA AND RISE TIME FOR ETEPLIRSEN TREATED (N = 12) VS. EXTERNAL CONTROL COHORT (N = 13)

Source	Subject	6MWT (m)				NSAA Total Score				Rise Time (sec)				
		0	1	2	3	0	1	2	3	0	1	2	3	
Eteplirsen Study 201/202	2	416	430	416	378	28	26	27	25	3.2	4.9	5.6	6.2	
	3	366	444	425	324	31	24	18	7	4.3	5.9	12.6	53.5	
	4	389	371	331	355	27	23	21	24	3.1	4.9	6.8	13.1	
	5	374	302	293	247	23	22	14	8	8.2	16.8	27.7	unable	
	6	355	326	346	359	17	16	19	13	12	13.4	10.9	17.9	
	7	374	304	354	312	30	20	20	13	4.6	6.8	8.8	10.1	
	8	346	303	255	100	23	21	17	13	4.9	5.8	6.6	8.9	
	9	330	0	0	0	21	5	2	np	6.3	24.9	unable	unable	
	10	256	0	0	0	17	4	1	1	12.7	unable	unable	unable	
	12	351	330	314	298	27	20	18	11	12	34	unable	unable	
	13	400	368	367	301	24	20	21	14	6	10.5	9.3	24.1	
	15	401	492	450	483	31	32	30	25	3.5	3.6	4.6	8.2	
	Italian Telethon	(b) (6)	200.0	210.0	0.0	0.0	10.0	8.0	4.0	0.0	unable	unable	unable	unable
			380.0	352.0	326.0	195.0	31.0	26.0	20.0	14.0	2.9	3.7	17.0	unable
			373.0	259.0	305.0	273.0	24.0	13.0	11.0	8.0	4.09	5.04	8.09	np
		329.0	298.0	230.0	218.0	24.0	22.0	13.0	12.0	7.1	7.2	ES	no data	
		295.0	307.0	153.0	35.0	15.0	13.0	12.0	9.0	6.2	no data	unable	unable	
		380.0	285.0	250.0	0.0	23.0	13.0	7.0	3.0	no data	no data	no data	no data	
		325.0	301.0	210.0	0.0	29.0	27.0	13.0	3.0	2.37	10.03	np	unable	
		458.0	495.0	435.0	362.0	25.0	26.0	25.0	22.0	5.66	5.21	4.31	8.47	
		388.0	317.0	0.0	0.0	20.0	18.0	4.0	0.0	no data	8.0	unable	unable	
		388.0	395.0	356.0	0.0	19.0	15.0	16.0	10.0	9.0	10.0	16.0	unable	
LNMRC		327	0	0	0	No Data								
		451	421	320	no data	No Data								
		355	375	no data	no data	No Data								

np=not performed; ES=external support required

APPENDIX 5. SENSITIVITY ANALYSIS FOR 6MWT ETEPLIRSEN-TREATED VS. EXTERNAL CONTROLS

Sensitivity Analyses to Control for Potential Group Imbalances in Important Baseline Prognostic Factors

The pre-specified primary ANCOVA analysis included Baseline 6MWT as a covariate to control for potential imbalances between the groups (treated vs. untreated) in Baseline 6MWT distance, an important prognostic factor for loss of ambulation. When age, another important predictor of 6MWT was added as a covariate to the same analysis, the difference between the eteplirsen-treated patients and untreated external controls remained clinically and statistically significant (Row 1).

Sensitivity Analyses to Account for Potential Violations of the Data's Normality Assumption

To address potential violations of Normality Assumption, the changes from Baseline in 6MWT distance for all patients ($N = 12 + 13 = 25$) were ranked 1 to 25. Then the rank scores, which are not affected by large changes in 6MWT scores, were analyzed using ANCOVA. Two ANCOVA models were performed, the first included Baseline 6MWT as a covariate (Row 2) and the second included both Baseline 6MWT and age as covariates (Row 3). For both analyses, the difference between the eteplirsen-treated patients and untreated external controls remained statistically significant.

Sensitivity Analyses for Missing Data

Two patients in the external control cohort ($N = 13$) entered interventional clinical trials and therefore did not contribute data through Year 3. To account for any potential bias caused by this approach, a series of Mixed Model Repeated Measures (MMRM) analyses were performed to control for potential bias caused by missing data at later time points. The MMRM analysis uses all available data (i.e., Years 1, 2, and 3) to estimate the data's correlation structure between time points, thereby reducing the impact of missing data without explicit imputation. Two MMRMs were performed. The first included both Baseline 6MWT and age as covariates (Row 4), and the second was an MMRM analysis of the rank-transformed data, with both Baseline 6MWT and age as covariates (Row 5). For both of these analyses, the difference between the eteplirsen treated patients and untreated external controls remained statistically significant.

Additionally, a series of sensitivity analyses were conducted in which the last observed value for the first patient at 12 months (375 meters) and for the second patient at 29 months (252 meters) was imputed as a 36 month result (last observation carried forward or LOCF). This is a highly conservative approach as neither patient would be expected to remain stable over this period of time given their respective ages at Baseline (8.6 years and 11.5 years respectively). Three different ANCOVAs were performed using LOCF for missing data. The first included Baseline 6MWT as a covariate (Row 6), the second included both Baseline 6MWT and age as covariates (Row 7), and the third was an ANCOVA of the rank transformed data, with both Baseline 6MWT and age as covariates (Row 8). Even with these most conservative analyses, the difference between the eteplirsen-treated and untreated external control patients remained statistically significant.

APPENDIX 6. SENSITIVITY ANALYSIS FOR 6MWT IN ETEPLIRSEN TREATED (N = 12) VS. EXTERNAL CONTROLS AMENABLE TO ANY EXON SKIPPING (N = 50)

Potential Issue Addressed	Row	Comparison: Change from Baseline in 6MWT in Eteplirsen-Treated (N = 12) vs. Untreated External Controls (N = 50)	LS Mean Difference (meters)	P-Value
Bias Caused by Imbalance in Important Baseline Prognostic Factors	1	ANCOVA with Baseline 6MWT and age as covariates	74	0.0845
Bias Caused by Violation of Normality Assumption	2	ANCOVA with Baseline as a covariate, rank transformation as the outcome for 6MWT	NA ^a	0.0464
	3	ANCOVA with Baseline and age as covariates, rank transformation as the outcome for 6MWT	NA ^a	0.0544
Bias Caused By Missing Data	4	MMRM analysis with Baseline and age as covariates	73	0.0448
	5	MMRM analysis with Baseline and age as covariates and rank transformation as the outcome for 6MWT	NA ^a	0.0595
	6	ANCOVA with Baseline as a covariate and LOCF for missing data	71	0.0954
	7	ANCOVA with Baseline and age as covariates and LOCF for missing data	68	0.1128
	8	ANCOVA with Baseline and age as covariates, LOCF for missing data, rank transformation as outcome for 6MWT	NA ^a	0.0811

Abbreviations: 6MWT=6 Minute Walk Test; ANCOVA=analysis of covariance; LOCF=last observation carried forward; LS=least squares; MMRM=Mixed Model Repeated Measures; NA=not applicable

^a Not applicable as the data being analysed are rank-transformed.

APPENDIX 7. BASELINE CHARACTERISTICS OF STUDY 201/202 ETEPLIRSEN TREATED VS EXTERNAL CONTROL WITH LOSS OF AMBULATION

SOURCE	SUBJ.	Deleted Exon(s)	AGE (YRS)	HEIGHT (CM)	WEIGHT (KG)	6MWT (M)	NSAA (Total Score)	Steroid, Dose †, Regimen		
Eteplirsen Study 201/202	9	45-50	9.79	138	39.8	330	21	PRD	25	Continuous
	10	45-50	9.79	136	39.7	256	17	PRD	25	Continuous
LNMR	(b) (6)	50	11.8	UNK	UNK	327	UNK	DFZ or Eq.	UNK	Continuous
Italian Telethon		48-50	11.5	133	47	200	10	DFZ	0.8	Continuous
		49-50	8	131	33	380	23	DFZ	0.8	Continuous
		45-50	7.33	131	26	325	29	DLT	17.5	Continuous
		48-50	10.1	133	31	388	20	PRD	0.75	Intermittent
		49-50	8.1	127	39	388	19	PRD	0.75	Intermittent

Abbreviations: DFZ = Deflazacort; PRD = Prednisone; DLT = Deltacortene.

† Dose unit for eteplirsen-treated: mg. Dose unit for DMD Italian Telethon in mg/kg except P13 who received doses of 17.5mg

APPENDIX 8. INDIVIDUAL ITEMS OF NSAA

1. Stand
 2. Walk
 3. Stand from chair
 4. Stand R leg
 5. Stand L leg
 6. Climb R leg
 7. Climb L leg
 8. Descend R leg
 9. Descend L leg
 10. Gets to sitting
 11. Rise from floor
 12. Lifts head
 13. Stands on heels
 14. Jump
 15. Hop R leg
 16. Hop L leg
 17. Run
- Total score

**APPENDIX 9. UNTREATED CONTROL MUSCLE BIOPSY SAMPLES
 USED IN WEEK 180 DYSTROPHIN ANALYSIS**

Sample ID	Age (age at biopsy years)	Anatomical Location	Dystrophin Mutation	Baseline 6MWT	Source
01005	7	Biceps	Δ50	357 m	Study 201
01008	10	Biceps	Δ49-50	341 m	
01013	10	Biceps	Δ45-50	418 m	
01015	9	Biceps	Δ52	401 m	
DMD #1	7	Deltoid	Δ45-50	425 m	Study 301
DMD #2	15	Biceps	Δ45-50	421 m	
DMD #3	9	Biceps	Δ48-50	352 m	
DMD #4	7	Biceps	Δ45-50	402 m	
DMD #5	10	Biceps	Δ50	538 m	
DMD #6	7	Biceps	Δ49-50	383 m	
DMD #7	9	Biceps	Δ49-50	441 m	
DMD #8	9	Biceps	Δ48-50	306 m	
DMD #9	9	Biceps	Δ52	371 m	

**APPENDIX 10. INDIVIDUAL PATIENT RESULTS FOR PERCENT
 DYSTROPHIN POSITIVE FIBERS (PDPF)**

Patient ID	Multi-rater PDPF %	
	Week 180	Baseline ¹
01002	4.54	--
01003	1.42	--
01004	28.2	--
01006	20.72	--
01007	7.08	--
01008	12.75	1.09
01009	21.48	--
01010	23.96	--
01012	33.5	--
01013	19.14	2.58
01015	18.48	0.19

¹ Baseline muscle biopsy tissue was not available for most patients. For patients where it was available, baseline analysis was performed on the archived tissue using updated methodology coincident with Week 180 analysis.

Patient ID	Multi-rater PDPF % Untreated
DMD1	0.15
DMD2	0.29
DMD3	3.95
DMD4	0.39
DMD5	0.36
DMD6	1.11

APPENDIX 11. INDIVIDUAL PATIENT RESULTS FOR DYSTROPHIN FIBER INTENSITY

Patient ID	Fiber Intensity %	
	Week 180	Baseline ¹
01003	7.0	--
01004	28.8	--
01006	28.7	--
01007	12.0	--
01008	26.7	11.6
01009	23.0	--
01010	21.4	--
01012	26.1	--
01013	32.5	16.3
01015	30.7	7.4

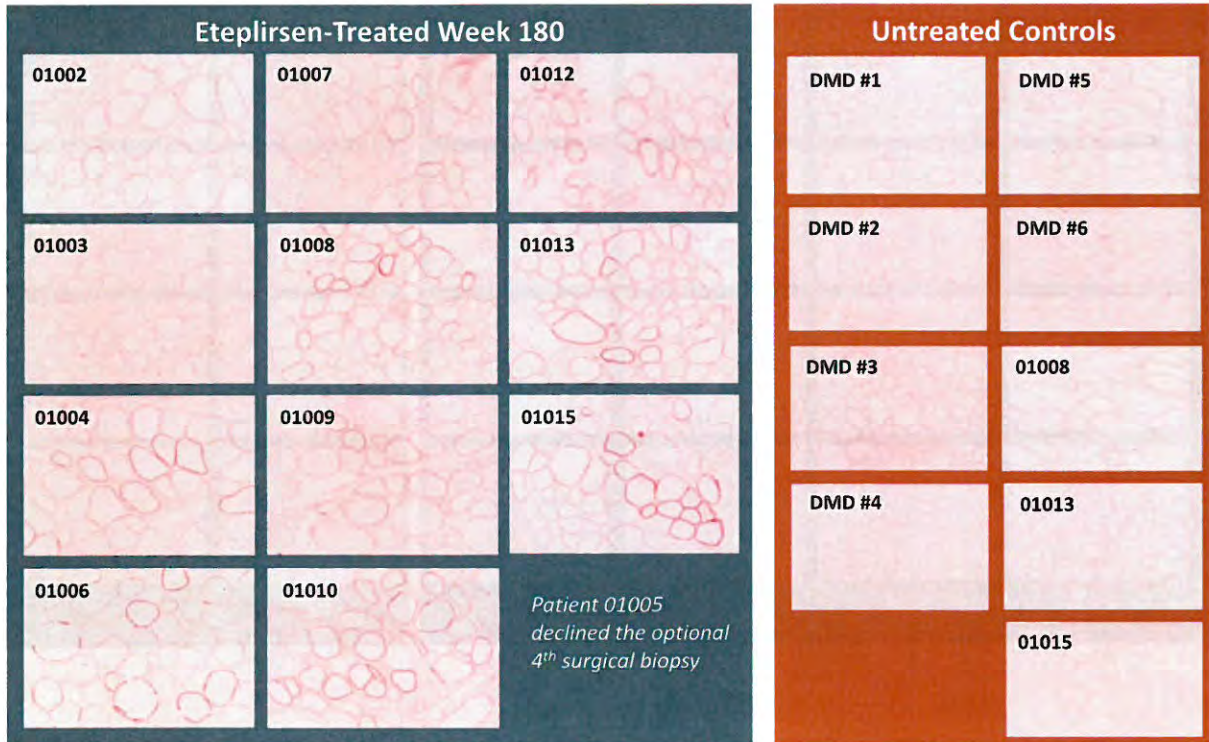
¹ Baseline muscle biopsy tissue was not available for most patients. For patients where it was available, baseline analysis was performed on the archived tissue using updated methodology coincident with Week 180 analysis.

Patient ID	Fiber Intensity % Untreated
DMD1	9.9
DMD2	6.1
DMD3	9.2
DMD4	3.5
DMD5	17.6
DMD6	3.1

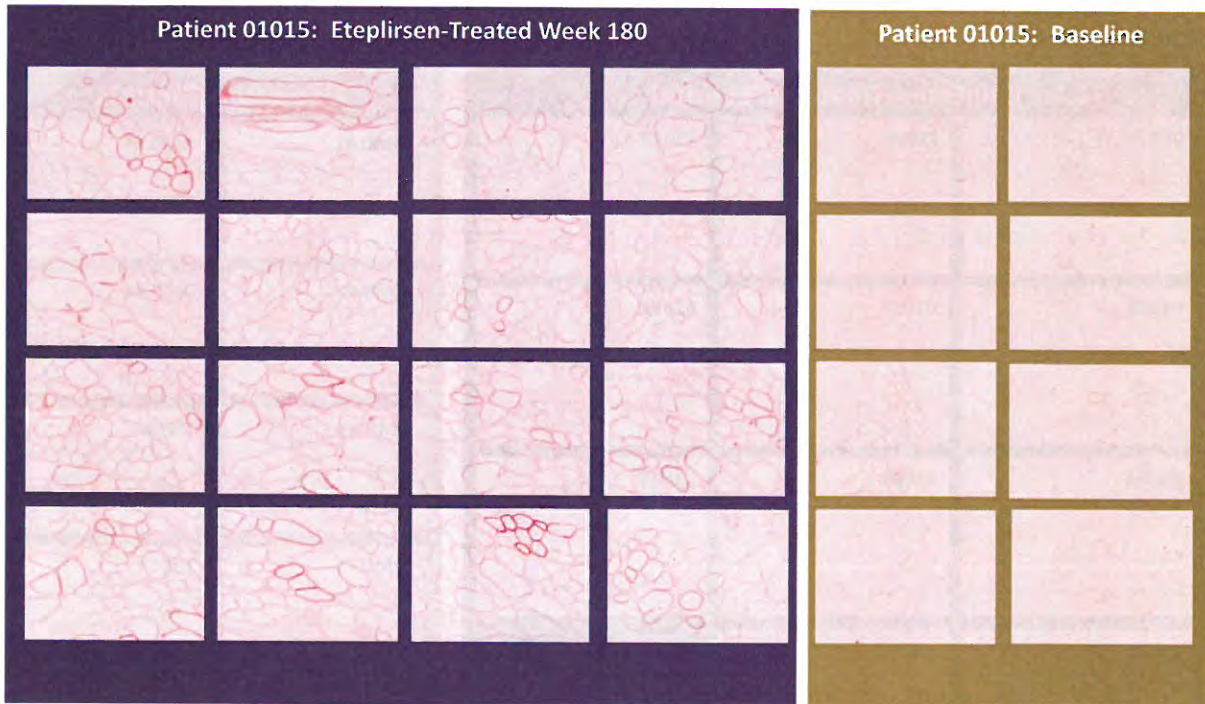
APPENDIX 12. DIGITAL MICROSCOPY IMAGES FOR ASSESSMENT OF PERCENT POSITIVE DYSTROPHIN FIBERS

Muscle biopsy cryosections were immunostained with monoclonal antibody MANDYS106 by indirect immunofluorescence. Fluorescence microscope digital images were captured at 20X magnification. To more clearly display relative intensity of fibers, the contrast was inverted from original fluorescence images to display a pseudo-bright field image.

One image per patient is shown and for comparison, one image per DMD untreated control sample.



All 16 images are shown that were analyzed for patient 01015 for muscle biopsy sample at Week 180 and at Baseline. Systematic random sampling of image fields for each stained tissue section was used to capture four 20X images per tissue section. Tissue was sectioned at 2 levels from each of 2 distinct muscle biopsy samples, resulting in a total of 16 images per patient at Week 180 (4 images, 2 tissue levels, 2 biopsy samples) and 8 images at baseline (4 images, 2 tissue levels, 1 biopsy sample).



APPENDIX 13. INDIVIDUAL PATIENT RESULTS FOR WESTERN BLOT

Patient ID	Western blot %	
	Week 180	Baseline ¹
01002	0.14 ⁴	--
01003	0 (BLOQ)	--
01004	0.96	--
01005	n.a. ²	0 (BLOQ) ³
01006	2.47	--
01007	0 (BLOQ)	--
01008	0.98	--
01009	0.52	--
01010	1.62	--
01012	0.38	--
01013	1.15	0 (BLOQ)
01015	2.05	0 (BLOQ)

Abbreviations: BLOQ = Below Limit of Quantification

¹ Baseline muscle biopsy tissue was not available for most patients. For patients where it was available, baseline analysis was performed on the archived tissue using updated methodology coincident with Week 180 analysis.

² Patient 01005 did not consent for fourth biopsy.

³ Baseline muscle biopsy tissue from patient 01005 was used in Western blot assays as there was not sufficient tissue remaining from patient 01008.

⁴ One of two replicate gels was above BLOQ of 0.25% while the other was below and treated as zero. The average of two gels is reported.

Patient ID	Western blot % Untreated
DMD1	0 (BLOQ)
DMD2	0 (BLOQ)
DMD3	0.37
DMD7 ¹	0.15 ²
DMD8 ¹	0 (BLOQ)
DMD9 ¹	0.20 ²

¹ Control DMD muscle biopsy tissue from DMD7, DMD8, DMD9 were used in Western blot assays as there was not sufficient tissue remaining from DMD4, DMD5, DMD6.

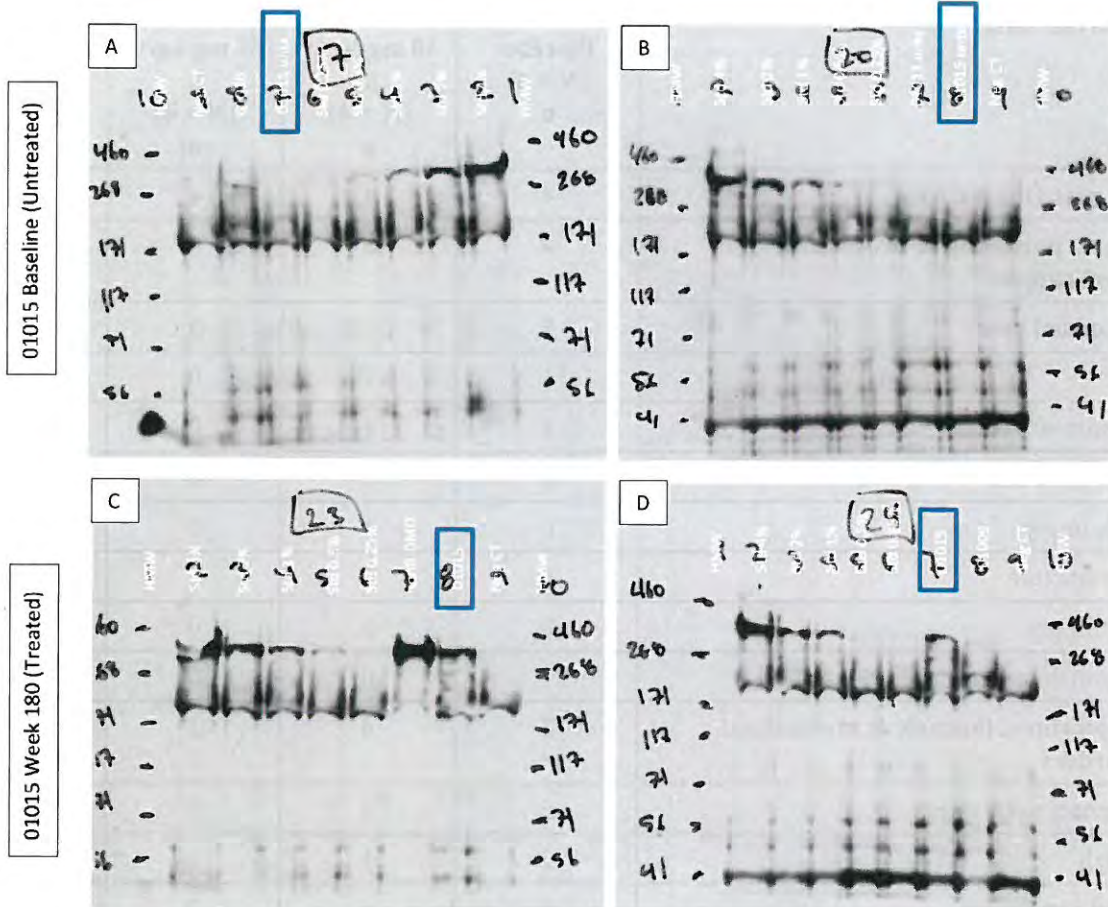
² One of two replicate gels was above BLOQ of 0.25% while the other gel was below and treated as zero. The average of two gels is reported.

APPENDIX 14. WESTERN BLOT ACCEPTANCE STANDARDS AND REPRESENTATIVE GEL IMAGES

All samples analyzed in the 4th biopsy by Western blot were run in duplicate on separate gels. NCL-DYS1 anti-dystrophin antibody was used to stain for dystrophin. A validated, sensitive method for Western blot was established with pass/fail criteria for each gel:

- 5-point standard curve (0.25 %-4 % of normal) included on every gel
 - Normal control muscle lysate spiked in DMD muscle lysate to control for equal muscle protein load in each lane
 - Lower limit of quantitation is 0.25 % of normal muscle
 - Pass criteria of $R^2 > 0.90$ to ensure standard curve linearity on each gel
- Negative control included on every gel
 - DMD muscle lysate used for standard curve (without normal control muscle lysate)
 - False positive reads prevented by setting gel pass criteria for negative lane density of < 0.25 % lane density to control
- Samples run blinded in duplicate on separate gels
- Alpha-actinin (muscle-specific protein expressed equally in DMD and non-DMD muscle tissue) used as control for equal protein load
 - Equal lane to lane protein load confirmed by pass criteria of $RSD < 50$ % of average actinin density for all lanes

Western Blot Images of 4 Separate Gels Illustrating Dystrophin Absence in Pretreatment Muscle of Patient 01015 (A Lane 7 + B Lane 8) and De Novo Dystrophin Protein Production After Eteplirsen Treatment at Week 180 in Tissue From the Same Patient 01015 (C Lane 8 + D Lane 7)



All gel images depicted here were obtained with a 30 minute exposure. All lanes (excluding high molecular weight lanes) were loaded with a consistent 50 μ g total protein load. Alpha-actinin, a muscle specific protein expressed equally in DMD and non-DMD muscle tissue, was used as a loading control to ensure equal protein load (not depicted here).

APPENDIX 15. ALL TREATMENT-EMERGENT ADVERSE EVENTS DURING THE 24-WEEK PLACEBO CONTROL PERIOD OF STUDY 201

System Organ Classification Preferred Term	Eteplirsen			
	Placebo (N = 4) n	30 mg/kg/wk (N = 4) n	50 mg/kg/wk (N = 4) n	All Eteplirsen (N = 8) n
At Least One TEAE	4	4	4	8
Injury, poisoning & procedural complications	4	3	4	7
Procedural pain	3	1	3	4
Fall	1	1	0	1
Incision site pain	1	1	0	1
Arthropod bite	0	1	0	1
Back injury	0	1	0	1
Foot fracture	0	0	1	1
Joint injury	0	1	0	1
Wound dehiscence	1	0	0	0
Respiratory, thoracic & mediastinal disorders	3	4	1	5
Oropharyngeal pain	3	3	0	3
Cough	2	1	1	2
Nasal congestion	2	1	0	1
Sinus congestion	0	1	0	1
Upper respiratory tract congestion	0	1	0	1
Musculoskeletal & connective tissue disorders	3	2	2	4
Pain in extremity	3	0	1	1
Back pain	2	1	0	1
Arthralgia	0	0	1	1
Bone pain	0	1	0	1
Muscle spasms	0	0	1	1
Musculoskeletal pain	0	1	0	1
Nervous system disorders	2	3	2	5

System Organ Classification Preferred Term	Eteplirsen			
	Placebo (N = 4) n	30 mg/kg/w k (N = 4) n	50 mg/kg/w k (N = 4) n	All Eteplirsen (N = 8) n
At Least One TEAE	4	4	4	8
Balance disorder	0	1	2	3
Headache	2	1	0	1
Dizziness	1	0	0	0
Somnolence	0	1	0	1
General disorders and administration site conditions	2	2	2	4
Pyrexia	2	1	0	1
Injection site pain	0	0	1	1
Malaise	0	0	1	1
Non-cardiac chest pain	0	1	0	1
Pain	0	0	1	1
Metabolism & nutrition disorders	2	2	2	4
Hypokalaemia	2	2	2	4
Gastrointestinal disorders	2	1	2	3
Vomiting	0	1	2	3
Abdominal pain	2	0	0	0
Diarrhoea	1	0	1	1
Nausea	1	0	1	1
Infections & infestations	3	0	1	1
Rhinitis	1	0	1	1
Enterobiasis	1	0	0	0
Nasopharyngitis	1	0	0	0
Soft tissue infection	1	0	0	0
Vascular disorders	1	1	1	2
Haematoma	1	1	1	2
Renal & urinary disorders	1	1	0	1
Polyuria	0	1	0	1
Proteinuria	1	0	0	0

System Organ Classification Preferred Term	Eteplirsen			
	Placebo (N = 4) n	30 mg/kg/w k (N = 4) n	50 mg/kg/w k (N = 4) n	All Eteplirsen (N = 8) n
At Least One TEAE	4	4	4	8
Skin & subcutaneous tissue disorders	0	2	0	2
Dermatitis contact	0	2	0	2
Petechiae	0	1	0	1
Urticaria thermal	0	1	0	1
Cardiac disorders	0	1	0	1
Tachycardia	0	1	0	1
Ear & labyrinth disorders	0	0	1	1
Motion sickness	0	0	1	1

Note: AEs are coded using MedDRA v14.0. AEs were attributed to the treatment being received at start of AE. TEAEs are those starting during or after the first infusion of study drug. Patients who experience a coded event more than once are only counted once per treatment received.

APPENDIX 16. TREATMENT-EMERGENT ADVERSE EVENTS DURING THE ETEPLIRSEN CLINICAL DEVELOPMENT PROGRAM

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Number of Subjects With a TEAE	4 (100%)	9 (60.0%)	5 (71.4%)	11 (100%)	4 (100%)	4 (100%)	63 (76.8%)	6 (100%)	88 (82.2%)	93 (81.6%)
Injury, poisoning and procedural complications	4 (100%)	3 (20.0%)	0	9 (81.8%)	1 (25.0%)	1 (25.0%)	33 (40.2%)	6 (100%)	50 (46.7%)	50 (43.9%)
Procedural pain	3 (75.0%)	0	0	2 (18.2%)	0	0	8 (9.8%)	6 (100%)	16 (15.0%)	16 (14.0%)
Contusion	0	0	0	1 (9.1%)	0	0	10 (12.2%)	3 (50.0%)	14 (13.1%)	14 (12.3%)
Excoriation	0	0	0	0	0	1 (25.0%)	11 (13.4%)	2 (33.3%)	14 (13.1%)	14 (12.3%)
Fall	1 (25.0%)	0	0	4 (36.4%)	0	0	7 (8.5%)	0	11 (10.3%)	11 (9.6%)
Arthropod bite	0	0	0	1 (9.1%)	0	0	5 (6.1%)	1 (16.7%)	7 (6.5%)	7 (6.1%)
Incision site haemorrhage	0	0	0	0	0	0	3 (3.7%)	1 (16.7%)	4 (3.7%)	4 (3.5%)
Joint injury	0	0	0	0	0	0	3 (3.7%)	1 (16.7%)	4 (3.7%)	4 (3.5%)
Joint sprain	0	1 (6.7%)	0	0	0	0	1 (1.2%)	3 (50.0%)	4 (3.7%)	4 (3.5%)
Foot fracture	0	0	0	0	0	0	2 (2.4%)	1 (16.7%)	3 (2.8%)	3 (2.6%)
Head injury	0	0	0	1 (9.1%)	0	0	1 (1.2%)	1 (16.7%)	3 (2.8%)	3 (2.6%)
Muscle strain	0	0	0	0	0	0	1 (1.2%)	2 (33.3%)	3 (2.8%)	3 (2.6%)
Post procedural haematoma	0	0	0	1 (9.1%)	0	0	1 (1.2%)	1 (16.7%)	3 (2.8%)	3 (2.6%)
Arthropod sting	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Limb injury	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Scratch	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Thermal burn	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Accident	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Ankle fracture	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Back injury	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Burns first degree	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Femur fracture	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Hand fracture	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Heat stroke	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Incision site erythema	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Incision site pain	1 (25.0%)	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Incision site pruritus	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Infusion related reaction	0	0	0	0	1 (25.0%)	0	0	0	1 (0.9%)	1 (0.9%)
Laceration	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Ligament sprain	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Lip injury	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Lower limb fracture	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Nail injury	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Radius fracture	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Skeletal injury	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Soft tissue injury	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Spinal compression fracture	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Sunburn	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Tooth fracture	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Wound dehiscence	1 (25.0%)	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Tooth avulsion	0	1 (6.7%)	0	0	0	0	0	0	0	0
Torus fracture	0	1 (6.7%)	0	0	0	0	0	0	0	0
Gastrointestinal disorders	1 (25.0%)	2 (13.3%)	0	8 (72.7%)	1 (25.0%)	2 (50.0%)	27 (32.9%)	5 (83.3%)	43 (40.2%)	43 (37.7%)
Vomiting	0	0	0	2 (18.2%)	1 (25.0%)	0	18 (22.0%)	3 (50.0%)	24 (22.4%)	24 (21.1%)
Nausea	1 (25.0%)	0	0	2 (18.2%)	0	1 (25.0%)	4 (4.9%)	2 (33.3%)	9 (8.4%)	9 (7.9%)
Abdominal pain upper	0	1 (6.7%)	0	2 (18.2%)	0	0	3 (3.7%)	3 (50.0%)	8 (7.5%)	8 (7.0%)
Abdominal pain	1 (25.0%)	0	0	2 (18.2%)	0	0	3 (3.7%)	2 (33.3%)	7 (6.5%)	7 (6.1%)
Diarrhoea	0	1 (6.7%)	0	1 (9.1%)	0	0	4 (4.9%)	2 (33.3%)	7 (6.5%)	7 (6.1%)
Dyspepsia	0	0	0	0	0	0	3 (3.7%)	1 (16.7%)	4 (3.7%)	4 (3.5%)
Constipation	0	0	0	1 (9.1%)	0	0	0	2 (33.3%)	3 (2.8%)	3 (2.6%)
Abdominal discomfort	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Haematochezia	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Abdominal distension	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Dental caries	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Dysphagia	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Flatulence	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Food poisoning	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Haemorrhoids	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Lip dry	0	0	0	0	0	1 (25.0%)	0	0	1 (0.9%)	1 (0.9%)
Lip swelling	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Oral pain	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Retained deciduous tooth	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Tooth impacted	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Toothache	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Musculoskeletal and connective tissue disorders	3 (75.0%)	2 (13.3%)	0	8 (72.7%)	1 (25.0%)	0	28 (34.1%)	6 (100%)	43 (40.2%)	43 (37.7%)
Back pain	2 (50.0%)	0	0	3 (27.3%)	1 (25.0%)	0	17 (20.7%)	3 (50.0%)	24 (22.4%)	24 (21.1%)
Pain in extremity	3 (75.0%)	0	0	2 (18.2%)	1 (25.0%)	0	10 (12.2%)	4 (66.7%)	17 (15.9%)	17 (14.9%)
Arthralgia	0	0	0	3 (27.3%)	0	0	8 (9.8%)	3 (50.0%)	14 (13.1%)	14 (12.3%)
Muscle spasms	0	0	0	0	0	0	3 (3.7%)	2 (33.3%)	5 (4.7%)	5 (4.4%)
Myalgia	0	0	0	1 (9.1%)	0	0	2 (2.4%)	2 (33.3%)	5 (4.7%)	5 (4.4%)
Musculoskeletal pain	0	0	0	0	0	0	3 (3.7%)	1 (16.7%)	4 (3.7%)	4 (3.5%)
Muscular weakness	0	2 (13.3%)	0	0	0	0	1 (1.2%)	2 (33.3%)	3 (2.8%)	3 (2.6%)
Coccydynia	0	0	0	1 (9.1%)	0	0	1 (1.2%)	0	2 (1.9%)	2 (1.8%)
Neck pain	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Tendonitis	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Bone pain	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Groin pain	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Joint swelling	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Osteopenia	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Scoliosis	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Tendinous contracture	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Tendon disorder	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
General Disorders and Administration Site Conditions	2 (50.0%)	0	2 (28.6%)	3 (27.3%)	2 (50.0%)	2 (50.0%)	23 (28.0%)	5 (83.3%)	35 (32.7%)	37 (32.5%)
Catheter site pain	0	0	0	0	1 (25.0%)	0	7 (8.5%)	2 (33.3%)	10 (9.3%)	10 (8.8%)
Infusion site haematoma	0	0	0	0	0	0	6 (7.3%)	1 (16.7%)	7 (6.5%)	7 (6.1%)
Fatigue	0	0	0	1 (9.1%)	1 (25.0%)	0	4 (4.9%)	0	6 (5.6%)	6 (5.3%)
Catheter site haematoma	0	0	0	2 (18.2%)	0	0	1 (1.2%)	1 (16.7%)	4 (3.7%)	4 (3.5%)
Infusion site extravasation	0	0	0	0	0	0	2 (2.4%)	2 (33.3%)	4 (3.7%)	4 (3.5%)
Pyrexia	2 (50.0%)	0	0	0	0	0	2 (2.4%)	2 (33.3%)	4 (3.7%)	4 (3.5%)
Influenza like illness	0	0	0	1 (9.1%)	1 (25.0%)	0	1 (1.2%)	0	3 (2.8%)	3 (2.6%)
Infusion site pain	0	0	0	0	0	0	2 (2.4%)	1 (16.7%)	3 (2.8%)	3 (2.6%)
Thrombosis in device	0	0	0	0	0	0	3 (3.7%)	0	3 (2.8%)	3 (2.6%)
Chest pain	0	0	0	1 (9.1%)	0	0	1 (1.2%)	0	2 (1.9%)	2 (1.8%)
Device occlusion	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Disease progression	0	0	0	0	1 (25.0%)	1 (25.0%)	0	0	2 (1.9%)	2 (1.8%)
Injection site pain	0	0	1 (14.3%)	0	0	0	0	1 (16.7%)	1 (0.9%)	2 (1.8%)
Non-cardiac chest pain	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Oedema peripheral	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Application site erythema	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Application site rash	0	0	0	0	0	1 (25.0%)	0	0	1 (0.9%)	1 (0.9%)
Catheter site haemorrhage	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Catheter site inflammation	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Catheter site related reaction	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Feeling hot	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Gait disturbance	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Infusion site rash	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Infusion site swelling	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Injection site haematoma	0	0	1 (14.3%)	0	0	0	0	0	0	1 (0.9%)
Irritability	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Malaise	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Pain	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Swelling	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Vaccination site pain	0	0	0	0	0	1 (25.0%)	0	0	1 (0.9%)	1 (0.9%)
Infections and infestations	3 (75.0%)	2 (13.3%)	0	5 (45.5%)	4 (100%)	2 (50.0%)	19 (23.2%)	6 (100%)	36 (33.6%)	36 (31.6%)
Upper respiratory tract infection	0	0	0	3 (27.3%)	2 (50.0%)	1 (25.0%)	5 (6.1%)	4 (66.7%)	15 (14.0%)	15 (13.2%)
Nasopharyngitis	1 (25.0%)	0	0	0	0	0	10 (12.2%)	4 (66.7%)	14 (13.1%)	14 (12.3%)
Rhinitis	1 (25.0%)	0	0	1 (9.1%)	3 (75.0%)	1 (25.0%)	0	1 (16.7%)	6 (5.6%)	6 (5.3%)
Ear infection	0	0	0	0	0	0	3 (3.7%)	0	3 (2.8%)	3 (2.6%)
Gastroenteritis viral	0	0	0	0	0	0	2 (2.4%)	1 (16.7%)	3 (2.8%)	3 (2.6%)
Hordeolum	0	0	0	1 (9.1%)	0	0	0	2 (33.3%)	3 (2.8%)	3 (2.6%)
Viral infection	0	0	0	1 (9.1%)	0	0	1 (1.2%)	1 (16.7%)	3 (2.8%)	3 (2.6%)
Gastroenteritis	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Influenza	0	0	0	0	0	0	0	2 (33.3%)	2 (1.9%)	2 (1.8%)
Pharyngitis streptococcal	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Post procedural cellulitis	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Body tinea	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Bronchitis	0	0	0	0	1 (25.0%)	0	0	0	1 (0.9%)	1 (0.9%)
Candidiasis	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Folliculitis	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Furuncle	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Incision site infection	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Sinusitis	0	1 (6.7%)	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Skin infection	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Tinea infection	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Tinea pedis	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Tooth abscess	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Tooth infection	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Viral upper respiratory tract infection	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Enterobiasis	1 (25.0%)	0	0	0	0	0	0	0	0	0
Lymphadenitis viral	0	1 (6.7%)	0	0	0	0	0	0	0	0
Otitis media	0	1 (6.7%)	0	0	0	0	0	0	0	0
Soft tissue infection	1 (25.0%)	0	0	0	0	0	0	0	0	0
Nervous system disorders	2 (50.0%)	1 (6.7%)	0	6 (54.5%)	2 (50.0%)	2 (50.0%)	20 (24.4%)	6 (100%)	36 (33.6%)	36 (31.6%)
Headache	2 (50.0%)	1 (6.7%)	0	5 (45.5%)	2 (50.0%)	1 (25.0%)	14 (17.1%)	5 (83.3%)	27 (25.2%)	27 (23.7%)
Dizziness	1 (25.0%)	0	0	2 (18.2%)	0	1 (25.0%)	3 (3.7%)	0	6 (5.6%)	6 (5.3%)
Balance disorder	0	0	0	0	0	0	2 (2.4%)	3 (50.0%)	5 (4.7%)	5 (4.4%)
Paraesthesia	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)

System Organ Classification Preferred Term	Eteplirsen									
	Placebo (N = 4)	Untreated (N = 15)	0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Psychomotor hyperactivity	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Somnolence	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	3 (75.0%)	1 (6.7%)	0	2 (18.2%)	0	0	28 (34.1%)	6 (100%)	36 (33.6%)	36 (31.6%)
Cough	2 (50.0%)	0	0	2 (18.2%)	0	0	12 (14.6%)	4 (66.7%)	18 (16.8%)	18 (15.8%)
Oropharyngeal pain	3 (75.0%)	0	0	0	0	0	10 (12.2%)	4 (66.7%)	14 (13.1%)	14 (12.3%)
Nasal congestion	1 (25.0%)	0	0	0	0	0	11 (13.4%)	2 (33.3%)	13 (12.1%)	13 (11.4%)
Rhinorrhoea	0	0	0	0	0	0	5 (6.1%)	2 (33.3%)	7 (6.5%)	7 (6.1%)
Epistaxis	0	0	0	0	0	0	4 (4.9%)	1 (16.7%)	5 (4.7%)	5 (4.4%)
Pharyngeal erythema	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Upper respiratory tract congestion	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Productive cough	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Respiratory disorder	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Sinus congestion	0	1 (6.7%)	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Sneezing	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Upper-airway cough syndrome	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Skin and Subcutaneous Tissue Disorders	0	1 (6.7%)	0	1 (9.1%)	0	1 (25.0%)	20 (24.4%)	5 (83.3%)	27 (25.2%)	27 (23.7%)
Rash	0	1 (6.7%)	0	0	0	0	9 (11.0%)	1 (16.7%)	10 (9.3%)	10 (8.8%)
Dermatitis contact	0	0	0	0	0	0	3 (3.7%)	1 (16.7%)	4 (3.7%)	4 (3.5%)
Ecchymosis	0	0	0	0	0	0	3 (3.7%)	1 (16.7%)	4 (3.7%)	4 (3.5%)

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Erythema	0	0	0	0	0	0	2 (2.4%)	1 (16.7%)	3 (2.8%)	3 (2.6%)
Papule	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Pruritus	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Rash papular	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Acne	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Alopecia	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Dermatitis bullous	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Drug eruption	0	0	0	0	0	1 (25.0%)	0	0	1 (0.9%)	1 (0.9%)
Ingrowing nail	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Intertrigo	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Keloid scar	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Nail discolouration	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Nail dystrophy	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Petechiae	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Rash pruritic	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Skin erosion	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Skin hyperpigmentation	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Skin irritation	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Urticaria	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Urticaria thermal	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Investigations	0	1 (6.7%)	0	0	0	0	12 (14.6%)	6 (100%)	18 (16.8%)	18 (15.8%)
Activated partial thromboplastin time prolonged	0	0	0	0	0	0	2 (2.4%)	3 (50.0%)	5 (4.7%)	5 (4.4%)

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
C-reactive protein increased	0	0	0	0	0	0	3 (3.7%)	2 (33.3%)	5 (4.7%)	5 (4.4%)
Blood creatine phosphokinase increased	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Blood glucose increased	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Body height below normal	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Protein urine present	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Blood amylase increased	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Blood creatinine increased	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Blood urea increased	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Blood urine present	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Breath sounds abnormal	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Lymphocyte count decreased	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Neutrophil count increased	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Red blood cells urine positive	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Urine analysis abnormal	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Urine ketone body present	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
White blood cell count decreased	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Wound healing normal	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Influenza A virus test positive	0	1 (6.7%)	0	0	0	0	0	0	0	0
Renal and Urinary Disorders	1 (25.0%)	0	3 (42.9%)	0	0	1 (25.0%)	7 (8.5%)	4 (66.7%)	12 (11.2%)	15 (13.2%)

System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Proteinuria	1 (25.0%)	0	0	0	0	0	5 (6.1%)	4 (66.7%)	9 (8.4%)	9 (7.9%)
Myoglobinuria	0	0	3 (42.9%)	0	0	0	0	0	0	3 (2.6%)
Chromaturia	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Crystalluria	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Enuresis	0	0	0	0	0	1 (25.0%)	0	0	1 (0.9%)	1 (0.9%)
Glycosuria	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Hypercalciuria	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Polyuria	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Urine odour abnormal	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Metabolism and Nutrition Disorders	2 (50.0%)	0	0	1 (9.1%)	0	0	7 (8.5%)	3 (50.0%)	11 (10.3%)	11 (9.6%)
Decreased appetite	0	0	0	1 (9.1%)	0	0	3 (3.7%)	0	4 (3.7%)	4 (3.5%)
Hypokalaemia	2 (50.0%)	0	0	0	0	0	2 (2.4%)	2 (33.3%)	4 (3.7%)	4 (3.5%)
Dehydration	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Obesity	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Vitamin D deficiency	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Psychiatric Disorders	0	0	0	0	0	0	10 (12.2%)	1 (16.7%)	11 (10.3%)	11 (9.6%)
Aggression	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Anxiety	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Insomnia	0	0	0	0	0	0	1 (1.2%)	1 (16.7%)	2 (1.9%)	2 (1.8%)
Antisocial behaviour	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Anxiety disorder	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Bruxism	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)

System Organ Classification Preferred Term	Eteplirsen									
	Placebo (N = 4)	Untreated (N = 15)	0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Euphoric mood	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Mood altered	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Sleep disorder	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Vascular Disorders	1 (25.0%)	0	0	2 (18.2%)	0	1 (25.0%)	4 (4.9%)	1 (16.7%)	8 (7.5%)	8 (7.0%)
Haematoma	1 (25.0%)	0	0	1 (9.1%)	0	1 (25.0%)	1 (1.2%)	1 (16.7%)	4 (3.7%)	4 (3.5%)
Flushing	0	0	0	0	0	0	3 (3.7%)	0	3 (2.8%)	3 (2.6%)
Pallor	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Cardiac Disorders	0	0	1 (14.3%)	1 (9.1%)	0	2 (50.0%)	2 (2.4%)	0	5 (4.7%)	6 (5.3%)
Tachycardia	0	0	0	1 (9.1%)	0	2 (50.0%)	1 (1.2%)	0	4 (3.7%)	4 (3.5%)
Cardiomyopathy	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Congestive cardiomyopathy	0	0	1 (14.3%)	0	0	0	0	0	0	1 (0.9%)
Pericardial fibrosis	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Sinus tachycardia	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Ear and Labyrinth Disorders	0	0	0	1 (9.1%)	0	0	1 (1.2%)	2 (33.3%)	4 (3.7%)	4 (3.5%)
Cerumen impaction	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Ear pain	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Motion sickness	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Tympanic membrane disorder	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Eye Disorders	0	0	0	0	0	0	1 (1.2%)	2 (33.3%)	3 (2.8%)	3 (2.6%)
Cataract	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Cataract subcapsular	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Conjunctivitis	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)

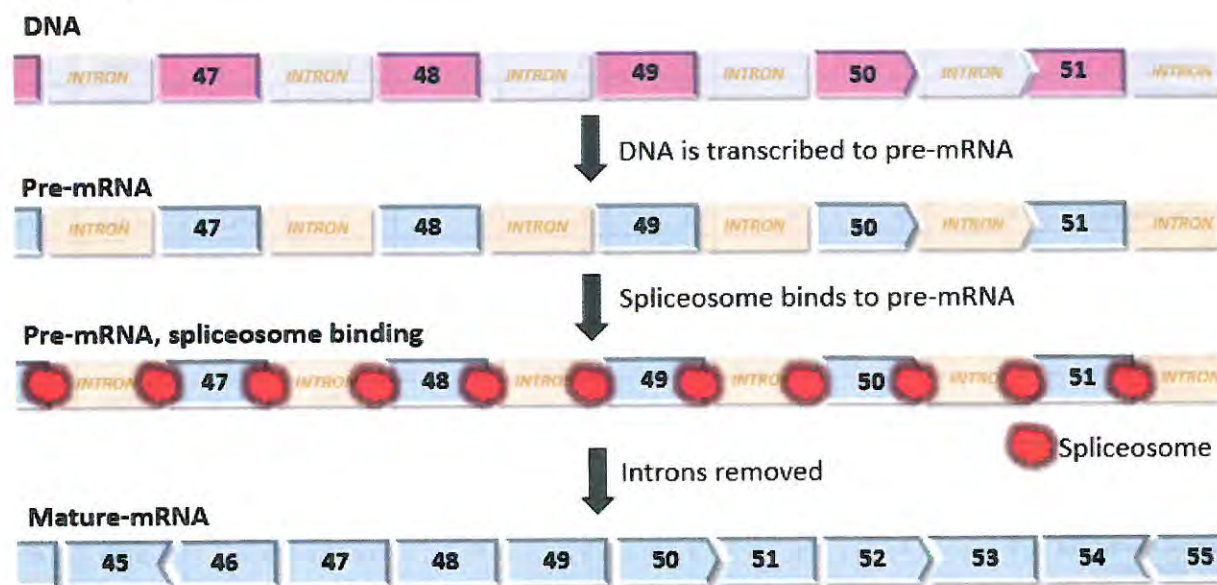
System Organ Classification Preferred Term	Placebo (N = 4)	Untreated (N = 15)	Eteplirsen							
			0.09 & 0.9 mg IM (N = 7)	≤4 mg/kg IV (N = 11)	10 mg/kg IV (N = 4)	20 mg/kg IV (N = 4)	30 mg/kg IV (N = 82)	50 mg/kg IV (N = 6)	All IV (N = 107)	All Eteplirsen (N = 114)
Erythema of eyelid	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Hypermetropia	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Immune System Disorders	0	0	0	0	0	0	2 (2.4%)	1 (16.7%)	3 (2.8%)	3 (2.6%)
Seasonal allergy	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Hypersensitivity	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Endocrine Disorders	0	0	0	0	0	0	0	2 (33.3%)	2 (1.9%)	2 (1.8%)
Goitre	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Growth hormone deficiency	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Reproductive System and Breast Disorders	0	0	0	0	0	0	2 (2.4%)	0	2 (1.9%)	2 (1.8%)
Pelvic pain	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Testicular pain	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Blood and Lymphatic System Disorders	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Platelet anisocytosis	0	0	0	1 (9.1%)	0	0	0	0	1 (0.9%)	1 (0.9%)
Congenital, Familial, and Genetic Disorders	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Cryptorchism	0	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)	1 (0.9%)
Neoplasms Benign, Malignant, and Unspecified (Incl. Cysts and Polyps)	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)
Skin papilloma	0	0	0	0	0	0	0	1 (16.7%)	1 (0.9%)	1 (0.9%)

APPENDIX 17. DMD, EXON SKIPPING AND ETEPLIRSEN MECHANISM OF ACTION

Central Dogma of Molecular Biology, Introns & Exons

Watson and Crick's proposed use of DNA by the cell, that is DNA is transcribed into RNA and then RNA is translated into protein, has been further elucidated to include the removal of introns from RNA prior to translation into protein. DNA and the pre-mRNA that is a direct copy of DNA contain both introns and exons. As shown in Figure A, the introns are removed from the pre-mRNA by protein complexes called spliceosomes to create the final, mature mRNA that is translated by the ribosome into protein.

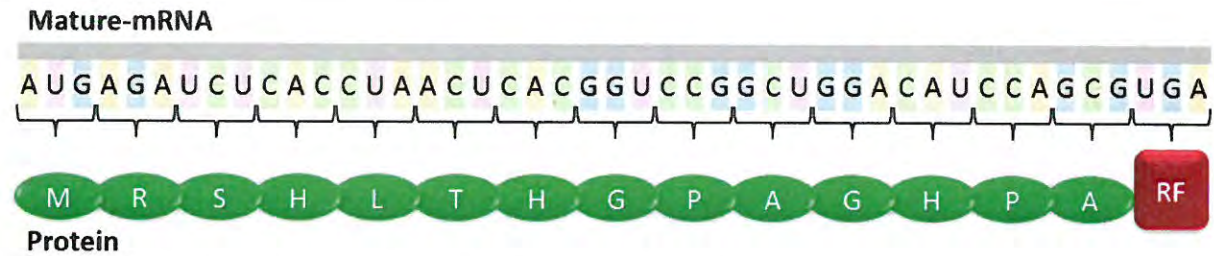
Figure A:



Translation

The ribosome translates mRNA into protein by reading the mRNA three nucleotides, or one codon, at a time. Each 3 nucleotide containing codon codes for a specific amino acid. Figure B, depicts a short mRNA sequence and its corresponding protein sequence.

Figure B:

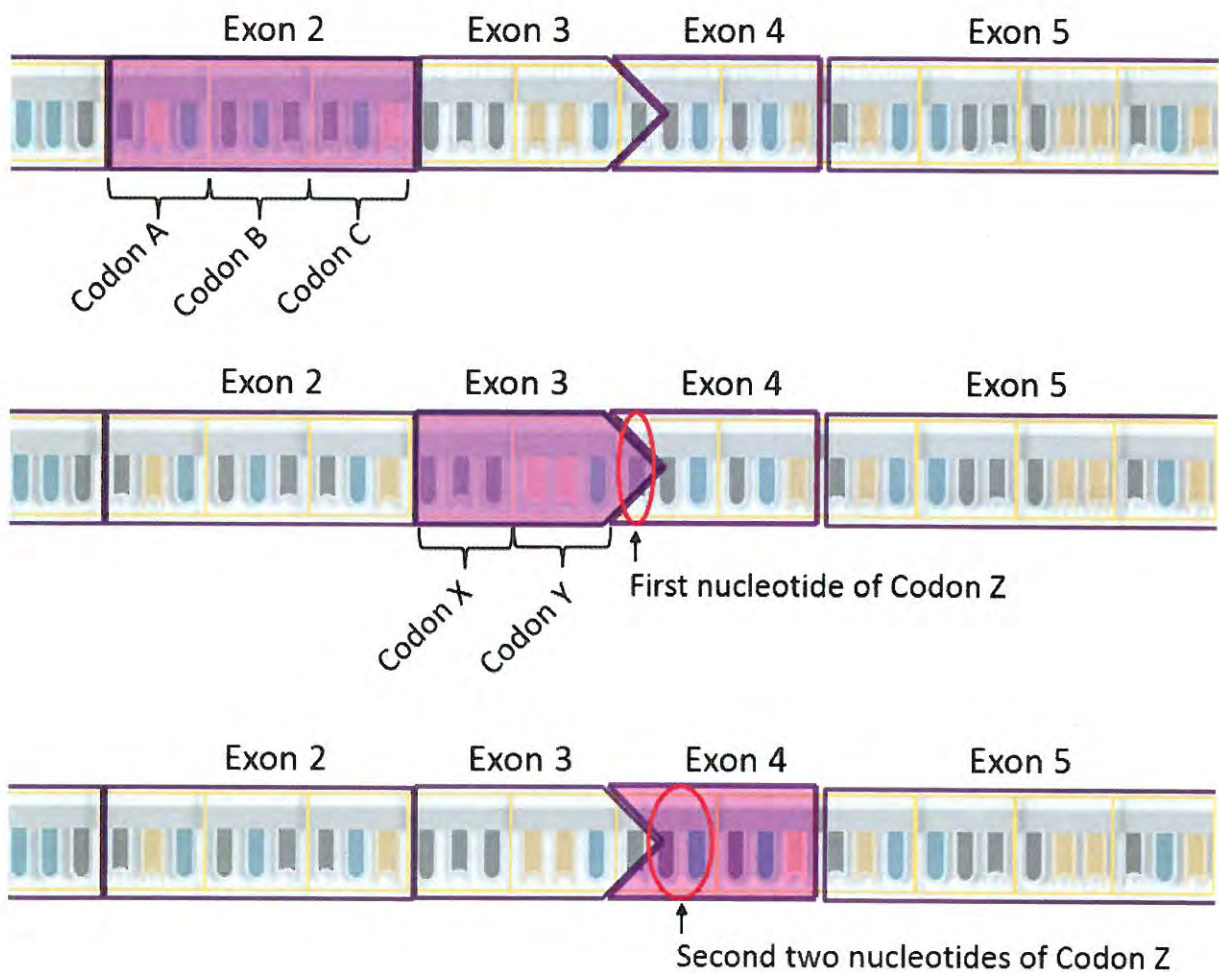


RF = release factor, binds to the stop codon to release the protein from the ribosome

Codon Splitting by Exons

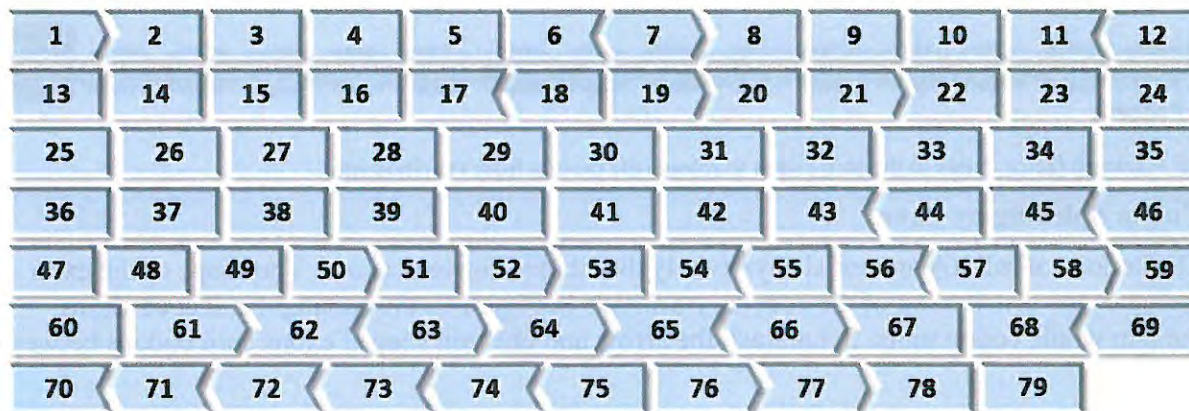
The codons of mRNA are not always evenly distributed between exons. The shape of the exon indicates the distribution of the codons. As shown in Figure C, the rectangular shaped exons contain whole codon units. In contrast, the arrow and chevron shaped exons split codons between them.

Figure C:



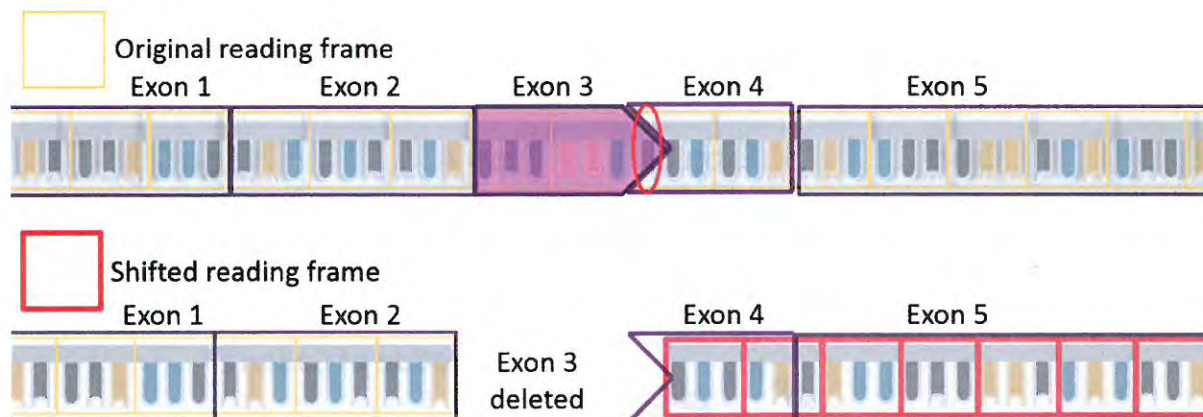
The dystrophin exon map is depicted in Figure D. Dystrophin is the longest known human gene, containing 2.4 million base pairs and 79 exons. A number of exons in the dystrophin gene split codons between them.

Figure D:



If all the exons are present, the splitting of codons between exons has no effect on the final protein. However, if as shown in Figure E, an exon that splits a codon is missing due to genetic mutation, the mRNA reading frame following the mutation is shifted and all subsequent amino acids will be incorrect. The resulting protein is non-functional and unstable.

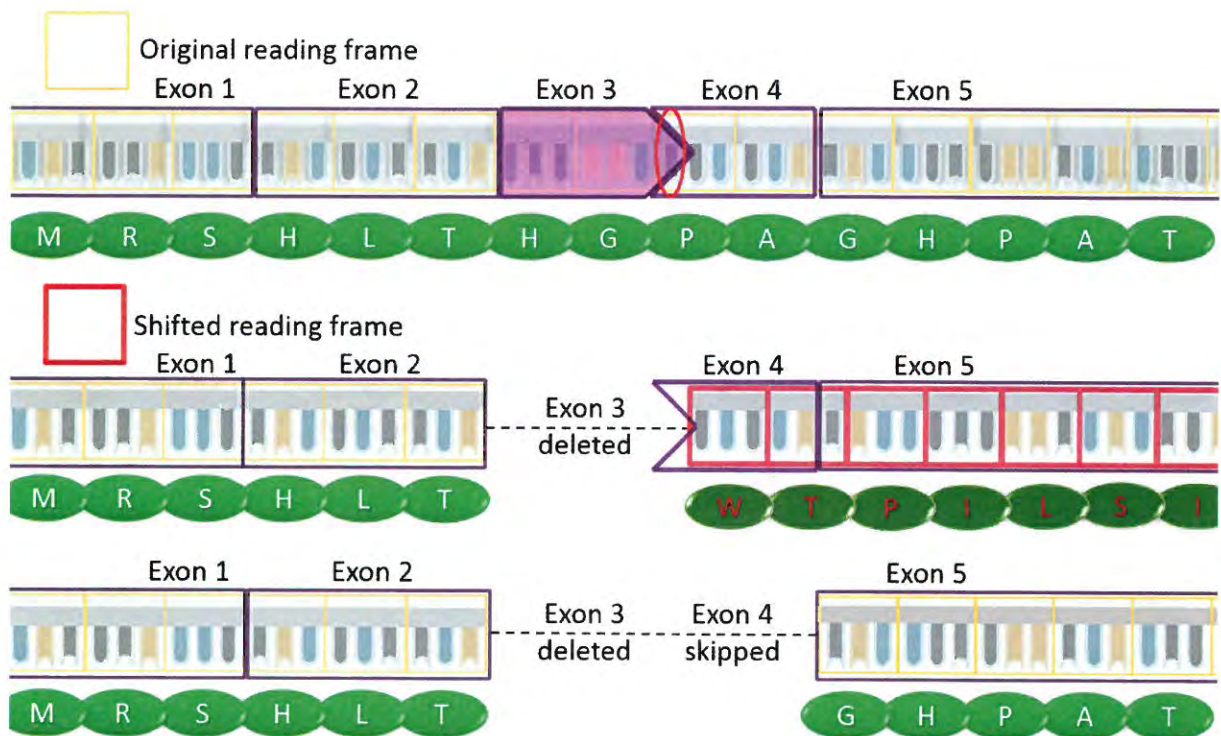
Figure E:



Restoration of the Reading Frame by Exon Skipping

Exon skipping aims to restore the mRNA reading frame by removing an additional exon from the final mRNA. As shown in Figure F, removal of an additional exon restores the reading frame following the mutation. The resulting protein will be missing the amino acids coded for by the missing exons, creating an internally deleted protein.

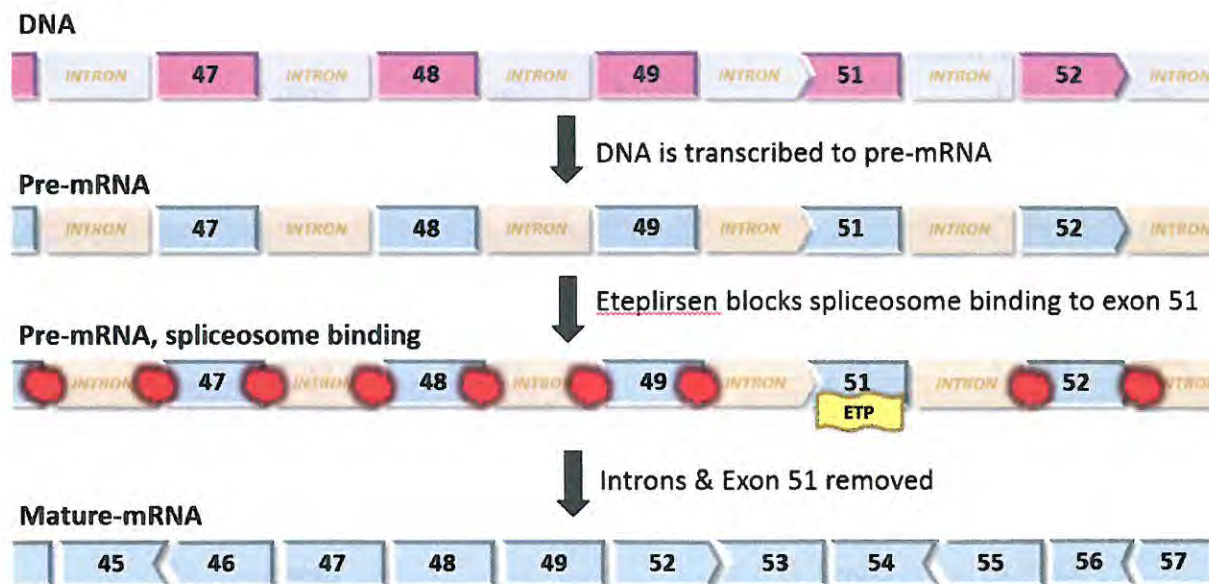
Figure F:



Eteplirsen Mechanism of Action

Eteplirsen enables exon skipping by binding to exon 51 of eteplirsen pre-mRNA and sterically hindering spliceosome binding. As shown in Figure G, if the spliceosome is unable to bind to exon 51, exon 51 will be removed along with the introns surrounding it and the reading frame will be restored.

Figure G:



Mutations Amenable to Exon 51 Skipping

A number of whole exon deletions are amenable to exon 51 skipping. Table A, provides examples that have been documented in the Leiden or UMD databases as well as the deletions tested in eteplirsen pivotal study 201/202.

Table A:

Population	Whole Exon Deletions Amenable to Exon 51 Skipping
Deletion documented in the Leiden or UMD databases	13-50, 19-50, 29-50, 31-50, 35-50, 40-50, 42-50, 45-50, 47-50, 48-50, 49-50, 50, 52
Mutations tested in Eteplirsen study 201/202	45-50, 48-50, 49-50, 50, 52

¹ Leiden DMD Mutation Database [Internet]. Center for Human and Clinical Genetics – Leiden Medical Center. 2003 – [cited 2015 Dec 1]. Available from: <http://www.dmd.nl>

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

**PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE**

January 22, 2016

**ETEPLIRSEN BRIEFING DOCUMENT ADDENDUM
NDA 206488**



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

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

FDACDER0003298

INTRODUCTION

Sarepta and the FDA have no more critical challenge than to reliably bridge and extend the benefits of medical innovation to patients. Eteplirsen has been developed as an innovative therapy, customized to treat a unique set of DMD genetic mutations, those which are amenable to skipping exon 51.

This addendum provides updated efficacy data as requested by FDA. It will also address Sarepta's position on the FDA's existing authority and mandate to exercise flexibility in the evaluation of data for a rare disease such as DMD. Finally, Sarepta will provide clarification of comments in the FDA briefing document that we believe are key inaccuracies.

UPDATED ETEPLIRSEN CLINICAL EFFICACY DATA: WEEK 216 LOSS OF AMBULATION AND 6-MINUTE WALK TEST RESULTS

Summary of Year 4 Loss of Ambulation (LOA) Status by Kaplan-Meier Analysis

A summary of the Kaplan-Meier analysis results comparing Year 4 LOA rates of eteplirsen-treated subjects and external controls is provided below.

Study 201/202 (n=12): 2 LOAs, 10 ambulatory, %LOA = 16.7%.

External control (n=13): 10 LOAs, 1 ambulatory, 2 missing data at year 4; %LOA = 89.7% by Kaplan-Meier analysis taking into account missing data cases; $p=0.004$ by log-rank test.

Six-Minute Walk Test

data The eteplirsen NDA was based on a large significant advantage of over 100 meters on the 6MWT for the eteplirsen-treated boys compared to external control boys at Year 3. This magnitude of effect was consistent and verified by several sensitivity analyses including those adjusting for covariates of baseline age and 6MWT (Section 6.5.1.1 of Sarepta's briefing document).

Subsequent to the NDA submission, the FDA requested additional Study 201/202 data through Week 216; the requested 6MWT data are provided in Table 1. All 10 of the eteplirsen boys who were ambulant at time of NDA submission remain able to walk at Week 216. Their ages at this point in the study range from 11.8 years to 15.2 years, with 4 of the boys aged 14 or older. This is in contrast to what was stated in the FDA Briefing Document for drisapersen, "by age 10-14, DMD patients become wheel chair bound" (Peripheral and Central Nervous System Drugs Advisory Committee Meeting November 24, 2015; NDA 206031 Briefing Document for Drisapersen, page 28).

In addition, Year 4 data for the external control patients amenable to exon 51 skipping have recently become available, are is provided in Table 2.

Table 1: Study 201/202 Subjects (n=12) with Results of 6MWT at Year 4

Dose Group	Subject Number	Baseline 6MWT	Year 3 6MWT	Year 4 6MWT	Age at Year 4
Placebo to 30 mg/kg	007	374	312	197	11.7
	008	346	100	55	14.2
Placebo to 50 mg/kg	005	374	247	143	11.7
	013	400	301	230	14.3
30 mg/kg	002	416	378	349	12.7
	006	355	359	332	14.2
	009	330	0	0	13.9
	010	256	0	0	13.9
50 mg/kg	003	366	324	192	11.0
	004	389	355	221	12.5
	012	351	298	237	14.6
	015	401	483	400	13.3

Table 2: External Control Subjects (n=13) with Results of 6MWT at Year 4

Subject Number	Baseline 6MWT	Year 3 6MWT	Year 4 6MWT	Age at Year 4
(b) (6)	380	195	*Missing	12.6
(b) (6)	295	35	0	13.3
(b) (6)	380	0	0	12.0
(b) (6)	329	218	0	12.8
(b) (6)	388	0	0	12.1
(b) (6)	388	0	0	14.1
(b) (6)	325	0	0	11.3
(b) (6)	458	362	300	14.2
(b) (6)	200	0	0	15.5
(b) (6)	373	273	0	13.0
(b) (6)	327	0	0	15.5
(b) (6)	451	240	0	15.2
(b) (6)	355	*Missing	*Missing	12.3

* External control patients with missing 6MWT data at Year 4.

** Of note, patients (b) (6) and (b) (6) were subsequently reported to have loss of ambulation with “0” meters on the 6MWT at ~4.5 years. In addition, external control patient (b) (6) was known to have lost ambulation with a 6MWT of “0” at 4.8 years.

Table 3: Summary of Year 4 6MWT Difference in Mean Change from Baseline between Study 201/202 Subjects and External Controls by Model (estimated mean difference, *p*-value)

Model	MMRM N= 12/13	ANCOVA N=12/11
Covariate: Baseline 6MWT	146.5, <i>p</i> =0.003	150.3, <i>p</i> =0.002
Covariates: Baseline 6MWT, Age	143.1, <i>p</i> =0.004	156.1, <i>p</i> =0.002
Rank transformed data analyzed Covariate: Baseline 6MWT	8.4, <i>p</i> =0.004	8.7, <i>p</i> =0.001

Conclusion

Based on available data for LOA and 6MWT status at 4 years, Study 201/202 patients performed better than EC patients in a statistically significant and clinically meaningful manner.

FLEXIBILITY REGARDING EVIDENCE REQUIRED TO MEET THE SUBSTANTIAL EVIDENCE STANDARD

FDA’s existing authority allows for the use of scientifically-driven flexibility in the application of the statutory standards for approval, in particular through the accelerated approval pathway for serious or life-threatening diseases as codified in the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on 09 July 2012. While application of regulatory flexibility has been most prevalent in the areas of oncology and HIV/AIDS, nowhere is the use of such flexibility more impactful than in the case of new therapies for the treatment of serious and life-threatening rare diseases. The need for innovative and flexible approaches to FDA review across divisions increases as more rare disease therapies are being developed, where the contextual knowledge of patients and their diseases often evolves in parallel with clinical development.

Authority for such flexibility is borne directly from federal regulations which state in part “[w]hile the statutory [substantial evidence of effectiveness] standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards.” The regulations go on to empower use of this flexibility by requiring the FDA “to exercise its scientific judgment to determine the kind and quantity of data and information... required to provide for a particular drug to meet the statutory standards” (21 CFR 314.105(c)). More recently, FDA affirmed in draft guidance that “[t]here is no specific minimum number of patients that should be studied to establish effectiveness and safety of a treatment for any rare disease.” (Guidance for Industry - Rare

Diseases: Common Issues in Drug Development, August 2015). Utilizing this authority, FDA allows for the broadest application of flexibility for new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists (21 CFR §312.80).

Congress embraced this flexible approach to drug evaluation in enacting Title IX of FDASIA in 2012. That law provided both the Findings and Sense of Congress with respect to FDA's authority to grant accelerated approval for drugs for serious and life-threatening diseases where the effect on a surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict clinical benefit. Uncertainty about whether clinical benefit would be verified and the possibility of undiscovered risks are the reasons that accelerated approval is reserved for drugs intended to treat serious conditions, such as the use of eteplirsen in the treatment of Duchenne muscular dystrophy. Importantly, FDA acknowledged that approval under such a pathway may involve "*fewer, smaller, or shorter clinical trials than is typical for a traditional approval...*" ((FDASIA Section 901(a)(1)(C)) and that "*trials using external controls, such as historically controlled trials, may be considered adequate and well-controlled, and may provide or contribute to evidence of efficacy to support approval.*" (FDA Guidance for Industry: *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment*, June 2015). There are numerous examples where FDA's flexibility has established regulatory precedent in rare diseases, including those described in the Sarepta briefing document and:

- Carbaglu[®] (carglumic acid): approved in March 2010 for treatment of N-acetylglutamate synthase (NAGS) deficiency based on a case series from fewer than 20 patients and comparison to a historical control group.
- Ceptrotin[®] (human plasma derived protein C concentrate): approved in March 2007 for the treatment of severe congenital Protein C deficiency based on a study of 18 patients using a comparison to historical control data.

Such variation in the type and quantity of evidence used by the FDA to assess the efficacy of novel therapeutic agents underscores the Agency's flexible approach to meeting standards for drug approval. It is clear in the context of the review of drugs for rare diseases FDA has the authority—and specific direction from Congress—to exercise flexibility in considering all of the available data.

CLARIFICATION OF KEY INACCURACIES IN THE FDA BRIEFING DOCUMENT

Dystrophin Analytical Methodology:

FDA Statement	Sarepta Clarification
<i>“It is important to note that the applicant digitally processed dystrophin images in their background material (images in Appendix 12) in such a way that low intensity values were preferentially increased to produce a higher intensity and higher contrast image.”</i> (FDA BD page 29 of PDF)	The digitally processed images referenced by FDA in this statement were included in Sarepta’s briefing document for demonstration purposes only, and it is far more important to note that the referenced images were not used in the analysis of fiber intensity, nor to score dystrophin-positive fibers.
<i>“Biomarker studies on the 4th biopsy obtained at Week 180 were conducted by the applicant with technical advice from FDA. However, the reliability of results remains questionable for a number of reasons, including the lack of independent confirmation.”</i> (FDA BD page 30 of PDF)	Methodology for dystrophin analyses of the fourth biopsy tissue samples, including confirmatory assessments of percent dystrophin-positive fibers (PDPF) analysis performed by 3 independent pathologists, were agreed with FDA prior to conducting any analyses of the fourth biopsy tissue samples. In accordance with the mutually agreed-upon protocols for the assessment of dystrophin-positive fibers in DMD muscle biopsy samples from the fourth biopsy obtained at Week 180, 3 independent pathologists performed a blinded assessment of the randomized muscle fiber microscopy images, which independently confirmed the results obtained by the pathologist at Nationwide Children’s Hospital (NCH). Assessment of PDPF at NCH indicated a significant increase in PDPF score ($p < 0.001$) relative to untreated control samples. This increase in PDPF score was confirmed by the 3 independent pathologists ($p < 0.001$).
<i>“Random measurement error can be large in comparison to the estimated amount of dystrophin.”</i> (FDA BD page 31 of PDF)	The random measurement error of our Western blot protocol for measurement of dystrophin levels was well below the observed difference between untreated and treated Week 180 biopsy samples. A rigorous validation of the Western blot method was reviewed by the FDA prior to Week 180 biopsy analysis. Validation data demonstrated a %CV of +/- 50% and a linear range ($R^2 > 0.9$) of sensitivity extending as low as 0.25% of normal.
<i>“There is no simple or reliable way to compare estimates of dystrophin amount derived from immunofluorescence with estimates derived from Western blot.”</i> (FDA BD page 35 PDF).	Correlation between dystrophin quantification by Western blot and IHC methods has been demonstrated by multiple laboratories (Taylor, 2012; Anthony, 2011; Anthony, 2014; Hathout, 2015 FDA Workshop on Measuring Dystrophin).

FDA Statement	Sarepta Clarification
<i>“In this context, the applicant selected three BMD patients as comparators for the Week 180 dystrophin studies, one of whom had low dystrophin level of about 2% of normal. However, the BMD patients selected by the applicant do not appear representative, and this patient may correspond to one of the rare BMD patients with very low dystrophin levels.”</i> (FDA BD page 34 of PDF)	BMD patient samples were not chosen to be representative; rather, they were selected in response to an FDA request to assess the relationship between dystrophin as measured by Western blot and immunofluorescence fiber intensity. Therefore, BMD samples were obtained that represented low, middle, and higher ranges of dystrophin expression. A comparable Western blot analysis-IHC correlation was presented by Hathout, et al. (MDA 2015 Scientific Conference poster, FDA-NIH workshop on measuring dystrophin, 2015), where BMD biopsies were chosen to represent low- and mid-level dystrophin expression. Consistently, their BMD low patient biopsy was 2% of normal.

Potential Clinical Impact:

FDA Statement	Sarepta Clarification
<i>“With these two comparisons of eteplirsen to placebo, there was a positive finding for only the lower dose (30 mg/kg) and for just one of the two time points (the later time point). The lack of an effect with the higher dose group tends to undermine the finding in the lower dose group and the lack of even a positive trend at the earlier time point (with a higher dose) sheds doubt on the finding at a later time point.”</i> (FDA BD page 7 of PDF)	The study was designed to see whether dose (50 mg/kg vs. 30 mg/kg) or duration was the most important criterion to enable consistent dystrophin production. • Duration of therapy was observed to be the critical variable when interpreting dystrophin levels. 12 weeks does not represent a clinically relevant duration of therapy (FDA BD page 26 of PDF). • Significant dystrophin levels were by measured at Week 24 for the 30 mg/kg dose, and, importantly, at Weeks 48 and 180 for both the 30 and 50 mg/kg doses by all dystrophin assay methods.
<i>“Arguably, placebo-treated patients who were blinded to treatment assignment from other controlled trials are more appropriate as matched controls than registry patients, as they may receive special care and attention as trial participants, and may be more highly motivated.”</i> (FDA BD page 13 of PDF)	The placebo patients from another study as referenced by the FDA are not appropriate for comparison with the eteplirsen-treated patients (FDA BD pages 8, 9, 40-44, and 50 of the PDF): Baseline characteristics are not comparable between eteplirsen and the proposed placebo group: • Placebo group included boys <7 years old • Placebo group included many patients with baseline 6MWT >440 meters which is outside the eteplirsen trial’s inclusion criteria Placebo patients were followed for only one year, whereas eteplirsen-treated patients were followed for 3 or more years:

FDA Statement	Sarepta Clarification
	• By virtue of the ambulatory requirement at study entry, older placebo patients (e.g. ≥ 11 years) were a group of pre-selected, better performing subjects. • The first year of an 11-year-old-at-baseline placebo patient (i.e. 11-12 years old) to the third year of a 9-year-old boy with 3 years of eteplirsen treatment (i.e. 11-12 years old) is not a valid comparison due to the difference in duration of observation, as well as the biased selection of the 11-year -old ambulatory placebo boy, irrespective of both patients having the same age at last assessment. • Comparison of eteplirsen-treated patients to the appropriately matched external control shows that more than one year is required to observe a divergence in disease progression between the two groups.
<i>“The robustness of the study result is a concern since a single patient could change the results substantially.”</i> (FDA BD page 69 of PDF)	This statement is inaccurate. A comprehensive sensitivity analysis was performed in order to address any potential issue regarding robustness of the data. Specifically: • Two patients were removed: the best performing eteplirsen and the worst performing external control patient. • Results demonstrated a robust 6MWT treatment advantage of >100 meters with nominal significance.
<i>“Finally, as the sponsor’s natural history study proceeded, some patients left to enter interventional clinical trials, further decreasing the similarity of the natural history cohort to the eteplirsen patients.”</i> (FDA BD page 47 of PDF)	The 2 external control patients who entered interventional trials did not diminish the comparability of the natural history cohort. Two types of sensitivity analyses were performed to confirm the magnitude of difference remained over 100 meters and maintained nominal significance: • MMRM using all available data • Last Observation Carried Forward imputation (conservative analysis assuming that the 2 control patients did not decline)

Regulatory Feedback:

FDA Statement	Sarepta Clarification
<i>“As the duration of exposure in Study 202 increased, the applicant proposed comparing the clinical course of treated patients to historical controls.”</i> (FDA BD page 38 of PDF)	The proposal to compare with historical control patients originated from the FDA. Specifically, a requirement to compare the clinical course of treated patients in Study 202 to matched patient-level historical control data was made by the FDA at the March 2014 guidance meeting, and reiterated at the September 2014 pre-NDA meeting. Sarepta had proposed an open-label confirmatory study comparing treated patients to

FDA Statement	Sarepta Clarification
	concurrent (not historical) untreated patients with exon deletions not amenable to skipping exon 51 (i.e. the PROMOV1 study).

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Temple, Robert

From: Farkas, Ronald
Sent: Wednesday, January 13, 2016 12:39 PM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Breder, Christopher D
Subject: Lou Kunkel, dystrophin discoverer and Sarepta advisor, new article

Lou Kunkel, discoverer of dystrophin, and advisor for Sarepta. Might be informative of Sarepta's strategy (These are, of course, points that patient advocates also argue)

- “Imagine, these trials are taking place for the real efficacy in the kids who are 7, 8, 9 years old. And they're in the phase of the disease where they're going to lose ambulation by 10 ... So imagine if you were told this is going to be a placebo-controlled trial and your child is one of the third that wasn't going to get drug. I wouldn't sign up for that trial.”
- Even though the company has gone to great lengths to show the drug produces dystrophin, Kunkel says “the levels of protein are not that high.” However, he said that over the course of patients' entire lifetimes, a small amount can add up to a significant benefit.
- eteplirsen is not going to be a cure-all; what you're going to need is an alternative approach that's independent of that; would probably synergize, and give you a positive synergistic effect

<http://www.bizjournals.com/boston/blog/bioflash/2016/01/duchenne-pioneer-says-fda-rejection-of-sarepta-s.html>

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1⁰⁰ pm
B51 Rm 6139

Blount, Aprile

Subject: CD-Brief Presentation for AC Mtg on Eteplirsen
Location: B51 Rm 6139

Start: Wed 1/13/2016 1:00 PM
End: Wed 1/13/2016 2:00 PM

Recurrence: (none)

Meeting Status: Accepted

Organizer: Diggs, Felicia
Required Attendees: Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Choy, Fannie (Yuet); Dunn, Billy; Breder, Christopher D; Rao, Ashutosh; Ware, Jacqueline H; Bhattaram, Atul; Ligon, Sharnell (CDER); Blount, Aprile; CDER 120 Calendar; Kozauer, Nicholas

Optional Attendees: Hung, Hsien Ming J; Ling, Xiang; LaVange, Lisa; Jin, Kun; Nevius, S Edward; Rosenberg, Amy

Date 1/13/16 1:00 p.m. – 2:00 p.m.

WO BLDG, 51, Rm. 6139

Topic: Review presentation for application eteplirsen, NME (NDA 206488) in preparation for AC meeting

CDER Staff Contacts: Fannie Choy, RPMS

CDER Executive Operations Staff Contact: Felicia Diggs, DEO liaison

Invited Attendees: Janet Woodcock, Richard Moscicki, Robert Guidos, John Jenkins, Doug Throckmorton, Robert Temple, Felicia Diggs, Sharnell Ligon, Fannie Choy, Ellis Unger, Billy Dunn, Eric Bastings, Ronald Farkas, Veneeta Tandon, Christopher D Breder, Ashutosh Rao, Evelyn Mentari, Sally Jo Yasuda, Alice Hughes, Jackie Ware; **OPTIONAL** Hsien Hung, Xiang Ling, Lisa LaVange, Kun Jin, Edward S Nevius, Amy Rosenberg

Reason for Briefing: The purpose of this meeting is to review the slide presentation and plan of actions eteplirsen, NME (NDA 206488) that will be presented during the Advisory Committee Meeting on January 22, 2016 to senior leadership. Eteplirsen proposed indication is for the treatment of patients with Duchene muscular dystrophy due to a deletion in the dystrophin gene that is amenable to exon 51 skipping.

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36 pages of draft language have been withheld as b(5) immediately following this page

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The sales to Moberg were "non-core" brands Prestige Brands is divesting to accelerate paying down debt and move toward its goal of a portfolio with 85% of revenue from "invest for growth" brands and 15% in non-core, or "manage for cash" brands to help support long-term organic growth.

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Duchenne Development: Data Sharing May Enable Trials To Move Beyond Six-Minute Walk

- 13 Jun 2017
- **Analysis**

[Emily Hayes @emilykatehayes emily.hayes@informa.com](#)

Executive Summary

Repeated trial failures in this rare disease space have given birth to new alliances – one backed by Critical Path and the other by the CureDuchenne advocacy group – that aim to model disease progression much more accurately through data sharing and rigorous analysis.

The infamous six-minute walk test is hardly a thing of the past in Duchenne trials – at least not yet – but two new alliances are hoping that by analyzing large pooled datasets they can understand disease progression better, paving the way for more refined use of the measure and also new endpoints targeted at patient segments.

Duchenne muscular dystrophy (DMD) trials are notoriously challenging. [Sarepta Therapeutics Inc.](#)'s antisense oligonucleotide *Exondys 51* (etplirsen) failed to demonstrate a significant benefit for the six-minute walk test, a standard measure of physical endurance often used in Duchenne trials, in the small Study 202.

In a controversial decision, the drug received accelerated approval from FDA for patients with a mutation of the DMD gene in September 2016, due to the intervention of Center for Drug Evaluation and Research director Janet Woodcock, against the advice of other officials. In that case, Woodcock concluded that an increase in dystrophin levels correlated with a lower rate of decline on a different measure – the North Star Ambulatory Assessment. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal FDA Debate](#)" - Pink Sheet, 20 Sep, 2016.)

Following approval of that drug, FDA recently decided that it was okay for the company to use implantable central venous devices in the ESSENCE Duchenne study of two other compounds, a move that will help speed enrollment. (See *sidebar for related story.*)

Other companies in the space have not had a happy regulatory ending.

After [BioMarin Pharmaceutical Inc.](#)'s drisapersen failed to show an improvement in the six-minute walk test the company went on to file an application with FDA anyway, but received a complete response letter. (Also see "[FDA Finds Fault With Third Duchenne Muscular Dystrophy Drug Filing](#)" - Pink Sheet, 23 Feb, 2016.) [PTC Therapeutics Inc.](#)'s ataluren failed to meet the primary six-minute walk test endpoint in a Phase III study and a filing subsequently received a refuse-to-file letter from FDA. (Also see "['File Over Protest' At US FDA: PTC To Pursue Rarely-Used Pathway For DMD Drug](#)" - Pink Sheet, 10 Jan, 2017.)

The OTC drugs and personal care products company will correct Structured Product Labeling information in the US NDC Directory for PediaCare Children's Plus Multi-Symptom Cold and Children's Plus Flu to include one of the products' active ingredient, phenylephrine.

[Prestige Brands Holdings Inc.](#) is responsible to correct information in FDA's National Drug Code Directory for two products in a line it sold a year ago, the *PediaCare* OTC allergy and cough/cold brand.

The manufacturer and marketer of OTC drugs and personal care products said it will correct the Structured Product Labeling (SPL) information in the NDC Directory for PediaCare *Children's Plus Multi-Symptom Cold* and *Children's Plus Flu* to include an active ingredient in the products, phenylephrine. Both liquid medicines, marketed under an OTC monograph, also contain chlorpheniramine and dextromethorphan.

The products are now marketed by Swedish firm [Moberg Pharma AB](#) following a deal announced in July 2016, but NDC information in the directory had not yet been updated to reflect that change. Thus, Prestige is responsible to correct the SPL as well as the NDC information.

In a June 1 [warning letter](#), FDA advised Prestige Brands that a review of the products' required listing showed the ingredient is listed on current labeling, but not in the SPL information that also is required for the NDC Directory. NDC owners must update each product's directory listing twice annually, by June and by December.

The warning from the Center for Drug Evaluation and Research stated that FDA removed the products' listing from the online NDC Directory and it will not be available for public viewing until the corrections are made. However, listings for the other products in the PediaCare line are accurate and remain accessible.

"This is an effort to maintain a correct and accurate database in order to protect and promote the public health," according to the warning letter.

The products will remain available while the NDC Directory information is inaccessible, says Prestige Brands.

Phil Terpolilli, director of investor relations, said the erroneous SPL information was submitted before Prestige Brands acquired the brand in 2010 from [Blacksmith Brands Inc.](#) and was not corrected before the Tarrytown, N.Y.-based firm sold PediaCare and several other product lines to Moberg. (Also see "[Prestige Brands Makes 'Seismic Shift' To OTC With Blacksmith Acquisition](#)" - Pink Sheet, 27 Sep, 2010.)

In an email, Terpolilli said that corrections are in process and "will include the marketing end date (i.e., the date on which the last batches distributed under our control will expire)."

Blacksmith Brands' NDCs came with the portfolio of products Prestige Brands acquired. "Accordingly, the contact information for that labeler code was updated with FDA, but there was no need to submit new drug listings as a result of the acquisition," Terpolilli said.

In addition to PediaCare, Prestige Brands divested its Fiber Choice and New Skin lines to Moberg for \$40m. (Also see "[Moberg Sustains Derma Drive, Acquires Prestige Brands' New Skin](#)" - Pink Sheet, 1 Jul, 2016.)

In December, Moberg exercised an option gained in the firm's agreement to acquire Prestige Brands' DermoPlast topical anesthetic brand for \$47.6m. The Stockholm-based firm, which operates a US business in Cedar Knolls, N.J, since early 2015 has been adding and selling brands with a goal of focusing its business primarily on derma products.

[Catabasis Pharmaceuticals Inc.](#)'s edasalonexent (CAT-1004) missed endpoints related to MRI T2 measures of leg muscles in a Phase II study. (Also see "[Catabasis Refutes MRI T2 Biomarker In Duchenne Study](#)" - Pink Sheet, 2 Feb, 2017.) The company is now looking at the four-step climb or ten-meter walk/run test for future studies.

"Virtually no Duchenne trials ever meet a primary endpoint, which is problematic in itself, because we don't know whether the trial failed, the drug failed or what. The last thing anyone wants at the end of a trial is uncertainty," Jane Larkindale, executive director of the Duchenne Regulatory Science Consortium (D-RSC) at the Critical Path Institute, said in an interview.

Natural History A Mystery

There are a number of reasons behind the trial failures. Duchenne is a rare disease and the patient population is very small – little has been published on the natural history, or the natural course, of the disease, making it hard to reasonably predict what will happen in a trial and to recruit the right patients.

The disease progresses differently in different children and it is difficult to know what is likely to happen in a trial, Susan Ward, co-founder of the Collaborative Trajectory Analysis Project (cTAP), noted. The challenge industry has been wrestling with over the last several years has been how to identify a fairly homogenous group of patients who will decline at a steady slow rate over the course of a study, she said.

"The trials become very noisy. There is a lot of variability – and the more variability, the more challenging it is to say whether you are seeing a drug effect," Ward said. "What we have learned as a field is that we really need to have a deeper, richer understanding of natural history than we had."

Using somewhat different models, the D-RSC and cTAP are both working to make that happen, through collaboration by industry, academic investigators and patient advocacy groups. (*See table below.*)

Formed as a non-profit in August 2015, the D-RSC is a partnership between the Critical Path Institute and the Parent Project Muscular Dystrophy (PPMD) advocacy group. (Also see "[C-Path Consortium Aims To Speed, De-Risk Duchenne R&D](#)" - Pink Sheet, 11 Aug, 2015.)

Academic members include investigators from the Cincinnati Children's Hospital Medical Center, the UC Davis Health System and Stanford University. And three pharma companies are members or collaborators – [Pfizer Inc.](#), [Sareptaand Santhera Pharmaceuticals AG](#).

The National Institutes of Health and FDA both have liaisons that attend D-RSC meetings.

Currently, the consortium has access to datasets encompassing about 800 patients who were either followed in natural history studies or who participated in placebo arms of clinical trials.

The D-RSC is collecting data in one integrated database for the Duchenne population and is in the process of developing a disease progression model that will guide development of suitable endpoints and biomarkers for use in efficient trials that will pass muster with FDA and other regulators. Aims include qualifying skeletal muscle MRI imaging as a prognostic or pharmacodynamic marker for DMD, with the blessing of regulators.

Critical Path's experience in rare diseases includes development of an imaging biomarker for use in polycystic kidney disease.

About half of the D-RSC data is currently directly available on a patient, anonymized level to consortium members and the alliance is free to publish its own analyses of all the data. The consortium envisions that ultimately all of the data will

be available directly not only to members but also to the public, assuming users agree to certain terms and conditions, as is required with other C-Path consortia efforts.

C-Path already created such an integrated, publicly accessible database for Alzheimer's disease and that project can serve as a model for Duchenne and other indications, Larkindale explained.

Abby Bronson, senior vice president of research strategy at the PPMD, told to the Pink Sheet that direct access on the patient level is "the holy grail – that's what sponsors and industry would really like."

Behind-The-Scenes Milestone Ahead

D-RSC development work includes collecting and presenting Duchenne data and terminology in accordance with the Clinical Data Interchange Standards Consortium (CDISC), which is now required for FDA submissions. (Also see "[FDA Therapeutic Area Standards Would Have To Clear Industry Testing](#)" - Pink Sheet, 30 Oct, 2013.)

D-RSC is about to pass a major milestone with the establishment of a therapeutic CDISC user guide for Duchenne terminology and data. In March, D-RSC sent out a user guide for public review and comments are due by July 6. The review is mostly aimed at the data management community, including people who are not necessarily experts in the disease.

"In order to facilitate a data sharing platform that houses multiple data sets, there needs to be a common language so these data sets can 'inter-operate.' In the drug development world, these are [CDISC standards](#) and are overseen by an organization that maintains the common data standards framework for all therapeutic areas," Bronson explained in a PPMD website [blog](#) entry.

"I know this may not sound like sexy stuff. Think of it this way though. It is as important as the behind-the-scenes ATM inter-operability that is in place, so that when you insert your ATM card at one bank, it can talk with your bank and seamlessly carry out whatever task you need to accomplish," Bronson wrote.

Meanwhile, cTAP is also collecting and analyzing data from placebo arms of trials and natural history studies of Duchenne disease. The cTAP public/private partnership was founded in October 2016 by the advocacy group CureDuchenne with Ward, a former pharmaceutical exec at [Millennium Pharmaceuticals Ltd.](#) and [Wyeth](#), and James Signorovitch, managing principal at the Analysis Group consultancy.

Industry members and/or collaborators of cTAP include [Pfizer Inc.](#), BioMarin, Sarepta, [Eli Lilly & Co.](#), and [Marathon Pharmaceuticals LLC](#).

Academic representatives include global Duchenne expert Eugenio Mercuri, of the Catholic University in Rome and Nathalie Goemans, of the Universitaire ziekenhuizen (UZ) Leuven. Mercuri leads a group of physicians across Italy who have pooled data into one registry and these data have been shared with cTAP and analyzed by the Analysis consultancy.

Today, cTAP has data from 33 centers across multiple different registries and can make apples-to-apples systematic analyses across all of the different databases, providing rigorous, quantitative evaluation of how consistent natural history is or isn't, Ward explained.

"That's hugely important for everybody in the field. Nobody can do that on their own," she said.

Overall, the cTAP consortium currently has longitudinal data for over 1,400-1,500 Duchenne patients. This includes patients who took part in Eli Lilly's Phase III study of *Cialis* (tadalafil) in DMD, though the company is no longer involved in development for this indication.

Members/collaborators do not have direct access to the data at the patient level. Rather, they contribute to the costs of collecting and analyzing the data and gain access to research projects determined by a joint steering committee, which includes companies and advocacy groups. The cTAP consortium is also publishing research, based on its analyses of the pooled data.

The Analysis Group's Signorovitch said that ensuring that the groups contributing the data have full control over its use has been "essential" in how cTAP operates and is the reason the consortium has been able to make fast progress.

"We have made a large number of groups comfortable with sharing their data with us," Signorovitch said.

Rethinking Endpoints

Commenting on trial failures in Duchenne, PPMD's Bronson noted the lack of information about typical disease progression, but also the small numbers in the studies and short length of time to show a benefit relative to placebo.

And it may be necessary to pivot away from the six-minute walk – it's a measure that was known in other neuromuscular diseases, so it is commonly used in Duchenne, but it has a lot of limitations in the disease, she said.

"Industry is usually pretty risk-averse, so they take something they think FDA will accept and know about," Bronson said.

One obvious limitation is that the measure can't be used across all disease stages (ambulatory to non-ambulatory), which forces sponsors to create trials specific to one of these populations or another, she said.

"From the boys' perspective, it is a hard test physically yet they will exert themselves to no end in the name of science and research. ... Sometimes there are falls during the test, which are heartbreaking to see and very detrimental to the boys," Bronson added.

The test is also hard for younger kids who sometimes have a hard time focusing, she said.

"We've worked hard to standardize the way the test is administered across trial sites and clinical trials and have worked to standardize the clinical evaluator training for the six-minute walk test in Duchenne to ensure the measure's validity. That said ... perhaps we will rely on it less and less in the future as we learn about other endpoints," Bronson said.

Bronson envisages that in the future, when more is known about disease progression, a combination of two or more outcome measures could be used. This could include the Northstar Ambulatory Assessment and the Performance of Upper Limb test.

For some drugs, the appropriate endpoint might be muscle strengthening, but in others it could be building muscle, which takes more time, and clearly children who are no longer able to walk need different measures, Ward said.

"It's not like a cookie cutter that you can stamp out: all trials need to look this way," Ward said.

The North Star Ambulatory assessment, which is a composite of a number of separate tests for general ambulatory function, has been used in Europe for some time and is starting to gain momentum in the US, Ward said.

So far, two peer-reviewed [publications](#) have been published through cTAP about Duchenne disease progression and help to identify boys with similar rates of decline in ambulatory function and explain more than half of the variability in trials. These analyses might be usable to help assess inclusion or exclusion criteria companies for trials.

"It's a great step in the right direction. We will try to improve on that," Ward said.

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FDANEWS

Supreme Court: 180-Day Biosimilar Exclusivity Can Start Any Time, Not Just After Approval

In a decision that reshapes the patent dance between biosimilar applicants and reference holders — and could affect the course of billions of dollars in the pharmaceutical industry — the U.S. Supreme Court ruled biosimilar manufacturers do not have to wait for FDA approval before beginning a six-month delay on commercial marketing.

Federal law requires biosimilar makers to notify reference holders of their intent to sell a competing version of their product at least 180 days before bringing it to market.

However, Sandoz — which developed the first U.S. biosimilar approved under the process, Zarxio (filgrastim-sndz), based on Amgen's Neupogen — argued that those 180 days can begin any time, and that waiting for FDA approval was not required. In addition, Sandoz did not provide Amgen with a copy of its biosimilar application, another early step required in the process. Amgen sued and the case was argued before the Supreme Court in April.

The high court unanimously ruled in Sandoz's favor on 180-day exclusivity, reversing a July 2015 Federal Circuit Court decision delaying the countdown clock's start until after FDA approval.

But the Supreme Court agreed with the Federal Circuit's ruling on aBLA disclosure, which had favored Sandoz's decision to not provide Amgen its application, however for different reasons — while the lower court reached the correct result, its logic was flawed, according to the June 12 opinion.

Sandoz's refusal to supply Amgen with a copy of its application does not serve as grounds for infringement and remediation alone, the Supreme Court said. However, the act of submitting an aBLA to the FDA does, and is seen as one of the first steps in the patent dance.

Additionally, those provisions of federal law are not enforceable by injunction, the opinion said, although injunctions may work under individual state laws. The Supreme Court sent that question back to the Federal Circuit, to re-examine whether California's unfair competition law applies, as the suit was originally filed there.

Justice Stephen Breyer, writing in a separate, one-paragraph concurrence with the Supreme Court's opinion, said Congress implicitly delegated authority to the FDA to interpret the requirements in the biosimilar approval process and that the agency may have the authority to alter the court's findings in the future.

During April's oral arguments, Breyer said the case had "huge implications for the future," and he wondered why the FDA had not issued clearer regulations to solve the problem, as opposed to bringing the case up through the courts ([DID, April 27](#)).

FDA's oncology drug advisory panel voted 14-1 May 25 to support approval of Hospira's epoetin alfa biosimilar. The one advisory panel member who voted against supporting approval did so because of lack of data regarding immunogenicity in two of the four proposed indications ([see related story](#)).

Pfizer's setback means that there are still no FDA-approved epoetin alfa biosimilars, despite the product being available in Europe for nearly a decade. -- *Nicholas Florko* (nflorko@iwpnews.com)

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FDA Urged To Broaden Use Of Flexible Approval Standard In Wake Of Sarepta DMD Drug Approval

June 23, 2017

CHICAGO -- A representative from pharmaceutical company Sarepta -- manufacturer of the controversial Duchenne muscular dystrophy drug Exondys 51 -- touted FDA's use of regulatory flexibility to approve Exondys 51, saying the approach has been frequently used for oncology drugs and could be a boon for the rare disease space. But one legal expert urged caution, saying FDA needs to ensure the validity of the science as it heads into implementing the 21st Century Cures Act, which will facilitate a more flexible approval approach. The issue came up during a panel discussion at the DIA annual conference this week.

FDA granted accelerated approval to Exondys 51 in September 2016, months after an advisory committee voted to not approve the drug ([see related story](#)). The approval sparked backlash from public health advocates who argued FDA showed too much flexibility when it approved the drug based on little scientific evidence that it was beneficial for patients. However, at the June 21 DIA panel, Sarepta's Shamim Ruff, senior vice president of regulatory affairs and quality, said "there are a lot of misconceptions out there" around the approval adding that "A lot of people seem to think that we got approval based on a 12-patient NDA ... it was a little more extensive than that."

Ruff explained that Sarepta provided data from two phase I studies and two phase II studies. The phase II studies consisted of what was "initially a randomized placebo controlled study. A 28-week study where 24 weeks had a randomized placebo control," Ruff said.

"We didn't know enough about the disease or the drug to know that we needed a longer study and now we know it can take up to two years before you can see a difference," she added.

The company's single-arm study provided individual patient data from the natural history studies and then, in addition to the 13 patients who were amenable to exon 51 skipping, data was provided from "a large number of patients who were anti-exon amenable, so again it wasn't just a tiny dataset," Ruff said. Sarepta also provided safety data from 114 patients "primarily from the phase I and phase II studies but also a number of ongoing clinical studies using eteplirsen," she said.

Ruff said the accelerated approval was "based on the totality of evidence" with dystrophin as a surrogate endpoint reasonably likely to predict benefit.

"And the support from reasonably likely comes from long-term experience ... both chemical and clinical data supported that low-level increase in dystrophin is reasonably likely to predict benefit," Ruff said. "And the patient voice that was very critical to this. The patients provided us with what their needs were and what they believed was clinically

meaningful. They provided information of a risk tolerance and it was clear that as far as the patients were concerned, small functional improvements or delay to loss in ambulation were clinically meaningful and this was certainly taken into consideration.”

Sarepta knew that there was a regulatory framework for flexibility for rare disease therapies, Ruff said. However, the FDA division the company worked with to get Exondys 51 approved “had never exercised this flexibility. They had been more used to the larger indications so had never worked really in the rare disease arena and they certainly were not used to accelerated approvals until very recently that was really the purview of the office of oncology drugs,” she said.

Ruff argued that flexibility is needed in the rare disease space.

“I worked in oncology for about 16 or 17 years prior to joining the rare disease arena, and I actually saw a lot of flexibility. To me, flexibility equals clinical judgment. I think it’s easy to interpret data from a large, or two large, randomized placebo controlled studies but when you get into the rare disease arena with targeted drugs, there needs to be clinical judgment ... Certainly in oncology there was always a lot of regulatory flexibility. The subpart H approval, or accelerated approval, was used pretty extensively ... FDA for oncology will often approve drugs on a single-arm study based on response rates. So it’s a paradigm that’s being used within FDA quite a bit,” she said.

Alexander Varond, associate at Goodwin Proctor, said FDA has for a long time used an accelerated approval pathway, also known as subpart H, and been flexible in its approval standards when there is an urgent need for a drug. And laws, such as the 2012 FDA Safety and Innovation Act (FDASIA), have only helped to codify “what FDA was already doing.” He also argues the pathway has not been heavily utilized but that may change with the implementation of the 21st Century Cures Act.

“The conversation has shifted and there’s greater discussion on subpart H, but there’s also this reluctance. And that reluctance is important because oftentimes the science isn’t adequate to support the use of some unvalidated surrogate endpoints. There needs to be a discussion here. There needs to be an active consideration of does this drug warrant a subpart H approval ... As FDASIA goes through and we see implementation of 21st Century Cures, subpart H is going to be used more,” Varond said.

Christine McSherry, executive director of the Jett Foundation, also argued that FDA should develop more standardized questions focused on benefit and risk for its advisory committee meetings.

According to McSherry, FDA’s current approach can lead to members voting no on a drug even if they think it is effective. She pointed to the April advisory committee’s vote to not approve the drug, which she said was based on an oddly worded question from FDA that did not address the real benefit of Exondys 51.

The final question posed to the committee asked: “Do the clinical results of the single historically-controlled study, study 201/202, provide substantial evidence, that is evidence from adequate and well-controlled studies or evidence from a single highly persuasive adequate and well-controlled study that is accompanied by independent findings that substantiate efficacy, that eteplirsen is effective for the treatment of DMD?”

McSherry argued that the wording of the question focused too much on whether the study was “well controlled” and not enough on the risk-benefit profile of the drug.

“[N]othing in this question, nor the other voting questions, actually reflected the risk-benefit profile of eteplirsen nor did it for the safety and efficacy. These questions had no bearing on the efficacy or safety. And what was really disturbing is that we felt like the division had done a really good job at dismantling the idea that this study was adequate and well-controlled, but what they couldn’t disagree with was the study’s safety and efficacy ... I think one of the things that we

learned about that is it would be better if FDA standardized questions across the board and really answered the question not of the well-controlled studies but let's talk about safety and efficacy of a drug. And we believe that if that had been in the questions, the panel wouldn't have been forced to answer in a negative way," McSherry said.

McSherry also posited that patient-reported outcomes (PROs) will be vital for companies developing rare disease therapies.

"I think that the implementation of patient-reported outcomes is an upcoming catalyst ... if it's done correctly it can really soar the field to where its needs to be," McSherry said.

The DMD patient advocate argued that PROs can shorten clinical trial timelines, lower costs and give FDA the data it needs to "support these messier type trials," McSherry said.

"Because [the trials are] not always going to be clean cut. There's going to be messy trials but there's going to be efficacy in there and we have to be able to pull it out. So I think that the development of PROs is going to be very important over the next five years. And I would love to see agency be supportive of that," she said.

PROs are already being used in oncology, Ruff added.

"It's being used considerably in oncology and certainly you can get full approval based on feeling better. There are two things that you need to do for regulatory approval: feel better or live longer in the oncology arena," she said.

Ruff also pointed to FDA's Oncology Center of Excellence as an example of something that could be used in the rare disease space. "I know rare diseases are many different diseases but so is oncology. It's hundred of different diseases," she said.

McSherry told the group that FDA's drug center director Janet Woodcock had "actually mentioned that to us. That would be her dream ... I think that's the way she would like to move things," McSherry said -- *Beth Wang* (bwang@iwpnews.com)

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OTC Monograph User Fees Would Cut Review Time, Allow For IT Platform

June 23, 2017

A draft document obtained by *Inside Health Policy* sets out expected performance goals for an over-the-counter monograph user fee program (OMUFA) under which FDA would see improved review timelines and more efficient review capacity by year four of the program. Assuming Congress enacts OMUFA and it goes into effect by Oct. 1, 2017, FDA and industry could expect to see an increase in OTC monograph review staff and reductions in review time, published draft and final guidance detailing processes, and the establishment of a public-facing information technology dashboard.

The document notes that it currently takes "many years" to make changes to a monograph but that reform will lead to substantially shortened timeframes for review of innovation OTC monograph order requests (OMORs), which consist of industry-requested changes to finalized monographs outside of the Drug Facts Label (DFL).

“FDA intends to reduce the time needed for action on monograph issues, going from the current reality of many years for each change, to a timeframe of less than two years in most circumstances, while still maintaining public comment between proposed and final orders, and maintaining FDA's standards for safety and efficacy,” the goals paper states.

In May, *IHP* obtained a discussion draft of the proposed bipartisan OTC monograph reform bill, which would authorize the FDA OTC user fee program and provide two years of exclusivity for a drug developer that submits original human data on its drug ([see related story](#)). The draft, proposed by Sens. Johnny Isakson (R-GA) and Bob Casey (D-PA), has not yet been attached to user fee legislation working its way through Congress, however industry groups and public policy experts -- including the Consumer Healthcare Products Association, the American Academy of Pediatrics and Pew Charitable Trusts -- are advocating for its inclusion ([see related story](#)).

If the new OTC user fee program is enacted, for the first three years FDA would be “substantially 'net-negative' in terms of effective review capacity,” the document states. During these years the agency would put in place the necessary review infrastructure and continue to carry out external mandates, including those related to the Sunscreen Innovation Act and the antiseptic consent decree.

Infrastructure implementation-related activities include: leadership development; development and posting of a nonbinding list of forecasted monograph activities; finalizing Category I ingredients from Tentative Final Monograph (TFM) to Generally Recognized as Safe and Effective (GRASE); reviewing sponsor requests for TFM Category II ingredients not yet deemed as GRASE to be reviewed for safety and efficacy; and implementation of a user fee collection system.

FDA aims to have 30 full-time employee equivalents (FTEs) in fiscal 2018, 24 in fiscal 2019, 23 in fiscal 2020, 19 in fiscal 2021 and nine during fiscal 2022. However, the document highlights that FDA will not see significant growth in review capacity until fiscal 2020 when there will be 64 FTEs, as the training process for new scientific reviewers typically takes two years. By fiscal 2022, FDA hopes to have 110 FTEs.

“[A]lthough new scientific reviewers begin review work immediately, new reviewers will not be fully effective immediately as scientific reviewers, and that effective review capacity will grow slowly at first. FDA scientific review work is highly technical and specialized, requiring knowledge and skills that must be taught after onboarding. Typically, two years are required for scientific reviewers to take all the necessary training, and acquire all the knowledge and experience needed to be fully effective,” the document states.

In developing the infrastructure for OTC monograph review, FDA will also develop a public-facing IT dashboard. Currently “no platform exists for the monograph, a lack which greatly hampers review efficiency,” the draft document states. The agency will develop specifications and award a contract by Oct. 1, 2018, to be implemented by Oct. 1, 2019. The agency also aims to establish an IT platform for receiving electronic submissions, archiving review work and generating reports, which should be fully functioning by April 1, 2022.

FDA plans to catalog and archive older documents containing important monograph ingredient information. However, because these documents are fragile, the process of sorting, scanning and archiving them can be costly and time-consuming, the goals document states, and industry does not support user fees being initially used for this work.

“Industry does not support provision of user fee funds to permit electronic archiving of these documents during the first five years of OMUFA, but agrees that cataloging them could have value to Industry, because some of the documents may contain data that Industry requestors could use to support order requests or other activities of interest to Industry. FDA and Industry have agreed that, among IT-related goals, the priority of creating the IT platform is higher than that of cataloging these paper documents, and therefore IT platform development would be pursued first,” the document states.

Temple, Robert

From: Bastings, Eric
Sent: Friday, September 30, 2016 6:45 AM
To: Dunn, Billy; Unger, Ellis; Temple, Robert; Jenkins, John K
Subject: The Eteplirsen Approval: Former FDA Officials Weigh In On The Science

The Eteplirsen Approval: Former FDA Officials Weigh In On The Science

- 29 Sep 2016
- OPINION



Ramsey Baghdadi [@Ramsey_Baghdadi](mailto:Ramsey_Baghdadi) ramsey.baghdadi@previsionpolicy.com

Executive Summary

A former CDER director, office director, division director, and supervisory reviewer agreed to comment for the record on the merits of the science that formed the basis of FDA's accelerated approval of the Duchenne Muscular Dystrophy therapy *Exondys 51*.

FDA's decision to grant accelerated approval to Sarepta's DMD drug *Exondys 51* (eteplirsen) has generated divergent opinions on what the approval means to the agency standards for approval and to the relationships between the different review levels within the Center for Drug Evaluation and Research.

Patient Advocacy With FDA Review Staff Will Be Tougher Post-Sarepta

By Cole Werble 23 Sep 2016

Efforts by CDER management to encourage more interaction between patients and FDA reviewers may be part of the collateral damage from the difficult FDA review of Sarepta's *Exondys 51*. The hopes of parents of boys with DMD pushed the regulatory flexibility by CDER management on this application – but may end up limiting the willingness of FDA reviewers to...

[Read the full article here](#)

Eteplirsen Review Offers Lessons For FDA, Advocacy Groups, Industry

By Sue Sutter 21 Sep 2016

Agency reviewers believed the line between patient input and external intimidation had been crossed; early data from the Sarepta muscular dystrophy drug's flawed development program stoked patient community expectations and made regulatory review difficult.

[Read the full article here](#)

Further coverage of those issues can be found in the sidebars, but behind them all is the important fundamental assessment on the quality of the science: do the data in the eteplirsen application support accelerated approval?

To bring in knowledgeable observations on the interpretation of the science behind the *Exondys 51* accelerated approval, we asked four former senior FDA officials to comment on the review. These are experts removed from direct involvement in the internal debates on the Sarepta application but experienced in the hard work of FDA regulatory science:

- Former Center for Drug Evaluation & Research Director Carl Peck
- Former Division of Neuropharmacology Drug Products Director Paul Leber
- Former Office of Drug Evaluation II Director Robert Meyer
- Former Supervisory Medical Reviewer Thomas Garvey

After a review of the [documents and scientific arguments](#) released by FDA at the time of approval, all four agreed to have their remarks published in their entirety for the record.

Carl Peck

Former CDER Director

Chairman & Founder, NDA Partners

First of all, this is regulation at its best. We have really competent people in FDA, all who understand the science and all who care about the patients. This is all legal, there is no malfeasance or anything like it. We are so lucky to have a transparent process here.

Second, there has been a concern expressed about a center director who gets involved in the review process. Again, that's regulation at its best. You don't want a center director who doesn't know or care about the science or a center director who doesn't care about the review. Remember, the authority to approve drugs resides with the HHS Secretary, that is delegated to the FDA Commissioner who in turn delegates it to the center director, who in turn delegates it to the office and division directors. During my time as center director, I personally reviewed and signed at least three NDAs. There is nothing unusual about this.

Looking through the summary review, these documents are really informative and powerful. The key issue that emerges is the meaning of the biomarker that they selected [dystrophin production]. The question is, is it going to benefit patients? The answer to that question is not entirely clear. As you read through the documents, Janet and Unger agree on a lot of things. The disagreement is over whether the evidence fits into the accelerated approval regulation. That is a judgment call, plain and simple.

My personal view is that Janet made the right decision. Because it's the decision I would have made.

My personal view is that Janet made the right decision. From the information that I have seen, that is the decision I would have made.

The idea that it weakens the standard I don't believe is true. A lot of these issues first evolved during the AIDS crisis that I, along with former Commissioner Frank Young and then David Kessler were thrust into. We wanted to have rules and good science that also gave these young men opportunity for relief and who were otherwise guaranteed a fatal outcome.

My conclusion on the Sarepta decision is not a feeling. It's the result of an analysis of the publicly available evidence. The basic approval criterion that we're used to for standard drugs is based on frequentist statistics – the P value gives you a very simplistic yes or no answer that can be misleading. Is it greater than 0.05 or less than 0.05? It formally excludes all other information or evidence. Lots of things happen in clinical trials and there is a lot of information to consider.

Although a formal Bayesian analysis that considers all available data was not undertaken in this instance, implicitly or intuitively, that is what Janet applied to this.

Am I convinced by the muscle data? No, not by itself. But by the totality of evidence? Yes.

What I think is in play here is the philosophical framework that each has brought to bear on the evidence and accelerated approval. Strong personalities stake out positions and sometimes it's hard to move them.

Paul Leber

Former Division of Neuropharmacological Drug Products Director

Director, Neuro-Pharm Group, LLC

Section 21 CFR 314.510 of FDA's regulations state that "FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit."

Dr. Woodcock, who held signatory authority for the Exondys 51 (eteplirsen) NDA, concluded (see her Center Director Decisional Memo) (1) "...that there is evidence from adequate and well-

controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells” and (2) “... that both the biochemical data and the clinical data lead me to conclude that an “increase in dystrophin production” is reasonably likely to predict clinical benefit in DMD.”

Viewed from a strictly scientific perspective, however, the evidence cited to justify the marketing of eteplirsen is quite weak, perhaps even grossly inadequate.

Accordingly, FDA’s decision to approve eteplirsen for marketing appears on its face to conform fully with the requirements of existing federal drug regulatory law and regulation.

Viewed from a strictly scientific perspective, however, the evidence cited to justify the marketing of eteplirsen is quite weak, perhaps even grossly inadequate. At the crux of the problem is the ill-conceived notion that an individual can determine in any substantively meaningful way whether an un-validated surrogate is likely to predict anything, let alone a drug effect. A belief, no matter how strongly held, is not scientific evidence. To meaningfully evaluate the predictive power of a surrogate one needs to determine whether, and if so, how a change in the surrogate is related to a change in the clinical status of patients over the full range of outcome states that are of potential clinical interest.

The scientific limitations of un-validated surrogates are well known; in 1992, when the accelerated approval rule was first published for comment, I submitted a formal comment to the administrative file of the pending regulation urging that it not be adopted.

I suspect the rule survives because it provides a way for the FDA to be flexible in its evaluation of “promising drugs” intended for the treatment of serious and life-threatening illness.

For the record, what I know of the eteplirsen derives from a cursory read of several documents explicating the views of FDA officials who were involved in an extensive and protracted internal debate concerning the ‘approvability’ of Sarepta’s NDA.

Robert Meyer

Former Office of Drug Evaluation II Director

**Director, Virginia Center for Translational & Regulatory Sciences at
UVA School of Medicine**

Focusing on the science of it over the process, from my point of view, I would characterize the database provided by the company to FDA as interesting and I would see there might be some evidence of an effect, but I would not see that there was a basis for approval based on substantial evidence.

To be honest, I had more concerns on the safety side than expressed in the FDA documents. Based on the small number of patients studied, there is only about a 1 in 20 chance of seeing an event from a safety perspective, meaning even something occurring at a rate of 1 out of 100 patients exposed can't be excluded. While no important signal was seen with eteplirsen, when you look at the predicate drug, Biomarin's drisapersen, which was not approved, it had some pretty serious side effects from a safety perspective.

I had more concerns on the safety side than expressed in the FDA documents. On efficacy, what puzzled me is that the treatment of dystrophin production as a valid surrogate seems less credible when viewed in context the Biomarin drug, and that did not seem to be incorporated into the review decision. Biomarin conducted a pretty substantial, rigorous, well-controlled trial so they did some pretty substantial work on this. In essence, the Biomarin program more robust and despite them showing some pharmacodynamic improvement on dystrophin and early function, the larger, longer trials failed.

One other thing to consider is the confirmatory data. If, for instance, the main trial to confirm the subpart H is a dose-response design without a placebo (and the Western Blots did not show a dose-response) the failure to show a difference between the regular dose and high arm could mean neither worked, the trial failed or both worked equally – and you won't know.

I think the decision reflects a tension between the staff within the center and Dr. Woodcock. She talked about the FDA's longstanding concern about never approving drugs that end up to be ineffective. She's expressed concern about denying drugs when the risk is the other way – not approving drugs that may be effective. That's a legitimate point of view, particularly for a very dire disease with no effective therapies. And the ultimate authority to approve drugs rests with the HHS Secretary and is delegated down the chain. She has the perfect right to intercede, but it is highly unusual.

Besides the internal staff, Janet did get to speak to the advisory committee directly and make these points to them. And still, they mostly recommended against it by a slim majority. So, she's not just acting against the decisions of the people in the review division, but also against the recommendation of the advisory committee.

The closest parallel to this is kind of decision is oncology. Sarepta did show four patients who are substantially out on treatment, who would have been predicted to have lost ambulatory function, but who have not. Most cancers at a late stage never see a regression, so if you see evidence of regression even in a small number of patients in an uncontrolled sample, that can be compelling.

So maybe this accelerated approval decision is not unprecedented, but the politics here seem pretty rare.

Tom Garvey

Former Supervisory FDA Medical Reviewer, Division of Cardio-Renal Drug Products

Founder, Garvey Associates, Inc.

Eteplirsen, a drug with a novel mechanism involving eliding translation of a mutated, dysfunctional exon, is aimed at Duchenne's Muscular Dystrophy (DMD), an inborn, X-linked genetic error resulting in inexorably progressive muscle wasting and death usually before the fourth decade for which no significantly effective therapy exists currently. Sarepta Therapeutics developed eteplirsen with considerable FDA input, and, seeking "accelerated approval" to market the drug, submitted a new drug application (NDA) to FDA on June 26, 2015.

Even without access to the primary data and other key information, it seems clear, on the basis of assessments by experienced and competent FDA reviewers and supervisors, that although the drug appears to be safe, the data submitted in the eteplirsen NDA do not meet the Agency's current evidentiary standards for effectiveness and, hence, the drug does not qualify for any sort of approval. As an aside, that this is the case appears to have been obvious very quickly after submission and raises the question of why there was not a refusal-to-file (RTF). There was no RTF, apparently, and, hence, FDA agreed to review the NDA indicating that the possibility of approval was entertained by somebody high enough in the FDA hierarchy to ensure filing.

By law, regulations and precedent, the eteplirsen NDA is not approvable. Yet, Janet Woodcock has asserted that regardless of the eteplirsen NDA's glaring deficiencies (even though the drug was developed with FDA's vigorous assistance) that the drug, is approvable for marketing.

I think that what Dr. Woodcock may really mean is that FDA's handling of drugs like eteplirsen for indications like DMD must change.

I think that what Dr. Woodcock may really mean is that FDA's handling of drugs like eteplirsen for indications like DMD must change. I am quite sure that FDA has been considering how to modify evidentiary standards for approval of drugs like eteplirsen, recognizing that recent advances in science and medicine are rapidly producing new knowledge and therapeutic approaches to previously intractable disease/conditions that may not fit well into the current regulatory framework. Beyond the thorny legal and epistemological issues, individualized or personalized medicine, to some extent driven by fast moving advances in understanding and manipulation of the genome and epigenome as well, have resulted in a new world of therapeutic endeavor and this must be considered.

This is not an easy problem. FDA's pace in dealing with such matters is typically and, perhaps, reasonably, glacial. It is possible, however, to accelerate the process.

Because of its many "warts," the eteplirsen NDA may not have been the best choice to prod FDA into action, but I suspect that Dr. Woodcock decided that something had to happen. Overall, I think the situation is not unusual in that FDA has, in the past responded to real-world situations (e.g., the need for HIV/AIDS drugs) of a sort that could only be encountered by FDA, by moving regulatory science forward to better serve and protect the public.

A positive aspect of the furor over eteplirsen is FDA's exemplary and laudable willingness to allow the public almost complete access to the intra-mural goings on.

Temple, Robert

From: Bastings, Eric
Sent: Tuesday, February 23, 2016 10:26 AM
To: Dunn, Billy; Unger, Ellis; Temple, Robert
Subject: Sarepta



[Peter Ciszewski](#)

Founder and Editor, Biotech 5

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Eteplirsen: The FDA's Lose-Lose Dilemma

Jan 21, 2016

There's a lot more at play with Sarepta's Food and Drug Administration (FDA) Advisory Committee (AdComm) meeting and Feb's Prescription Drug User Fee Act (PDUFA) date than the typical AdComm meeting. Whether or not the FDA approves eteplirsen for Duchenne muscular dystrophy (DMD) is important, but it is the behind-the-scenes story line that is most compelling. The FDA may find itself in a lose-lose situation with eteplirsen, with the government Agency (in the end) having to dig itself out from a bigger mess than the snow storm this weekend.

Last Friday, when the FDA released its briefing documents ahead of eteplirsen's review by the FDA's Peripheral and Central Nervous System Drugs AdComm, the Agency made an extremely persuasive case not to approve Sarepta's drug for DMD. In the briefing documents, the FDA determined that Sarepta's overall dataset did not provide evidence to support efficacy in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The FDA raised concerns regarding the comparison of eteplirsen-treated patients with the control group and whether dystrophin levels were increased by the drug. The FDA even cast doubt on eteplirsen's safety profile, suggesting that the dataset was too small to draw any valid conclusions.

The problem is, according to Sarepta and DMD parents and physicians, the FDA used misleading and flawed assumptions in their analysis of eteplirsen. In an [addendum](#) to the FDA briefing documents, Sarepta highlighted 10 clarifications. In a [letter](#) written on Tuesday (Jan 19), DMD Patient Advocate and mother of a participant in Sarepta's eteplirsen Study 201/202 trials, Terri Ellsworth highlighted six items in the briefing documents that she and the 9 other trial parents believe are either false or misleading.

Some have even speculated that the Sarepta decision is turning out to be a battle within the FDA between the Agency's Hierarchy (Drs. Billy Dunn, John Jenkins, and Janet Woodcock) and the FDA's Division (in this case, Drs. Eric Bastings and Ronald Farkas). Traditionally, the FDA's Divisions held significant power, since they are the ones writing the guidance documents and recommendations for approval.

The FDA's lose-lose dilemma goes like this: If eteplirsen **is not approved**, there will be a hostile response from patients, advocates, and Congress aimed at Dr. Janet Woodcock (and the Hierarchy). The FDA also knows that by rejecting eteplirsen, the situation will not "go away," as parents and advocates will continue to fight and perhaps dig in even deeper against the FDA. However, if the FDA **approves** eteplirsen, Drs. Farkus and Bastings will feel that it will be perceived that the FDA is lowering its standards.

Drs. Billy Dunn, Eric Bastings, Ellis Unger, Ronald Farkas, Robert Temple, John Jenkins, and Janet Woodcock are going to have some explaining to do regarding the Sarepta briefing documents if eteplirsen is not approved. Patient advocates like Teri Ellsworth, Christine McSherry, and Jenn McNary are not going to take an eteplirsen rejection lightly. As mothers with DMD children in the trials, it is surprising that the FDA did not reach out to them for some input. Rare diseases are classified as such because they are unique, and there are not many physicians and researchers who truly understand them. In the rare disease community, it is widely understood that the patients and parents are the true experts in the disease state. During the eteplirsen AdComm meeting, we are likely to hear a lot about "Patient-Reported Outcomes." It is telling that in the FDA's briefing document, "Patient-Reported Outcomes" was not mentioned once, nor does it seem that the FDA reached out to patients and their families for their input.

Although many Wall Street analysts and investors believe that there is a very low likelihood of eteplirsen gaining approval (due primarily to the FDA's stance in the briefing documents), there are some who think that the pressure is on the FDA and that they will need to approve this drug. If the FDA does not approve eteplirsen, there will be a perception that there was a bias in the briefing documents, a disregard of the patient community for input, and an unwillingness to consider FDASIA. Considering these three points, the FDA may have dug themselves into a hole, and the only way out will be conditional approval.

Philips, Howard

From: Temple, Robert
Sent: Tuesday, January 26, 2016 12:42 PM
To: Woodcock, Janet; Dunn, Billy; Jenkins, John K; Clarke, Mary Beth
Subject: Re: rescheduled AC for eteplirsen

I just want to be sure we have enough time to fully review the 4 year data and all aspects of the hist controlled trial. The (b) (5) should allow that

Sent from my BlackBerry 10 smartphone.

From: Woodcock, Janet
Sent: Tuesday, January 26, 2016 12:08 PM
To: Dunn, Billy; Jenkins, John K; Clarke, Mary Beth; Temple, Robert
Subject: RE: rescheduled AC for eteplirsen

I am ok with this. The advocates can arrange something—a video or something—if completely needed. I just talked to Mary Beth and John J and Bob T who had a slightly different understanding. If you folks can come to an agreement, what you do is fine with me. I would still prefer using a hotel though, but I think the (b) (5) would be too early for that. Also, the (b) (5) might be too soon for us to have fully reviewed the most recent cohort compar that the firm has submitted. There are no good answers here, so it is up to you folks. Certainly made the right call on the snow! jw

From: Dunn, Billy
Sent: Tuesday, January 26, 2016 12:01 PM
To: Woodcock, Janet
Subject: rescheduled AC for eteplirsen

Janet,

As you know, we advised Sarepta last week when we postponed the AC that (b) (5) was a working date.

When we discussed it in person, you were moving towards canceling an obligation you had on that day, which we have been told you did cancel (as Bob also indicated he would, so he could attend the AC), and we made preliminary plans to move forward with that date.

Polling of the AC members has revealed that near complete availability – we only have one voting member who will not be available (a new member that would not have participated in the AC last week), and the non-voting industry representative will not be available, but we have a backup industry representative. So, the makeup of the committee is intact.

We contacted Sarepta to get final confirmation from them that (b) (5) would be acceptable, and they have confirmed that date is acceptable to Sarepta and that all their external consultants are available. They will not be missing any personnel that they want to bring to the AC.

We know that you have received some feedback from an advocate regarding this date. One of the primary objections they raised was the lack of availability of two folks, (b) (6), without whom “There literally cannot be an adcom...” As I just noted, Sarepta has all their external consultants arranged and available.

It was a bit puzzling to us as it seemed that the advocate was perhaps trying to speak for the sponsor, but we have sorted that out and the date is acceptable to both FDA and Sarepta. Given that mutual agreement, we want to check with you to make sure that you are ok with continuing to move forward with the (b) (5) date. Notwithstanding the enormous sensitivity and

understanding we have for the points the advocate has made and the logistical issues for public attendees, we are strongly in favor of officially announcing a rescheduled date of (b) (5). If both we and the sponsor support this date, and the committee is available, then that takes care of the most important components, and I am confident that the advocacy community will ultimately be able to accommodate it to a reasonable degree.

(b) (6) are both unabashedly pro-etepirsen and I can understand the enthusiasm the advocates have for their presence, but they will not be playing a formal role in the proceedings. As an aside, I attended a high-profile plenary lecture of (b) (6) and it was remarkably poor.

We need to move quickly on this (today, according to AC staff) so I wanted to make sure to touch base directly with you before moving forward with ensuring that all involved at FDA are ok with this date.

Billy

Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Friday, January 29, 2016 1:35 PM
To: Unger, Ellis
Cc: Breder, Christopher D; Bastings, Eric; Farkas, Ronald; Temple, Robert; Dunn, Billy; Choy, Fannie (Yuet)
Subject: RE: Sarepta IR

All,

Eric has looked at the revisions and cleared the version below. IR was sent to Sarepta today. Thanks

Fannie

Please send the following request:

- 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.

From: Unger, Ellis
Sent: Friday, January 29, 2016 1:24 PM
To: Breder, Christopher D; Choy, Fannie (Yuet); Bastings, Eric; Farkas, Ronald; Dunn, Billy; Temple, Robert
Subject: RE: Sarepta IR

I'm not so much worried about the difficulty on our end, but when we say all source documents, including materials on the 6MWT, we're basically asking for everything ever generated on these kids. That would not be an information request that could be fulfilled in a timely fashion. It seems unreasonable. In other words, we need to tell them what we want.

From: Breder, Christopher D
Sent: Friday, January 29, 2016 10:09 AM
To: Unger, Ellis; Choy, Fannie (Yuet); Bastings, Eric; Farkas, Ronald; Dunn, Billy; Temple, Robert
Subject: RE: Sarepta IR

I was intentional so that things did not get left out. I am somewhat concerned about their being selective in what gets sent, though I appreciate, especially since they will be in a foreign language, that this will increase the difficulty on our end.

From: Unger, Ellis
Sent: Thursday, January 28, 2016 5:52 PM
To: Choy, Fannie (Yuet); Bastings, Eric; Farkas, Ronald; Dunn, Billy; Breder, Christopher D; Temple, Robert
Subject: RE: Sarepta IR

All,

In re-thinking, I think the first bullet needs revision/clarification. What do we mean by “[all source documents](#)?” Do we mean every medical record in existence for each of the boys? I don’t think so. I think we need to focus this particular request.

How about:

- For the participants in the natural history cohort of your New Drug Application ([REDACTED] (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 ambulation and 6-minute walk tests
 - All medical records related to physical disability and assessment of NSAA
 - Records of all phone calls between the study site(s) and the participants
 - Spreadsheets and data files used to record test results

Please give this some thought.

Ellis

From: Choy, Fannie (Yuet)
Sent: Thursday, January 28, 2016 3:53 PM
To: Bastings, Eric; Unger, Ellis
Cc: Farkas, Ronald; Dunn, Billy; Breder, Christopher D; Temple, Robert; Choy, Fannie (Yuet)
Subject: RE: Sarepta IR

Below is a clean version of the Sarepta IR. Please let me know if this is final. Thanks Fannie

- Please send electronic copies of [all source documents](#) for the following study participants in the natural history cohort for your application [REDACTED] (b) (6)
 - These documents should include all materials related to their performance on the six minute walk test, including minutes or records of phone calls between the study site(s) and the participants, and medical records related to each participant’s ambulation and physical disability.
- 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.

From: Temple, Robert
Sent: Thursday, January 28, 2016 11:24 AM
To: Unger, Ellis; Bastings, Eric
Cc: Farkas, Ronald; Dunn, Billy; Breder, Christopher D; Choy, Fannie (Yuet)
Subject: RE: Sarepta IR

Looks good to me. No more suggestions.

From: Unger, Ellis

Sent: Thursday, January 28, 2016 10:47 AM

To: Bastings, Eric

Cc: Farkas, Ronald; Temple, Robert; Dunn, Billy; Breder, Christopher D; Choy, Fannie (Yuet)

Subject: RE: Sarepta IR

My suggestions – other people may also have some.

- Please send electronic copies of all source documents for the following study participants in the natural history cohort for your application: (b) (6)
 - These documents should include all materials related to their performance on the six minute walk test, including minutes or records of phone calls between the study site(s), and the participants, and medical records related to each the participant's ambulation and physical disability.
- 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.

From: Bastings, Eric

Sent: Thursday, January 28, 2016 10:08 AM

To: Unger, Ellis

Cc: Farkas, Ronald; Temple, Robert; Dunn, Billy; Breder, Christopher D; Choy, Fannie (Yuet)

Subject: Sarepta IR

Ellis,

Here is our draft request. Any edits?

Eric

- Please send electronic copies of all source documents for the following study participants in the natural history cohort for your application (b) (6)
 - These documents should include all materials related to their performance on the six minute walk test, including minutes or records of phone calls between the study site(s), and the participants, and medical records related to the participant ambulation and physical disability
- 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

Please provide this information within 7 business days from receipt.

Philips, Howard

From: Jillapalli, Devanand
Sent: Monday, February 01, 2016 4:52 PM
To: Temple, Robert
Subject: Advice reg: Muscular Dystrophy Coordinating Committee meeting on 4/27/16

Hi Dr. Temple,

I am writing to seek your advice about a briefing for the Muscular Dystrophy Coordinating Committee (MDCC) regarding the regulatory outcome of two DMD NDAs – Biomarin’s drisapersen (which we now know is a Complete Response) and Sarepta’s eteplirsen, at the next scheduled meeting on 4/27/16. I represent the FDA at the MDCC. As you know, Congress ("MD-CARE Act" 2001; P.L. 107-84) authorized the establishment of the MDCC to coordinate activities across the National Institutes and with other Federal health programs and activities relating to the various forms of muscular dystrophy. The NIH is represented by several of its institute Directors, and Dr. Steven Katz, the Director of NIAMS, is the current Chair of MDCC. Several federal agencies including the FDA and, importantly, many patient advocacy groups attend these meetings which are held twice a year. Depending on the outcome for Sarepta’s drug, especially if it is a Complete Response, the committee’s leadership is concerned that there will be lot of questions from patients and their advocacy groups and, therefore, am reaching out to you regarding your thoughts about a senior FDA official attending the upcoming meeting on 4/27/16. Looking forward to your advice. Thanks.

Dev Jillapalli

(I recently moved from Division of Neurology Products to the Office of Orphan Products)

Philips, Howard

From: Eggers, Sara
Sent: Monday, February 01, 2016 12:04 PM
To: Unger, Ellis
Cc: Vaidya, Pujita; Walker, Susanne T.; Temple, Robert; Frey, Patrick
Subject: RE: Example Frameworks RE: Clinical Review Template (CRT) WG

Thanks much Ellis for putting thought into this. Your point about not being able to weigh benefits and risks in this case is valid, and Bob did not complete a BRF in his decision memo, with the same reasoning.

However, the clinical review template does call for a BRF even if the standard for efficacy has not been met. Drisapersen is our first example of a BRF that address this situation, and moreover it is one of only a few examples of a BRF articulating a complete response for any reason.

DSAT felt that this case was a nice example because the Division took care to convey the unmet medical need (which was high profile publicly) and to make the point that unmet medical need does not trump the need to demonstrate effectiveness. Billy Dunn's BRF (the DD) in particular follows the guidelines provided in our template, for example by discussing what additional evidence would be needed to support the B-R assessment.

So, perhaps it is not the best example of a typical decision, but we felt it was useful in showing what different types of BRF we can expect.

Our WG will review many BRFs over the next year. Since we already sent this out for the WG's review, I suggest that we keep this example as is.

Sound reasonable?

Sara

From: Unger, Ellis
Sent: Saturday, January 30, 2016 11:50 AM
To: Eggers, Sara
Cc: Vaidya, Pujita; Walker, Susanne T.; Temple, Robert; Frey, Patrick
Subject: RE: Example Frameworks RE: Clinical Review Template (CRT) WG

(b) (4)

. Could you find another example(s)?

From: Eggers, Sara
Sent: Friday, January 29, 2016 4:50 PM
To: Joffe, Hylton; Walker, Susanne T.; Temple, Robert; Unger, Ellis; Beitz, Julie G; Albrecht, Renata; Sile, Helen; Doi, Mary; Frey, Patrick; Pai-Scherf, Lee; Popat, Vaishali; Loewke, Sally A; Donohue, Kathleen
Cc: Schrieber, Sarah J; Roberts, Jeff; Goldstein, Marc *; Valerie Overton (Valerie.Overton@erg.com); Woodward, Shanon *; Vaidya, Pujita
Subject: Example Frameworks RE: Clinical Review Template (CRT) WG

Dear colleagues,

Our CRT/Benefit-Risk Workgroup will resume on Friday, Feb. 5. If you have a chance before then, it may be helpful to review two example frameworks that reflect the type of frameworks we are seeing so far. Although we are sending the whole review, you need only to look at Section 1, which includes the Benefit-Risk Frameworks. Please let me know if you have any questions. We look forward to a rich (and very full!) discussion on Friday.

Sara

1. Ixazomib (OHOP), primary clinical reviewer

<< File: Ixazomib_NDA208462_Primary.pdf >>

2. Drisapersen (DNP), primary clinical review AND division director review

<< File: Drisapersen_NDA206031_Primary_Efficacy.pdf >> << File: Drisapersen_NDA206031_DD.pdf >>

*****Meeting Background*****

Background: This WG started in 2013, tasked with revising the clinical review and management templates to incorporate the Benefit-Risk Framework (BRF). I believe our last WG meeting was in May 2015. A staged implementation of the templates began with NME NDAs and original BLAs submitted to the Center after March 1, 2015, and the implementation has been supported by a monthly training offering as well as a BRF writing course and individual coaching. All templates are available on the [21st Century webpage](#). There is also a dedicated page [2015 Clinical and Review Management Templates Homepage](#).

With the implementation underway, the role of the Clinical Review Template Working Group will now evolve into a review, advisory and support role in the implementation of the BRF and templates. Defining tasks of this WG will be to:

- Review progress and advise on the template implementation, including internal websites, training and individual support
- Review Benefit-Risk Frameworks completed as part of the template rollout; advise on general direction of BRFs and identify opportunities to strengthen guidance or training
- Monitor progress on a formal evaluation of the BRF into the review process (conducted by Eastern Research Group)
- Review user and audience feedback on the new templates and advise on potential modifications or enhancements in future revisions.

The WG will likely convene every two months. We have valued each members' contribution on the WG to date, and we encourage you to continue participating if your schedule allows. If you are no longer able to participate in the WG, please let me know.

January 12 Meeting Purpose:

1. To review the new role of the CRT WG (and maybe a new name)
2. To review updates on the implementation and training, as well as the evaluation project
3. To provide initial feedback on a sample of BRFs completed as of January 1, 2015 (will be sent in advance)

Web-ex will be provided.

Philips, Howard

From: Breder, Christopher D
Sent: Monday, February 01, 2016 8:36 AM
To: Farkas, Ronald; Bastings, Eric; Dunn, Billy; Unger, Ellis; Temple, Robert; Bhattaram, Atul
Subject: RE: how loss of ambulation reported in Sarepta controls

That seems to correspond to what they said in the last meeting, that these losses of ambulation were determined by a phone call report, not a clinic visit as is now being reported.

cdb

From: Farkas, Ronald
Sent: Saturday, January 30, 2016 1:59 PM
To: Bastings, Eric; Dunn, Billy; Unger, Ellis; Temple, Robert; Breder, Christopher D; Bhattaram, Atul
Subject: how loss of ambulation reported in Sarepta controls

I see in Sarepta's new addendum their explanation for if 6MWT was measured per-protocol for patients who lost ambulation, or only was "reported", perhaps by telephone: for 3 of the patients, it is missing/reported – see below.

Thanks

Ron

Of note, External Control patients (b) (6) and (b) (6) were subsequently reported to have loss of ambulation v meters on the 6MWT at ~4.5 years. In addition, external control patient (b) (6) was known to have lost with a 6MWT of "0" at 4.8 years.

Table 2: External Control Subjects (n=13) with Results of 6MWT at Year

Subject Number	Baseline 6MWT	Year 3 6MWT	Year 4 6MWT	Age
(b) (6)	380	195	* Missing	12.6
(b) (6)	295	35	0	13.3
(b) (6)	380	0	0	12.0
(b) (6)	329	218	0	12.8
(b) (6)	388	0	0	12.1
(b) (6)	388	0	0	14.1
(b) (6)	325	0	0	11.3
(b) (6)	458	362	300	14.2
(b) (6)	200	0	0	15.5
(b) (6)	373	273	0	13.0
(b) (6)	327	0	0	15.5
(b) (6)	451	Missing	0	15.2
(b) (6)	355	* Missing	* Missing	12.3

* External Control patients with missing 6MWT data at Year 4.

Philips, Howard

From: Unger, Ellis
Sent: Monday, February 08, 2016 2:38 PM
To: Temple, Robert; Jenkins, John K
Subject: Fw: NDA 206488 / eteplirsen - Urgent Request for Tcon with FDA

Sent from my BlackBerry.

From: Dunn, Billy <Billy.Dunn@fda.hhs.gov>
Sent: Monday, February 8, 2016 2:01 PM
To: Unger, Ellis
Cc: Bastings, Eric
Subject: FW: NDA 206488 / eteplirsen - Urgent Request for Tcon with FDA

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Thursday, February 04, 2016 10:58 PM
To: Dunn, Billy; Choy, Fannie (Yuet)
Cc: Matthew Rael
Subject: Re: NDA 206488 / eteplirsen - Urgent Request for Tcon with FDA

Dear Dr. Dunn,

[Follow-up to meeting with Dr. Woodcock on 2/3/2016](#)

In light of the upcoming PCNS Drugs Advisory Committee for eteplirsen being delayed beyond February 23rd, we hereby request a teleconference with the Division to discuss the following points:

1. The recent information request received from FDA on 1/29
2. The timing of the rescheduled PCNSDAC Date
3. The impact on the PDUFA goal date for the NDA.

Yesterday, Dr. Kaye, myself and Frank Sasinowski had a telephone conversation with Dr. Woodcock regarding her decision to delay the Advisory Committee meeting by ~ 4-5 weeks. Dr Woodcock stated that she found the difference in the Loss in Ambulation data at 4 years for the eteplirsen 201/202 patients vs the untreated External Control boys striking and compelling and wanted a few weeks to allow FDA to verify these data. She also emphasized that she wanted a united front between FDA and Sarepta at the eteplirsen AC meeting. Dr Woodcock also confirmed that she would stay fully engaged and would personally attend the AC.

Please note that Sarepta would like to work collaboratively with the FDA and will endeavor to provide the information requested as soon as possible.

Our attendees would be as follows:

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

- Shamim Ruff, Senior Vice President, Regulatory Affairs and Quality
- Helen Eliopoulos, MD, Senior Director, Strategic Medical Advisor
- Petra Duda, MD PhD, Medical Director
- Kris Piper, Senior Director, Clinical Quality Assurance
- Paul Allesandro, MS, Director, Regulatory Affairs
- Matthew Rael, MS, Senior Manager, Regulatory Affairs

We request that this meeting take place early next week.

Upon confirmation, we will provide a teleconference number.

Regards,

Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality

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

e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

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Philips, Howard

From: Dunn, Billy
Sent: Monday, February 08, 2016 7:38 AM
To: Unger, Ellis; Bastings, Eric
Cc: Temple, Robert; Locicero, Colleen L; Lowy, Naomi
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Ellis,

If Dr. Jenkins has requested it, then we probably should go ahead and get it scheduled. Happy to discuss today.

Billy

From: Unger, Ellis
Sent: Friday, February 05, 2016 6:13 PM
To: Bastings, Eric; Dunn, Billy
Cc: Temple, Robert; Locicero, Colleen L; Lowy, Naomi
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Eric/Billy,

I ran this by Dr. Jenkins today (during my PMAP), and he suggested/requested that we have another CD briefing to talk about strategy for the continuing review and upcoming ACM. We'd had a post-AC meeting on the schedule with Dr. Woodcock, but cancelled it.

I think we should try to get on her schedule in the next 2 weeks.

Any thoughts?

Ellis

From: Farkas, Ronald
Sent: Wednesday, February 03, 2016 2:58 PM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Breder, Christopher D
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Ellis,

I talked with Tony El Hage about FDA's ability to inspect Sarepta's external control sites. Not unexpectedly, he said it was not possible in the time frame we are thinking about, and even if time wasn't a consideration it would be difficult because the sponsor got 13 patients from something like a dozen different sites, so any meaningful inspection would seemingly need to go to multiple sites (although I don't think we actually know how many or which patients came from which sites).

Tony recommended, however, that we ask the applicant to conduct an independent audit of the external control data. We described what we are looking for in some detail (recent IR below), so would need to add a request about the external audit. I'd recommend something like the following so that we can understand what subset of the clinical population the 13 selected patients represent:

We request that you conduct an independent audit of the clinical sites for the external control patients. In addition to the items in our information request of 29 January, 2015, the audit should account for the disposition of all Duchenne

patients screened at the clinical sites for potential enrollment into the natural history cohort (e.g. both non-exon 51 and exon-51 skippable patients, and including patients who did not enroll in the natural history study).

Thanks
Ron

- 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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Philips, Howard

From: Unger, Ellis
Sent: Monday, February 08, 2016 4:47 PM
To: Ligon, Sharnell (CDER)
Cc: Jenkins, John K; Temple, Robert; Dunn, Billy; Choy, Fannie (Yuet); Locicero, Colleen L
Subject: Request for Center Director Briefing

Hi Sharnell,

ODE-I would like to request a Center Director briefing with Dr. Woodcock on the NDA for eteplirsen for the treatment of Duchene muscular dystrophy (DMD), NDA 206488.

The purpose of the briefing is to discuss the ongoing review of the eteplirsen NDA, and what will be presented during an Advisory Committee Meeting in April. We would like to discuss the strengths, limitations, and uncertainties of the data, particularly with respect to the comparison between the open-label eteplirsen group and a contemporary untreated external control group.

Invitees from ODE-I should probably include the same individuals who were present at the CD briefing on 1/13/16: Fannie Choy (RPM contact for the NDA), Robert Temple, myself, Billy Dunn, Eric Bastings, Ronald Farkas, Veneeta Tandon, Christopher D Breder, Sally Jo Yasuda, Alice Hughes, Colleen Locicero, and Jackie Ware.

Eteplirsen proposed indication is for the treatment of patients with Duchene muscular dystrophy due to a deletion in the dystrophin gene that is amenable to exon 51 skipping.

Ellis

From: Jenkins, John K
Sent: Monday, February 08, 2016 12:10 PM
To: Unger, Ellis
Subject: AC

Ellis

I just spoke to Janet and she confirmed she wants to attend the eteplirsen meeting. She has vacation planned for early April, so we will need to work around that. May need to move toward mid-April. ACS should check with Sharnell.

JW also agreed with my suggestion that we meet on the registry issues and questions we need to address. Please be sure to follow up with Sharnell on getting that scheduled ASAP.

John

Philips, Howard

From: Walsh, Sandy
Sent: Monday, February 08, 2016 10:18 AM
To: Dunn, Billy; Jenkins, John K; Shreeve, Chris; Rawlings, Kimberly; Temple, Robert; Unger, Ellis; Woodcock, Janet; Whyte, John; Klein, Richard M; Prasad, Salina (FDA); Morin, Steve; Kremzner, Mary E; Chew, Catherine
Cc: CDER Trade Press; Rodriguez, Jennifer; Bolek, Michelle; Conover, Katie; Choy, Fannie (Yuet); Farkas, Ronald; Bastings, Eric; Ware, Jacqueline H; Horowitz, Sarah; Auchincloss, Kalah; Diggs, Felicia; Haughey, Laurie; Kotz, Deborah; Choi, Moon Hee; Choy, Fannie (Yuet); Ngo, Diem-Kieu (CDR,USPHS); Ventura, Jeff; Walinsky, Sarah; Peterson, Jayne E; Klein, Richard M
Subject: Sarepta's statement on eteplirsen

FYI only -- Sarepta's announcement today regarding the status of eteplirsen.

Sarepta's statement:

<http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=2136367>

Sarepta Therapeutics Receives Notification of PDUFA Extension for Eteplirsen

PDUFA goal date extended by standard extension period of three months to May 26, 2016

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Feb. 8, 2016-- Sarepta Therapeutics, Inc. (NASDAQ:SRPT), a developer of innovative RNA-targeted therapeutics, today announced that the U.S. Food and Drug Administration (FDA) will require additional time to complete its review of the New Drug Application (NDA) for eteplirsen, for the treatment of Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping. In a notice received from the FDA, the Prescription Drug User Fee Act (PDUFA) date for eteplirsen has been extended to May 26, 2016. The rescheduled date for the Peripheral and Central Nervous System Advisory Committee meeting has not yet been determined.

The FDA notified Sarepta that its January 8, 2016 submission of 4-year clinical effectiveness data, which included additional six minute walk test (6MWT) and loss of ambulation data compared to a historical control, has been designated as a major amendment to the NDA. The FDA stated that the PDUFA goal date has been extended by three months to allow for a full review of the submission. As described in the Sarepta Advisory Committee Briefing Document Addendum, the principal basis for establishing the effectiveness of eteplirsen is a comparison of patients in Study 201/202 to a historical control group.

“While our primary goal is to bring treatment to patients with Duchenne as quickly as possible, we appreciate the efforts of the FDA to conduct a complete review of all of the data supporting our NDA and we remain committed to working closely with them throughout the remainder of the regulatory process”, said Edward Kaye, Sarepta's interim chief executive officer and chief medical officer.

The FDA has previously granted eteplirsen Priority Review status, which is designated for drugs that provide a treatment where no adequate therapy exists. The FDA also granted Rare Pediatric Disease Designation to eteplirsen, as well Orphan Drug Designation and Fast Track Status.

It is estimated that Duchenne muscular dystrophy affects approximately one in every 3,500 – 5,000 boys born worldwide, with 13 percent of people with the disease having mutations addressable by eteplirsen/exon 51 skipping.

Sandy Walsh

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669 / Cell: 240-328-7088
sandy.walsh@fda.hhs.gov



Philips, Howard

From: Jenkins, John K
Sent: Tuesday, February 09, 2016 6:58 PM
To: Unger, Ellis
Cc: Dunn, Billy; Temple, Robert
Subject: Re: Briefing Document Issues Final.pptx

Ellis

I understand your concerns. When Janet mentioned the (b) (6) call to me the other day she said she told her this was her (b) (6) view of the data and could be presented if she wanted during the OPH. I had no idea how detailed her analyses were. I think this is an issue we can put to JW tomorrow; i.e. what are we to do with these "data". I suspect she will say we should consider them since we are supposed to approach our reviews with an open mind to the possibility that we made a mistake or missed something. Still an odd process that has been exacerbated by the AC delay.

On Rich, I agree this is awkward and I think we need to address this tomorrow as well.

On the AC member (b) (4)

John

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Unger, Ellis
Sent: Tuesday, February 9, 2016 5:48 PM
To: Jenkins, John K
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Briefing Document Issues Final.pptx

John,

I have some concerns here. Rich has recused himself, and yet he seems to have some involvement.

And I am not comfortable talking with anyone about a pending application. Even if we were to guarantee that FDA was in 100% listening mode with (b) (6), the optics don't seem appropriate to me.

Also, on a related subject, I continue to have concerns about a having patient voting on an AC (b) (4)

Ellis

From: Moscicki, Richard
Sent: Tuesday, February 09, 2016 4:27 PM

To: Dunn, Billy; Unger, Ellis

Subject: Briefing Document Issues Final.pptx

Janet asked me to join her for a discussion with [REDACTED] (b) (6) patient advocate. [REDACTED] (b) (6) subsequently sent this slide deck to me with her concerns regarding the eteplirsen briefing document. I send it to you to review and consider. Rich.

Philips, Howard

From: Unger, Ellis
Sent: Tuesday, February 09, 2016 4:40 PM
To: Dunn, Billy; Temple, Robert
Cc: Locicero, Colleen L
Subject: RE: Briefing Document Issues Final.pptx
Attachments: Briefing Document Issues Final.pptx

I don't understand this. Is it possible to hold a discussion on a pending application with someone other than the applicant (or EMA)?

From: Moscicki, Richard
Sent: Tuesday, February 09, 2016 4:27 PM
To: Dunn, Billy; Unger, Ellis
Subject: Briefing Document Issues Final.pptx

Janet asked me to join her for a discussion with (b) (6) patient advocate. (b) (6) subsequently sent this slide deck to me with her concerns regarding the eteplirsen briefing document. I send it to you to review and consider. Rich.



Philips, Howard

From: Farkas, Ronald
Sent: Tuesday, February 09, 2016 6:27 PM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Breder, Christopher D; Bhattaram, Atul; Rao, Ashutosh; Choy, Fannie (Yuet)
Cc: Ling, Xiang; Jin, Kun
Subject: revised eteplirsen slides
Attachments: Eteplirsen key points.pptx

All,

Most recent eteplirsen slides, revised and expanded greatly from last CD briefing, sending widely because of short notice of meeting with JW tomorrow.

There are several groups of new figures that show more clearly that eteplirsen- and the applicants control patients appear to be very similar, based on Chris' observation that the applicant's aligning patients by years of observation obscured the key relationship between age and loss of ambulation, and obscured the key issue that the eteplirsen data is truncated immediately prior to clearly approaching loss of ambulation. (NSAA left below, and 6MWT right)

Thanks

Ron

(b) (5)



Eteplirsen

Duchenne Muscular Dystrophy In Patients with
Mutations Amenable to Skipping Exon 51

FDA Efficacy Review

(b) (5)

138 pages of draft language have been withheld as b(5) immediately following this page

1

Philips, Howard

From: Farkas, Ronald
Sent: Wednesday, February 10, 2016 1:22 PM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Breder, Christopher D; Choy, Fannie (Yuet)
Subject: eteplirsen slides for CD briefing today
Attachments: Eteplirsen JW 2 10 16.pptx

All,

There were a few different thoughts about exactly which slides to include, and I've also made some additional edits, but these would be the slides for the meeting with JW today.

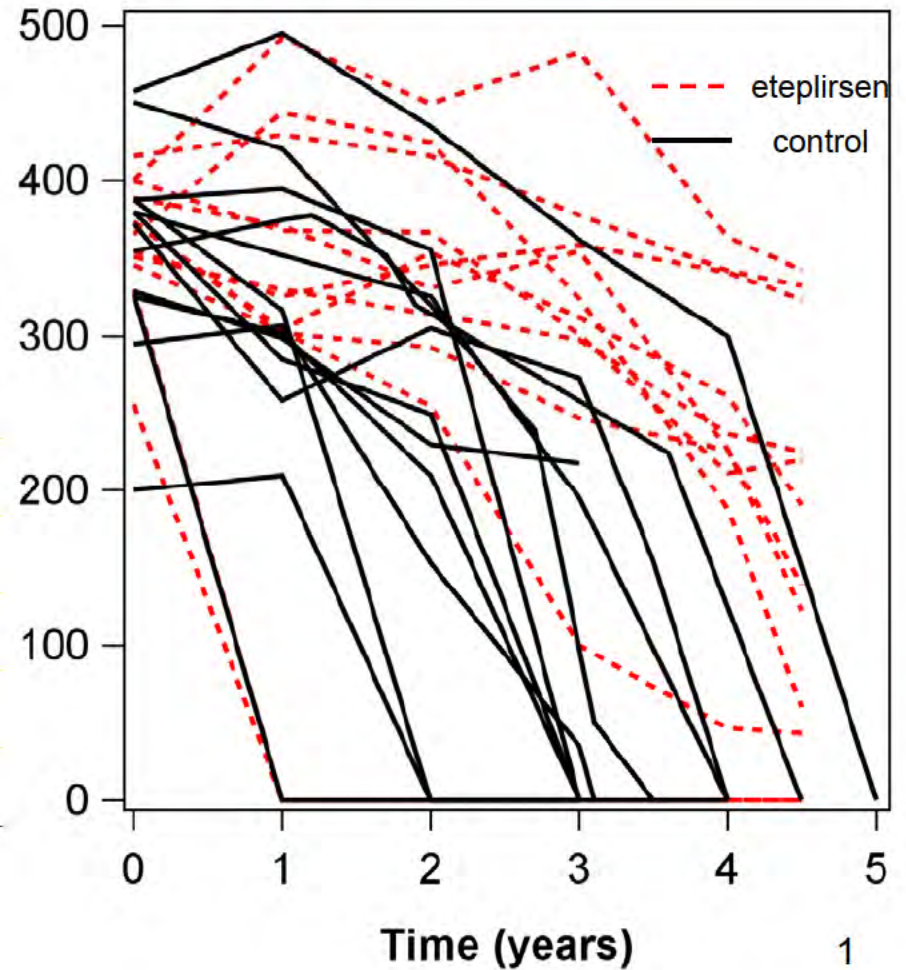
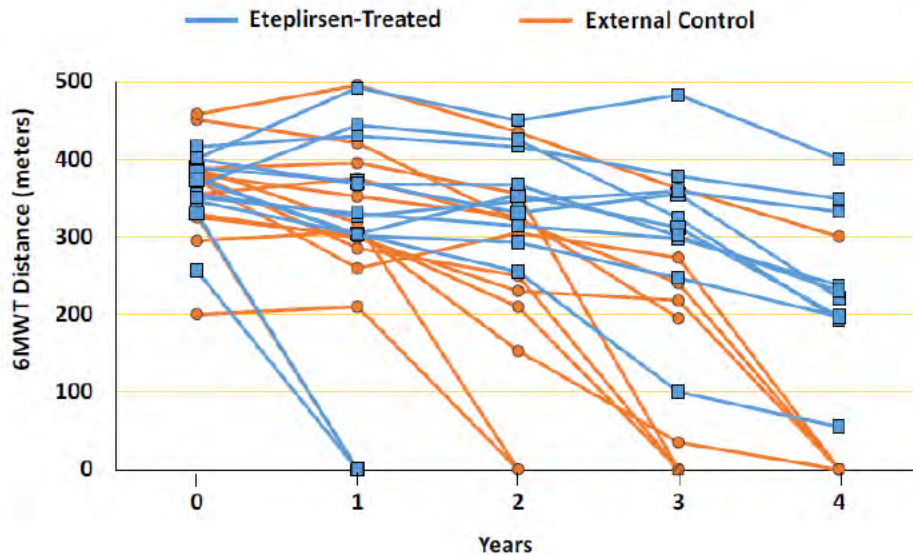
Thanks

Ron



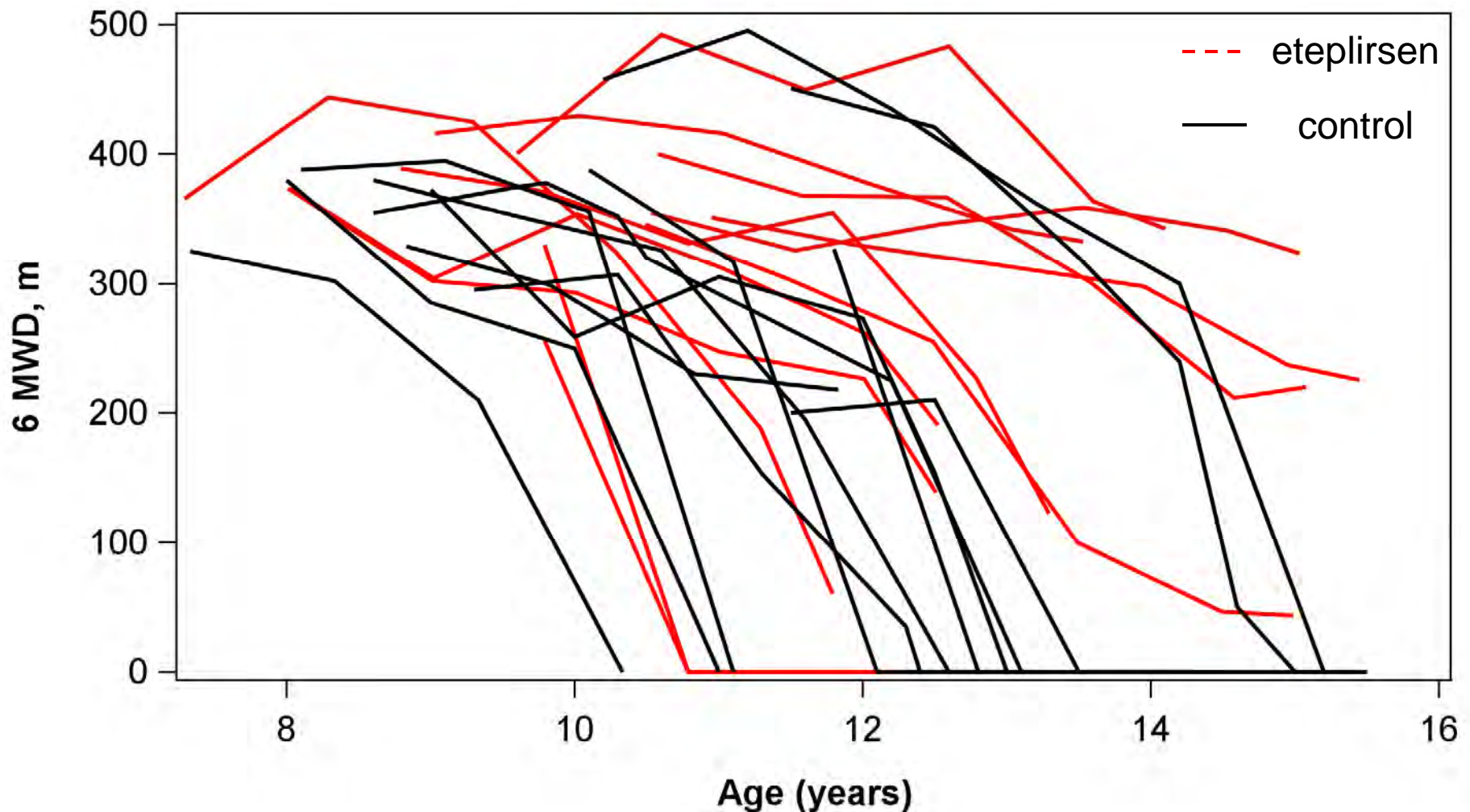
Data affected by truncation and misalignment

Year 4 Individual 6MWT, Eteplirsen-Treated vs. External Control (Exon 51)



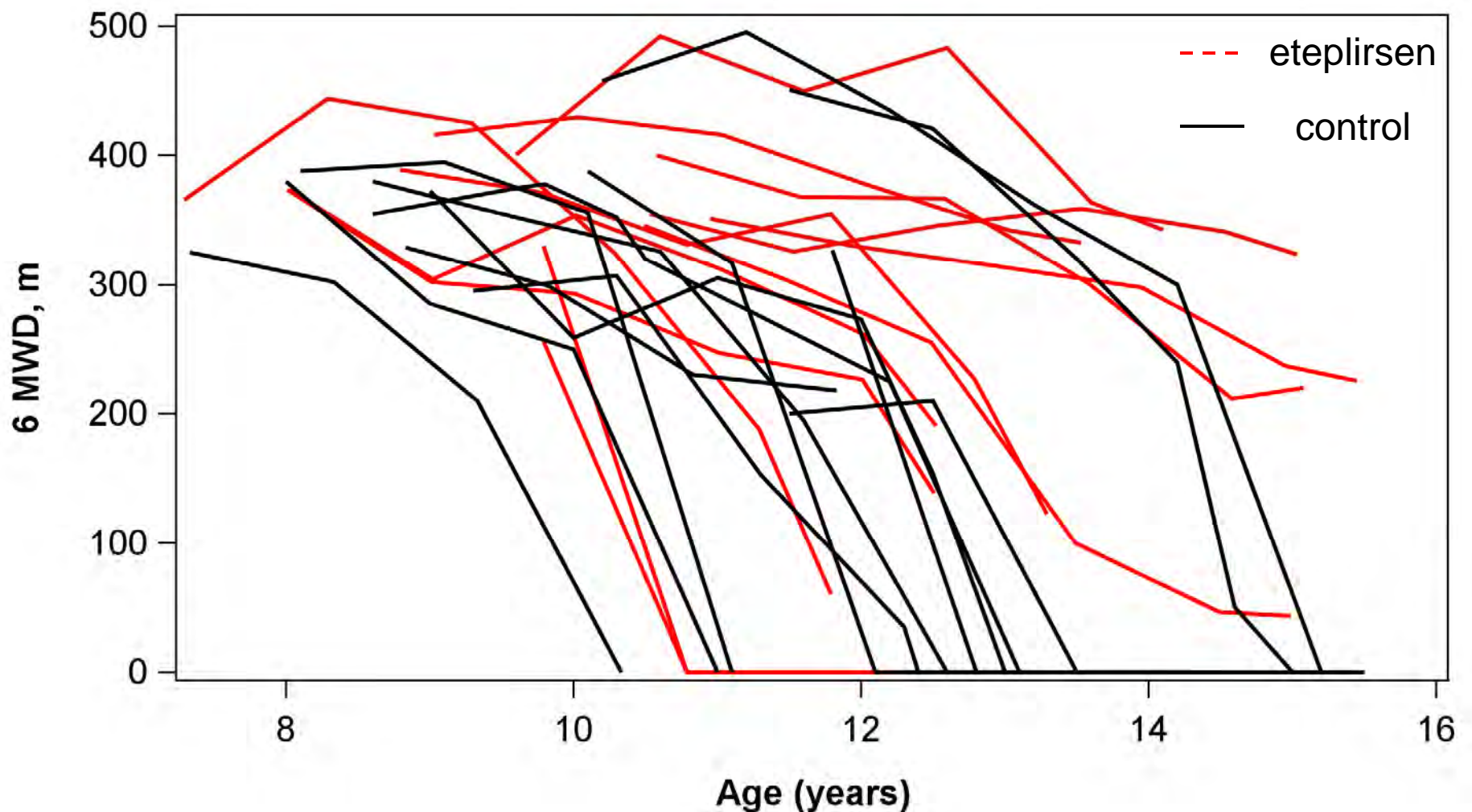


Eteplirsen patients and controls not matched more than grossly by age



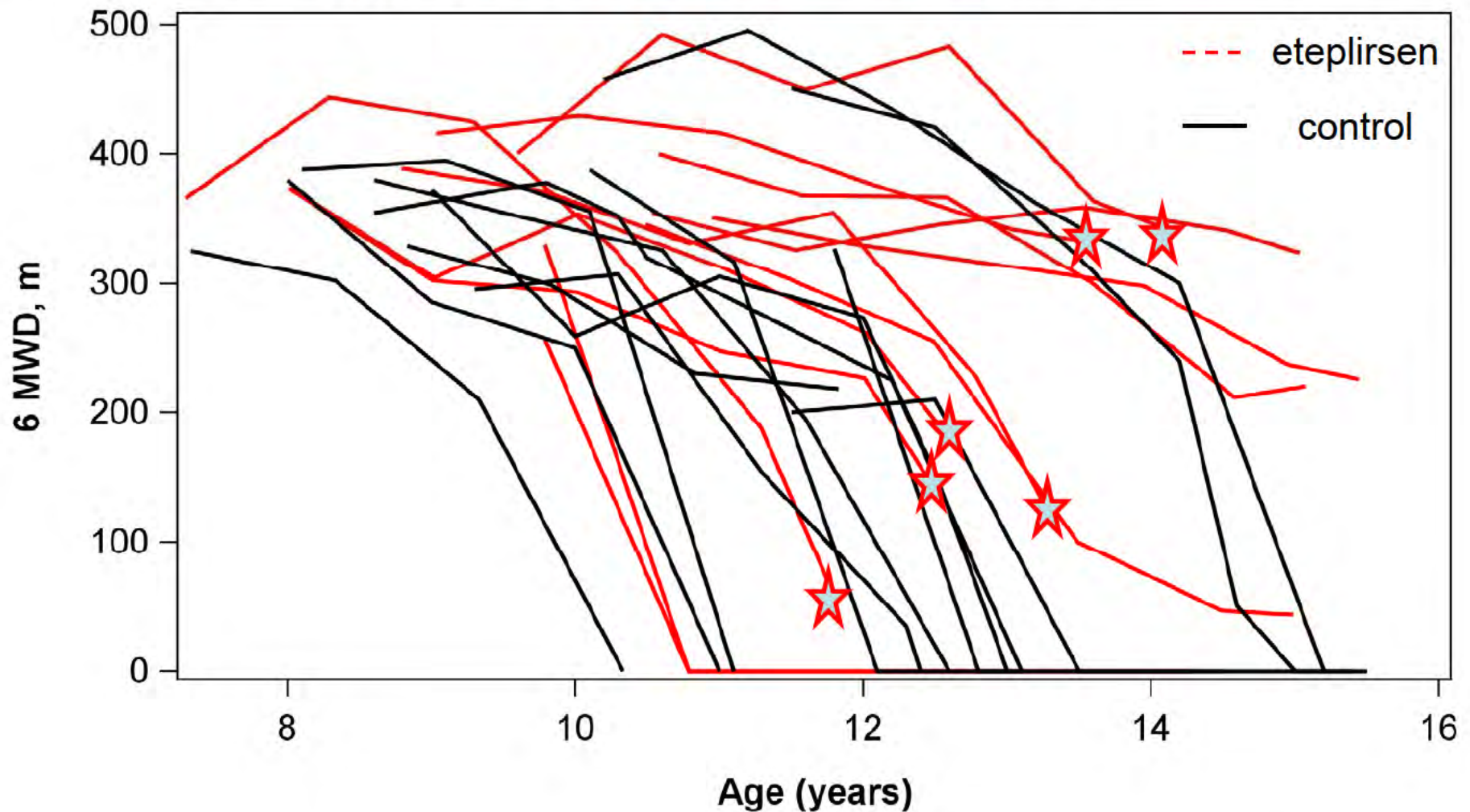


Viewed against age, the importance of data truncation becomes clearer



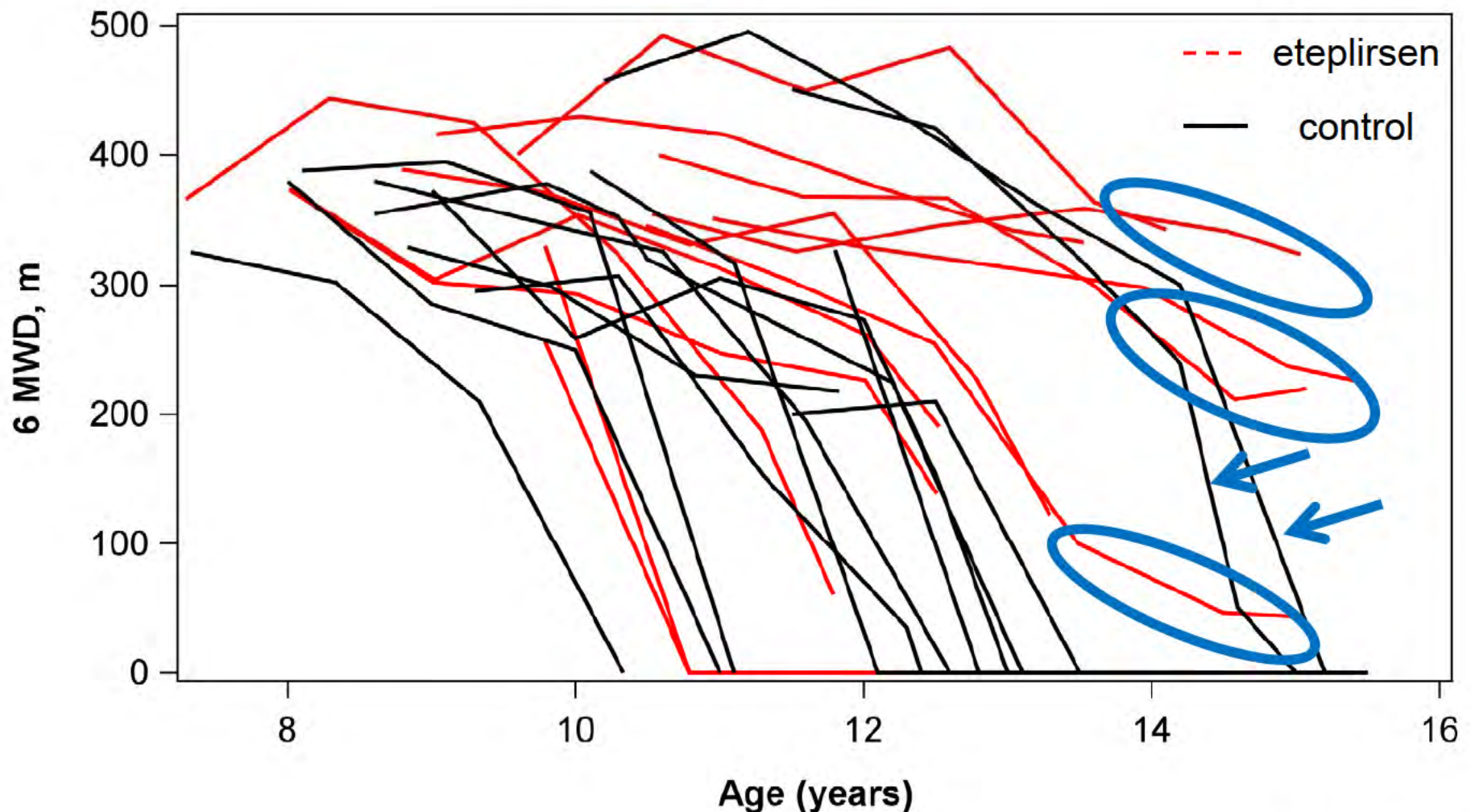


Eteplirsen patients indicated by a star decline in 6MWT closely overlapping controls, but truncated





Some eteplirsen patients have less steep decline in final year measured (circles) vs controls (arrows)





Critical to understand that ambulation not a “hard” (black and white) endpoint

Depends on conscious care decisions

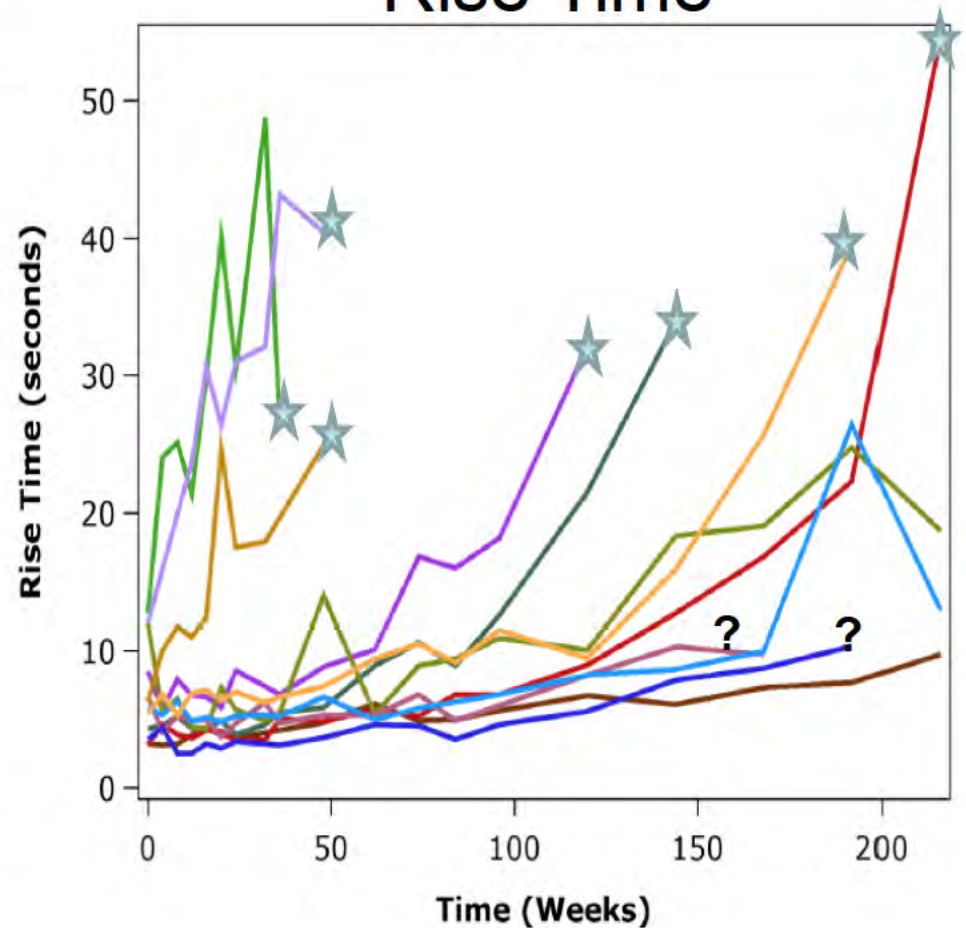
- “Transition to a wheelchair usually is a gradual process” *
- “Children often experience renewed independence once they fully transition to a power wheelchair. For many parents and caregivers, it is painful to accept that a child needs help getting around, but it is better for the child to have mobility using help from braces, scooters, or wheelchairs—and the independence it gives the child—than not to be able to move as freely as possible”^o

*www.mda.org/disease/duchenne-muscular-dystrophy/signs-and-symptoms

^ohttp://www.parentprojectmd.org/site/PageServer?pagename=Care_stage_nonambulatory

- Majority of eteplirsen patients unable, or nearly unable to rise (and several now with 6MWT of less than 100 m)
- patients outside of efficacy studies may have chosen wheelchair use

Rise Time



★ unable
? missing



Findings on another endpoint, the North Star Ambulatory Assessment (NSAA), further suggest that underlying disease progression was similar in all eteplirsen-treated patients and historical patients



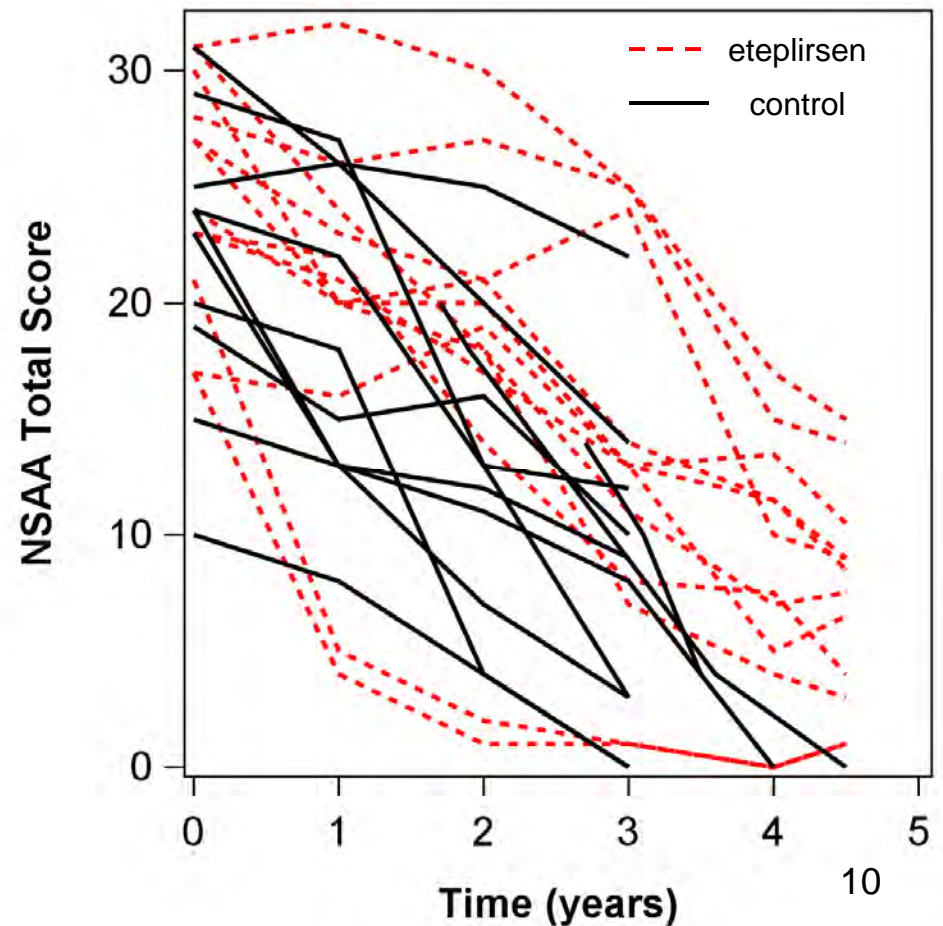
North Star Ambulatory Assessment (NSAA)

- Because of the problems with use of 6MWT in historically controlled trials described earlier, FDA advised the applicant to present data from a measure that might more directly represent muscle strength
- NSAA a measure of underlying ambulatory **abilities**, such as ‘rise from floor’ that support specific **activities** such as walking
- Similar to 6MWT, score still depends on supportive care and effort, and is partially based on subjective assessment of evaluator and therefore susceptible expectation bias in open-label studies

NSAA

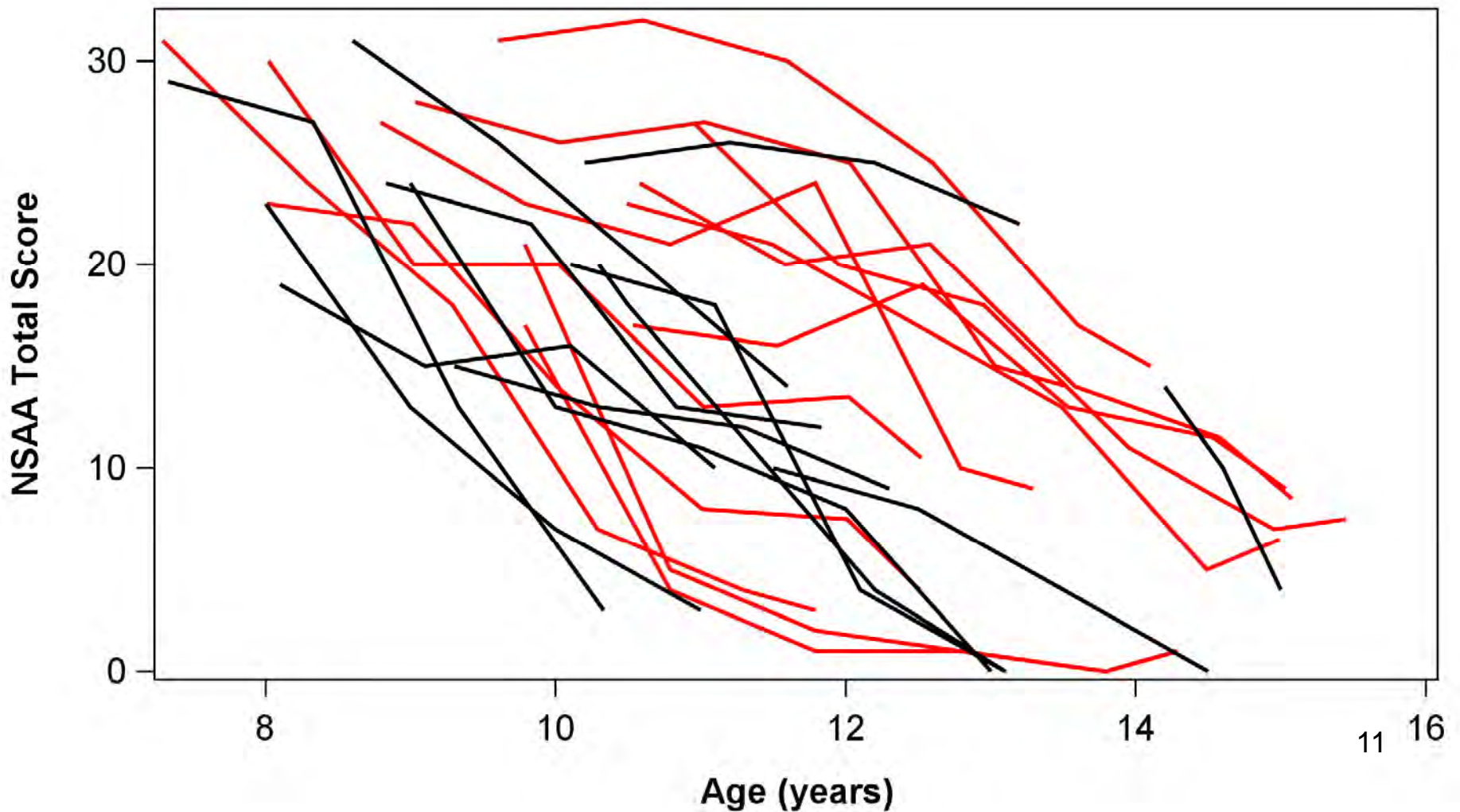
Eteplirsen vs. Applicant's Historical Controls

- Notable that the course of all eteplirsen patients was roughly similar to controls for NSAA
- All patients, treated and controls, decline steeply



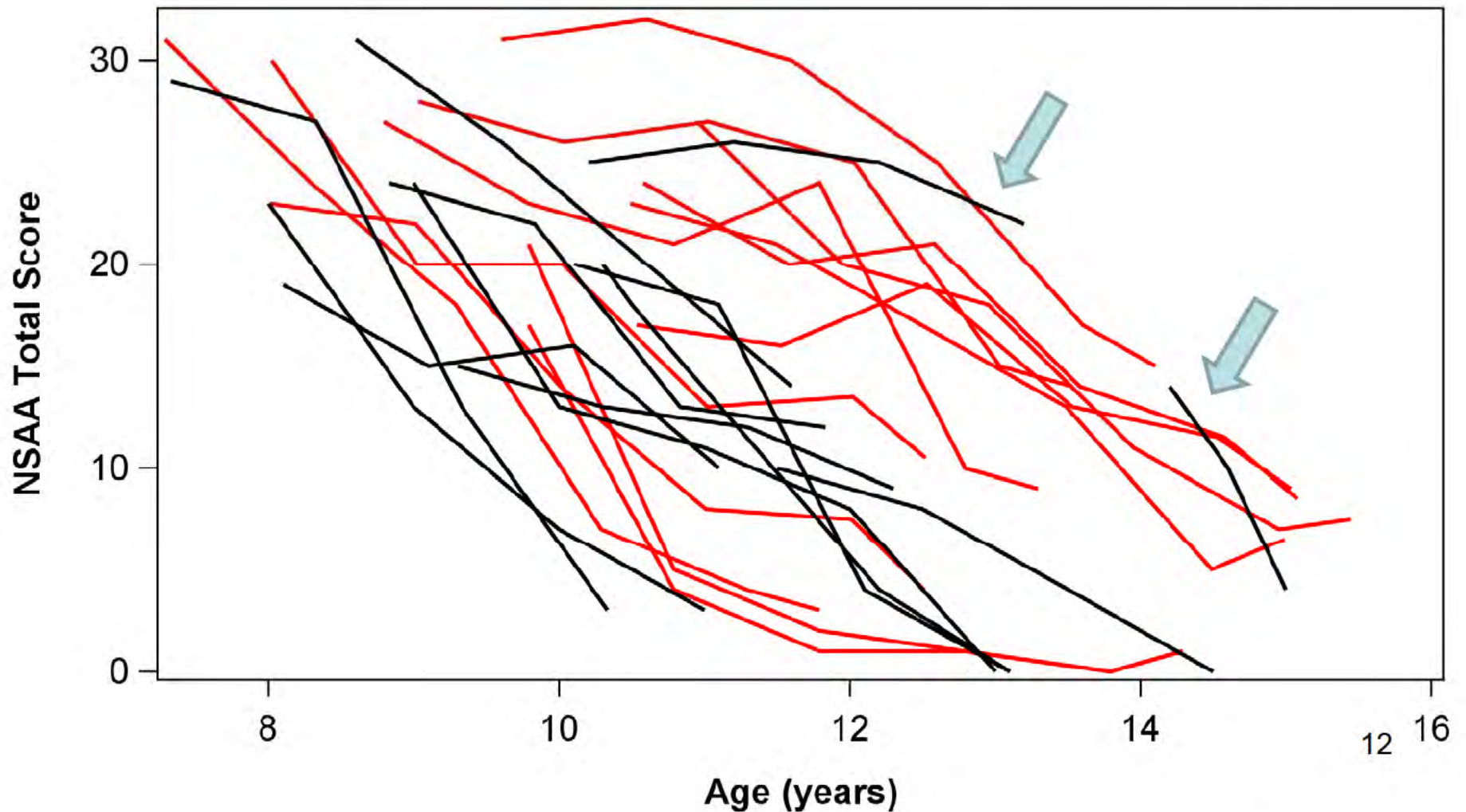


Viewed against age, lines “shift” relative to viewing by years of observation



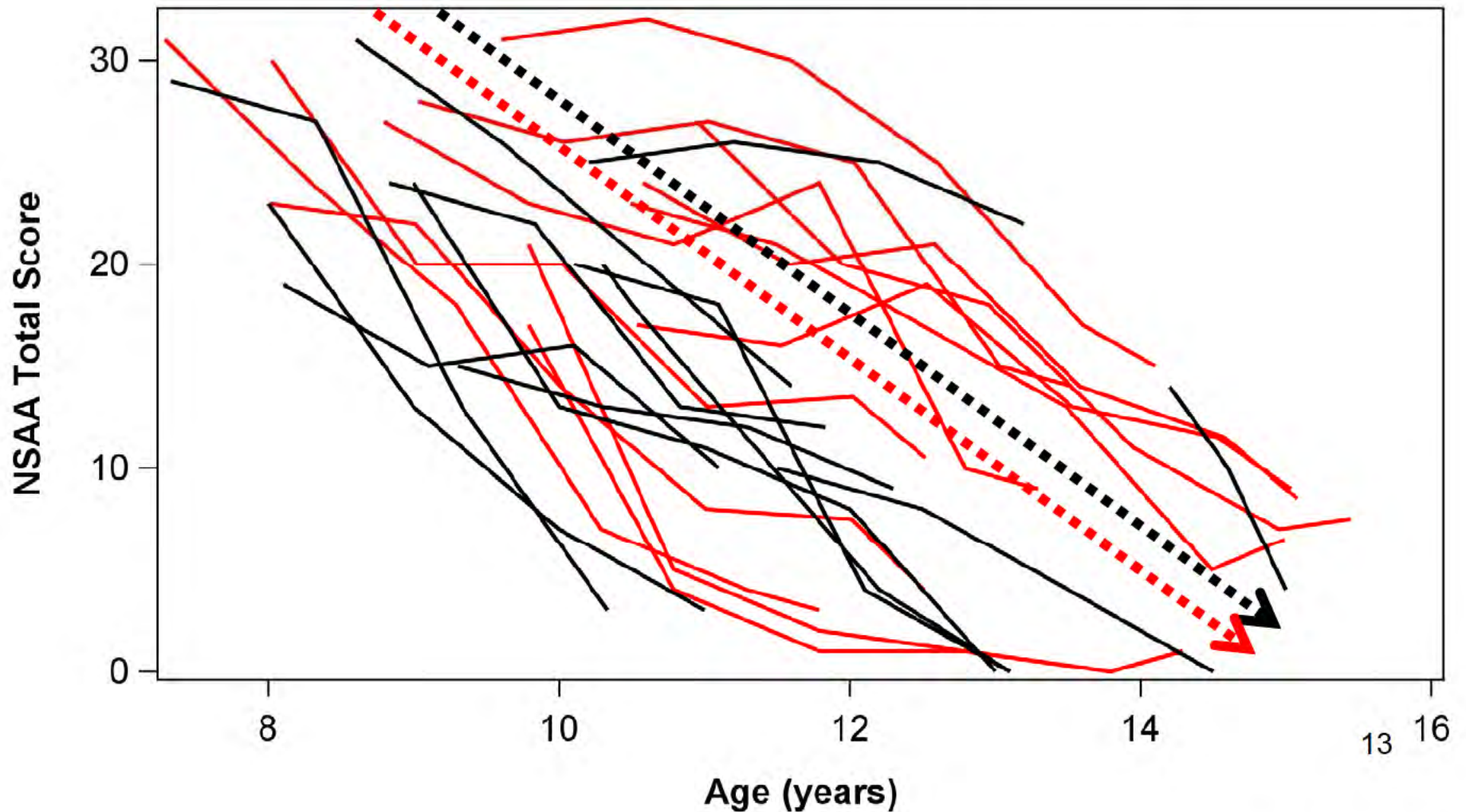


Viewed against age, eteplirsen patients bounded by controls (arrows) (more red lines right from lack of matched controls)



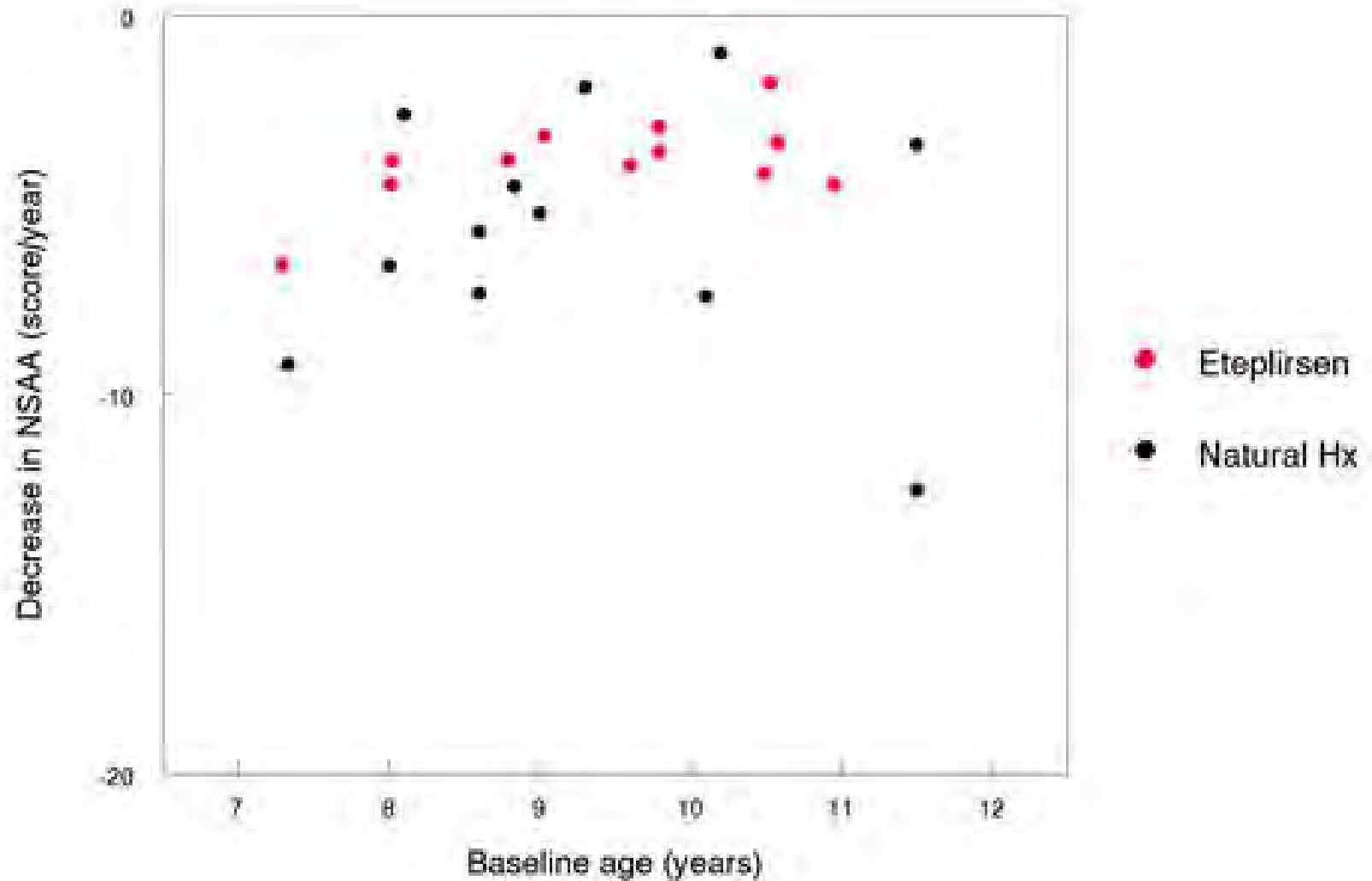


Similar change of NSAA shown for all patients - declining from “upper left” to “lower right” (arrows for illustration only)



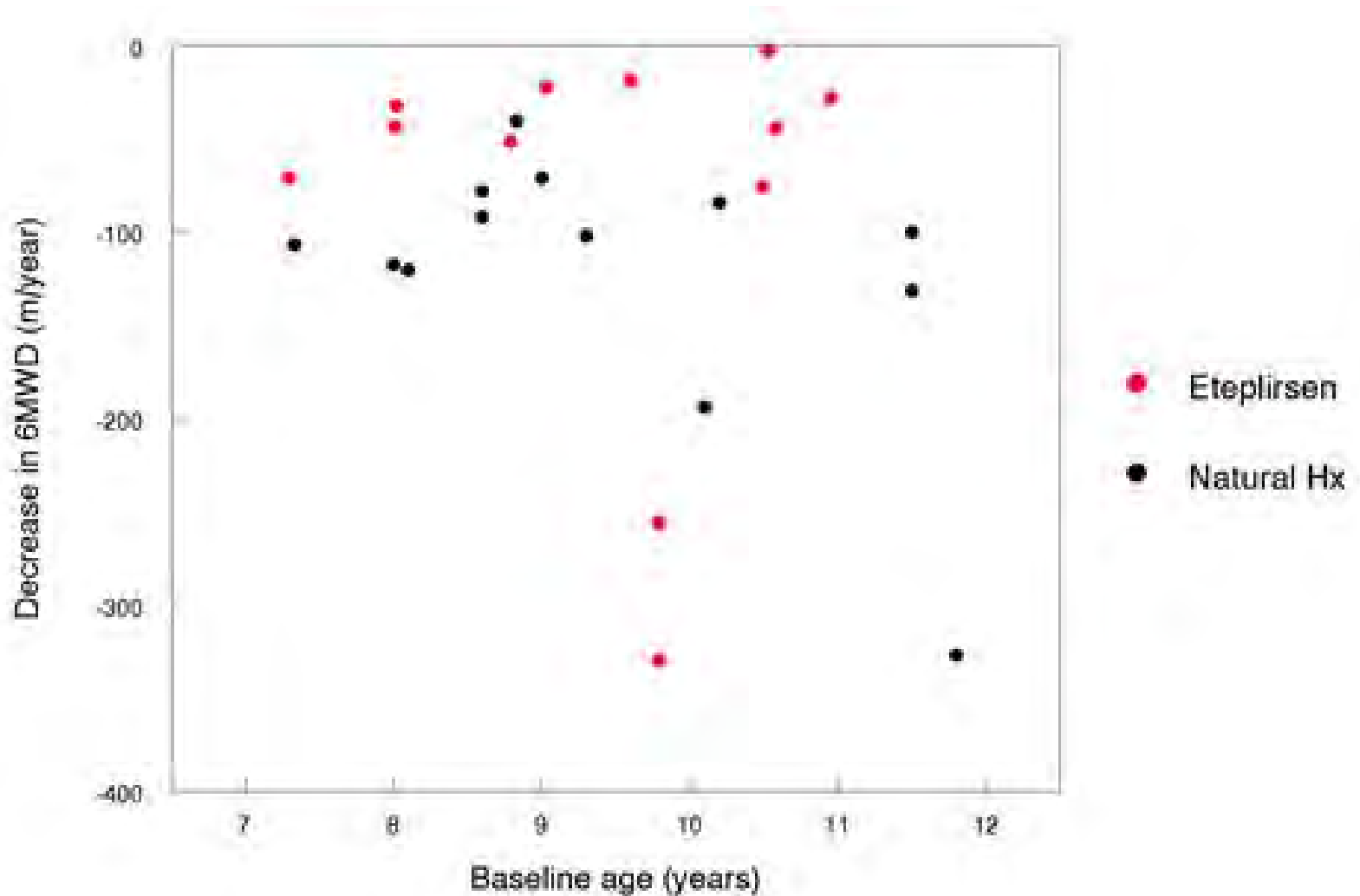


Slope analysis, NSAA





Slope analysis, 6MWT



Temple, Robert

From: Jenkins, John K
Sent: Thursday, February 18, 2016 5:34 PM
To: Unger, Ellis; Temple, Robert
Subject: RE: FDA Information Request: re: NDA 206488 / Week 240 Eteplirsen Data

E-mails crossed. As you will see, they also reached out to Janet by e-mail. I do not have that exchange, but Janet says she told them it was in their interest to submit the data since that is the pivotal component of their NDA. We can discuss in the meeting I just requested with Janet how to break this cycle of tattle-tale to the Center Director.

John

From: Unger, Ellis
Sent: Thursday, February 18, 2016 5:29 PM
To: Jenkins, John K; Temple, Robert
Subject: FW: FDA Information Request: re: NDA 206488 / Week 240 Eteplirsen Data

They skipped the two of you. We had a t-con today, which was constructive.

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Wednesday, February 17, 2016 11:29 AM
To: Dunn, Billy; Choy, Fannie (Yuet)
Cc: Ed Kaye; Woodcock, Janet; Moscicki, Richard; Unger, Ellis
Subject: RE: FDA Information Request: re: NDA 206488 / Week 240 Eteplirsen Data

Dear Dr. Dunn,

We are very surprised by FDA's request below (dated 12 February) for Week 240 eteplirsen data. We would like to understand your rationale and intent for this request since we have already provided Week 216/"4-year" data on 8 January, 2016. This is likely the most longitudinal data set collected in DMD.

We are also concerned by this request for the following reasons:

- The Week 240 data for eteplirsen will not be available until mid-May (in raw data form only).
- The last time such a request for expedited updated information was made for Week 216 (4-year) eteplirsen data, FDA used this information inappropriately in the PCNSDAC Briefing Document where 4-year eteplirsen data was compared to 3-year External Control data.
- The request for any updated data, can only be appropriately interpreted if the external control data is also updated accordingly.

Following Sarepta's fulfillment of the FDA request for 4 year data, we importantly discovered that 10 of the 13 patients in the external control group, lost ambulation compared to only 2 of the 12 eteplirsen patients. This led to FDA's reasonable request for updated source documentation for external control data which in turn led to PDUFA extension. The PDUFA date has now been extended by 90 days to 26 May, purportedly to review and verify the 4-data data submitted in the NDA amendment dated 8 January, 2016.

We are extremely concerned that any further unbalanced data submission would not serve the purpose of a collaborative and unbiased approach requested by Dr Woodcock.

We look forward to working with you closely to provide source data for the 4-year External Control functional data and proceeding with the Advisory Committee meeting without any additional delays.

Regards,
Shamim

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



215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Friday, February 12, 2016 1:27 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 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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Temple, Robert

From: Unger, Ellis
Sent: Thursday, February 18, 2016 7:10 PM
To: Jenkins, John K
Cc: Dunn, Billy; Temple, Robert; Kweder, Sandra L
Subject: RE: Meeting to discuss strategy for DMD NDA review and AC

John,

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In terms of the request for longer-term F/U on the Sarepta boys, we explained that we're interested in getting the critical data. They said that all testing is to be completed for all 12 boys by mid-April. They said it could take them a week or two to get the data, because it goes from Nationwide Children's to (b) (4) and then to Sarepta. We explained that we are not interested in any statistical analyses, we're just interested in the 6MW distances, rise times, and NSAA results. We noted we only wanted these 3 parameters on 12 patients = 36 data points. They seemed agreeable. They must have figured out that we can't extend the clock more than once, because they didn't bring that up.

I explained to them that they'll want to make the most solid case they can in comparing the 12 Sarepta patients to the 13 patients in the registry. I suggested that they get as much data as they can, because it is in their best interest – it's really in everyone's best interest – for them to establish that the walking distances from the registry patients are reliable.

In terms of inspections, we learned a few other things. The 10 patients in Italy do not actually go to the Mercuri site for care/studies. They are seen in 3 (I think) locations. They say that Italian law prohibits them (and regulatory authorities) from looking at patient records/data, unless patients have given permission and the records are anonymized.

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We also told them it would be important for them to try to establish that they selected their 13 patients from ALL of the patients in the 2 registries (i.e., they didn't hide any patients). As I've mention in the past, I think their selection of 13 patients from the patient list they provided was completely straightforward (steroids = yes, age >7, Exon 51 amenable = Y).

Having said all of this (sorry for length here), strategizing about the AC is a good idea.

Ellis

From: Jenkins, John K
Sent: Thursday, February 18, 2016 5:31 PM
To: Dunn, Billy; Unger, Ellis; Temple, Robert; Kweder, Sandra L

Cc: Jenkins, John K

Subject: FW: Meeting to discuss strategy for DMD NDA review and AC

This relates to continuing contacts between the sponsor and Janet on every issue raised between DNP and the company. The most recent one was apparently triggered by a DNP request that the sponsor submit the most recent update on the long-term follow up of the boys, which apparently is due to occur in April. They thought this was going to trigger another delay in the AC and another extension of the clock for a major amendment (even though the PDUFA goals letter clearly states that only one extension for a major amendment can occur in a review cycle). We also need to discuss the current status of getting more information about the registry and data collection and what, if any further action we may take on our part to get more complete information (e.g., sending an FDA employee to visit the site, contact the local regulatory authority for assistance). Finally, we need to strategize for the AC. Janet is concerned about the tone of our presentation and who will be presenting for FDA. I suggested we manage this in a small meeting rather than the larger meetings that occur for briefings.

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John

From: Jenkins, John K

Sent: Thursday, February 18, 2016 5:26 PM

To: Ligon, Sharnell (CDER)

Cc: Dunn, Billy; Unger, Ellis; Temple, Robert; Kweder, Sandra L; Woodcock, Janet; Jenkins, John K; Vail, Victor H

Subject: Meeting to discuss strategy for DMD NDA review and AC

Sharnell

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To: Dunn, Billy; Choy, Fannie (Yuet)
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p 617-274-4009 c (b) (6)
e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

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Division of Neurology Products
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Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
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Thanks

John

etepirsen

Temple, Robert

From: Unger, Ellis
Sent: Friday, February 19, 2016 1:25 PM
To: Bastings, Eric
Cc: Dunn, Billy; Farkas, Ronald; Choy, Fannie (Yuet); Jenkins, John K; Temple, Robert
Subject: RE: Follow-up from teleconference between FDA, CINRG and UCD study chairs on DMD Natural History Study
Attachments: CNRG contract.doc

I was just speaking with Billy on the phone, and this came up.

I haven't actually read it yet, but this agreement will need to lay out precisely what we can, and cannot, use the data for. Can we use it in our reviews to compare with the eteplirsen boys? If so, can we show the data at an ACM? If so, we'd obviously remove the actual patient identifiers, but maybe they don't want us to show it under any circumstances. This will all need to be crystal clear.

From: Bastings, Eric
Sent: Friday, February 19, 2016 1:12 PM
To: Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: FW: Follow-up from teleconference between FDA, CINRG and UCD study chairs on DMD Natural History Study

Ellis,

We has a telecon with the CINRG folks earlier this week, and they are willing to give us access to their DMD natural history database. However, they requested we enter a confidentiality agreement.

I tried to edit the agreement to make it fit for the purpose, but I assume we have to run this by some of our lawyers. Do you have any idea of the process to follow? Also, who will sign it at FDA?

Eric

From: Choy, Fannie (Yuet)
Sent: Wednesday, February 17, 2016 3:59 PM
To: Dunn, Billy; Bastings, Eric; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: FW: Follow-up from teleconference between FDA, CINRG and UCD study chairs on DMD Natural History Study

All,

Please see email and attached documents from CINRG coordinator following yesterday's TC.

Do we need the lawyer to review the document for confidentiality & non-disclosure agreement?

I don't know who would need access to the documents. I placed the documents in a folder in the DNP shared drive for now – link attached. Please let me know what you decide.

[\\cdsnas\dndpdms1\CINRG](#)

Thanks
Fannie

From: Morgenroth, Lauren [<mailto:LMorgenroth@childrensnational.org>]
Sent: Wednesday, February 17, 2016 2:36 PM
To: Choy, Fannie (Yuet)
Cc: Cnaan, Avital; Arrieta, Adrienne; Craig McDonald (Research); ehenricson@ucdavis.edu
Subject: Follow-up from teleconference between FDA, CINRG and UCD study chairs on DMD Natural History Study

Dear Fannie Choy,

In follow-up to a teleconference that was held yesterday between the FDA, members of the Cooperative International Neuromuscular Research Group (CINRG) Coordinator Center which is housed within Children's National in Washington, DC and the University of California (UCD) study chair for the Duchenne Muscular Dystrophy (DMD) I am sending two documents:

- 1) Blank Template Non-Disclosure agreement for Children's National as data will be provided via Children's National Coordinating Center
- 2) Current multicenter protocol that is ongoing within the CINRG network and participating centers around the world

We will also provide copies of the study case report forms. We are collating the original case report forms that were used between 2005 and 2012.

If you have any questions please let me know.

Thanks,
Lauren

Lauren Morgenroth, MS, CGC
Operations Manager and Central Genetic Counselor
Children's National Health System
Cooperative International Neuromuscular Research Group (CINRG)
Email: lmorgenroth@childrensnational.org
Phone: (b) (6)
We stand for children.
www.ChildrensNational.org
www.cinrgresearch.org
Twitter: @cinrgresearch

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Temple, Robert

See class
etepilsen

From: Breder, Christopher D
Sent: Friday, February 26, 2016 10:41 AM
To: Farkas, Ronald; Bastings, Eric
Cc: Unger, Ellis; Bhattaram, Atul; Dunn, Billy; Temple, Robert
Subject: RE:
Attachments: nsaa.doc

[Here is an analysis of the NSAA data](#)
cdb

From: Breder, Christopher D
Sent: Friday, February 26, 2016 10:11 AM
To: Farkas, Ronald; Bastings, Eric
Cc: Unger, Ellis; Bhattaram, Atul; Dunn, Billy
Subject:

Just a note to let you know what I'm up to so we don't duplicate efforts (or if you have advice, that would be appreciated)

I am consolidating all of the xpt and xls files related to natural history.

- They reported data in terms of 0, 12, 24, and 36 month increments but there are data on a few that precedes this period and is still adhering to the > 7 year old criteria. I think for this reason and because of the reasons I espoused when I previously sent out graphs based on age, that age is a better parameter for comparison between groups.
- The columns in this dataset with "baseline" are a bit confusing, because I entered the value they presented before finding the data on a few of them where they were younger. Since the baseline data will only be useful for covariates in calculations, I will fix that later, when I am sure I am not missing any data sources.

My next step will be to add the etepilsen kids and present comparisons. For missing data based on "unable to perform" I will likely impute 2x the maximum value for that test in the nonmissing data for that test since "999" puts it off the chart.

cdb

Philips, Howard

From: Unger, Ellis
Sent: Friday, March 04, 2016 5:51 PM
To: Temple, Robert
Subject: FW: revised eteplirsen memorandum for AC meeting
Attachments: UPDATED CDTL MEMO ETEPLIRSEN 13.doc

From: Farkas, Ronald
Sent: Friday, March 04, 2016 4:37 PM
To: Bastings, Eric; Dunn, Billy; Unger, Ellis
Subject: revised eteplirsen memorandum for AC meeting

All,

This is an extensively revised version of my memo prepared for the previously scheduled eteplirsen AC meeting. It would be helpful to get your feedback on this as soon as you are able so that I know I'm going the right way with revising the AC slides.

Thanks

Ron

MEMORANDUM

DATE: March 20, 2016

FROM: Ronald Farkas, M.D., Ph.D.
Clinical Team Leader
Division of Neurology Products, CDER, FDA

TO: Members and Invited Guests of the Peripheral and Central Nervous Systems
Drugs Advisory Committee (PCNS AC)

SUBJECT: Clinical Team Leader Memorandum for New Drug Application (NDA) 206488, for
the use of Exondys 51 (eteplirsen) for the treatment of Duchenne muscular
dystrophy in patients with mutations amenable to exon 51 skipping

Preface

(b) (5)

69 pages of draft language have been withheld as b(5) immediately following this page

1

FDACDER0003594

Philips, Howard

From: Temple, Robert
Sent: Wednesday, March 09, 2016 7:16 PM
To: Dunn, Billy; Bastings, Eric; Farkas, Ronald; Breder, Christopher D; Unger, Ellis
Subject: FW: Eteplirsen

I couldn't open any of the attachments. Could you?

From: kim danboise [mailto: (b) (6)]
Sent: Wednesday, March 09, 2016 7:03 PM
To: Commissioner FDA
(b) (6) Billy; Farkas, Ronald; Temple, Robert; Jenkins, John K; Temple, Robert;
Subject: Eteplirsen

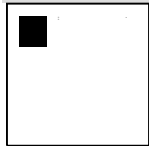
Dear Dr. Dunn: FDA really needs to do a complete overhaul at DNP:

Sarepta 4-Year Data Analysis Of Eteplirsen To Treat DMD

Mar. 9, 2016 6:42 PM ET

|

About: [Sarepta Therapeutics, Inc. \(SRPT\)](#)



BosCaptn

⊕ Follow(1 follower)

Long/short equity, event-driven, biotech, research analyst

[Send Message](#)

Summary

Wall St. underestimating approval.

Major catalyst.

Upcoming Adcom expected.

Possible approval (PDUFA) date May 26, 2016.

Year 4 Data Analysis

Review of Eteplirsen to Treat DMD

Compiled from Sarepta's (NASDAQ: [SRPT](#)) public data for week 216 (Year 4) of Study 201/202 for Exon 51.

This is an independent analysis of publicly available information.

By [@BosCaptn](#), et al.

Additional Contributors:

- Co-author of the statistical data analysis by Yang Jiang, Masters Harvard University, Columbia PhD student
- NSAA and Rise Time supplemental graphs by Greg Wierenga ([@dubya1](#))
- Editing by David Jorgensen ([@BassReelz](#)), and Greg Wierenga

Abstract

The FDA has discounted the External Controls submitted by Sarepta. Here, we establish that intermittent vs. continuous dosing of steroids is insignificant. Furthermore, we demonstrate that P values for the 6MWT comparison between treatments with Eteplirsen vs. External Controls have increased consistently culminating in significant values for years three and four. Finally, we show that Eteplirsen slows the loss of ambulation, conferring an important clinical benefit.

A snow delay of Sarepta Advisory Committee (Adcom) meeting and pre-release of the FDA Adcom Briefing Documents (BD) resulted in a flurry of reports, news articles, and social media storm filled with opinions and emotions. This report assumes you are up to date on the current status of the company's drug Eteplirsen (Etep) and the approval process within the FDA.

To provide minimal background, the Sarepta supplied FDA briefing document on Etep is [here](#).

The original FDA prepared analysis is [here](#).

Also, on January 8, 2016, SRPT replied with a major addendum to fix many inaccuracies in the FDA briefing document. That addendum is [here](#).

For experts and statistics people with a good knowledge of P-values and clinical trial data analysis, you may want to just jump ahead to the last section of this report with the statistical data analysis. The stats review section is completed by Yang Jiang, currently a Columbia PhD

student with a Masters from Harvard University. Yang has a strong understanding of statistical analysis and used IBM SPSS Statistics to complete the analysis.

Of major concern is the use of External Control for the 12 patients on the Eteplirsen trial for over four years. On the original FDA review, the FDA chose to throw out the EC chosen by Sarepta in favor of a less accurate set of data from Drisapersen (Drisa) control group, a competing drug company that recently received a complete response letter from the FDA. This report looks into the 6MWT data provided by Sarepta through the original sponsor document and Addendum.

Finally, we will look at the reasons the FDA chose the seemingly less accurate Drisa control data. We will examine these reasons mentioned in the BD including: 1) intermittent steroid use by the Sarepta EC, 2) lower steroid use by the EC, 3) physical therapy, 4) selection bias by choosing the control group after year three data, 5) general inability to accept the trial as not well controlled, "double blinded placebo randomized trial."

Table Of Contents

Section 1: Detail analysis of week 216 data.

Section 2: Arguments related to FDA briefing documents.

Section 3: Statistical data analysis of week 216 data.

Section 4: Report additions, corrections, and deficiencies.

Section 1 - Detail Analysis

The first step is to dive into the data. Sarepta provided the exact yearly details of all patients and EC data through year three in its original FDA document. It then included year four data in the Addendum.

Here is the Etep data as copied from those documents:



The following is the Sarepta EC data:



**Highlighted columns (year one and two) come from the original sponsor document while the rest of the data is from the Addendum.*

To data mine from here, we need to do some calculations to get the "closest" yearly age.

Since Sarepta trials are based on a 48-week year, we use the following calculation example:



This gives us yearly ages accurate to within 0.1 year (about a month). Doing just a quick glance at the two data packages, you can see 10 out of 11 controls have gone off their feet, with loss of ambulation (LOA). Yet, only two out of 12 from the Etep data set are LOA. This is pretty convincing on its face, but what about ages? We all know the progression of DMD. The youngest patients grow stronger as they get older, but start a downward curve and eventually end in loss of ambulation generally from 10 to 14 years. There are outliers, those that continue to walk longer. There are also outliers on the low end, those that have loss of ambulation younger than normal.



So with the presented data, here is some data mining to determine the certainty of the efficacy of Etep. Some will yell this isn't even necessary, "it's bloody obvious." Yet, the FDA briefing document seems to imply the opposite.

First is a simple spaghetti line chart of every participant in the 202 study:



More on the "Twins" later, for now recognize the solid lines are Etep group, the dashed lines are External Control group. Each line represents yearly data from the start of the Sarepta (201/202) trial including an initial baseline six-minute walk test (6MWT). Without a well-trained eye, you might not "see" the inherent treated patient benefit. The data includes yearly data points out to 216 weeks (4.15 years).

When looking closer, you can notice a majority of the External Control are going loss of ambulation (LOA) around 13 years of age. There's an outlier above 15 years, and there are outliers 10 to 11 years of age. While Etep has a majority of patients still walking over 200 meters on week 216 data, with a majority over 13 years of age.

It could be inferred that loss of ambulation could be the primary endpoint, and in fact, that in itself provides a strong conclusive evidence of efficacy. But to complete a data analysis with 6MWT as the endpoint, let's look further.

To get a better understanding of the data, we will present the same data in a scatter chart, dropping all the same data points on a similar chart and calculate a linear average for each group. The first is a scatter chart with all the same data points:



Now you can start to see the clear benefit of Etep over the untreated group. There is a mean difference of +74 meters for all data points (overall, including baseline). Key to this type of comparison is age. Older patients will drop faster. So are we comparing apples to apples? You can see in the full comparison of ALL data points the average age of EC is 11.4 and Etep is 11.2, very close but let's dig further.

Understanding the significance of the 6MWT on two variables is the key to properly interpreting the data. The "Age" of the patient is one variable. This is the only value we have to match the probable 6MWT curves on a historical basis. The second variable is "Years on Etep" with a value from 0 to 4, meaning the five data sets from baseline to year four (or specifically to week 216). To get a good graphical image of these, we have a 3D graph.



This representation is not the typical representation Sarepta has used in the past. To look at this 3D graph properly, you must realize ALL data for the External Control group is in the front row with the EC in green. The Etep treated patients are in blue. The Etep baseline (0 Years on Etep) is also in the front row with only 10- and 11-year-old patients. Younger patients are excluded from the graph because we are concerned only with the older patients (for the long-term efficacy and to keep the 3D visually interpretable).

Each subsequent row is a following year on Etep, finally with the back row showing the Year 4 data of Etep treated patients.

The graph clearly shows the drop in 6MWT by age as the EC patients reach 13 and 14 and finally the mean 6MWT drops to the lowest point with only one EC patient reporting non-LOA at age 15. In contrast, those older age patients continue to walk with a higher mean 6MWT on the later years while on Etep. This is shown by the longer blue bars on the right side of the chart with patients' ages 13 through 15.

Finally, let's show the data in a box plot. This is what those in the statistical analysis field may consider the best graphical representation. A box plot shows the "whiskers" on each plot to help visualize the outliers, or as a way of showing the distribution of the data.



**EC Year 4 results include one 300 meter, ten 0 meter, and two missing values.*

Now let's take a look at some post-hoc analysis of the data. While the FDA clearly has a strong bias against any post-hoc analysis, the FDA BD does its own backwards post-hoc analysis by suggesting intermittent steroid use as a "reason" to throw out the Sarepta EC data and selecting Drisa EC after year three. So the following charts show the same data with the five intermittent steroid EC patients removed. This shows that the Etep patients still have a clear improvement over the EC patients without intermittent steroid. In other words, the Etep patients continue to perform better. This is further confirmed with statistical analysis in the final section, where the intermittent steroid control shows "Not Significant" ($p=0.899$).



**These two graph views leave the one Etep intermittent patient while removing all the EC intermittent patients in the data set, for a theoretical disadvantage bias against the Etep group*

Additionally, let's look at the removal of the "Twins." There is an argument they should be removed as it is "reasonable" to accept this as a modified intent to treat (MITT) as it is nearly impossible for a drug that shows long-term statistical benefit but little short-term benefit as being useful to compare 6MWT in a situation where the patient goes LOA in the short term. The "Twins" went LOA at six and 10 months after going on Etep.

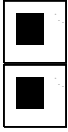
Reference



In fact, when looking at the EC selection criteria below, Sarepta correctly takes this into consideration by only selecting EC patients that have at least one year of 6MWT data. Therefore, the External Control is actually biased with stronger patients.

To get to the real nuts and bolts of a proper data analysis, it's best to understand the "age" of the patient as its impact on the predictability of the 6MWT curve. Therefore, age might normally be used a covariate as a confounding interacting variable. But, as we examine the selection criteria of the EC, we find age is properly matched between groups. This is further confirmed in the close average ages shown in the graphs above. In other words, age is not a significant predictor for **this data set** when controlling for year and group. This is confirmed by Yang in the statistical analysis section below.

As Sarepta presents in its October 1, 2015, data update, the EC is a selection filter of n=186 of the only two published data sets with at least three years of data (matching four years of data now).



Reference

As mentioned in the above Sarepta slides, "equivalent care standards including steroid use" in the selection criteria. As well our post-hoc analysis above confirms any difference in Steroid "intermittent" use does not dismiss the significant difference between groups.

Finally, here are a few more graphs to represent different views:



**Exclude EC intermittent*



**Full data set*



**All patients, all data points baseline to four years.*



**NSAA and Rise Time data analysis and charts prepared by Greg Wierenga*

Summary

To summarize, there is significant difference between groups that demonstrates Eteplirsen provides long-term benefit. At year two, the p-value of $p=0.199$ with a 90-meter mean difference is a step in the right direction. The probability continues to improve with each subsequent year. Finally years three and four conclude with significant probability ($p=0.016$ and $p=0.002$ respectively) and a significant mean difference (160 and 169 meters respectively), showing a very strong benefit for the Eteplirsen treated group.

Philips, Howard

From: Bastings, Eric
Sent: Tuesday, March 15, 2016 1:29 PM
To: Unger, Ellis
Cc: Temple, Robert; Dunn, Billy
Subject: FW: Eteplirsen AC package
Attachments: Eteplirsen AC Cover Final.doc; Eteplirsen CDTL memo cleared.docx; Eteplirsen_FDA AC BD 012216.pdf

Ellis,

Attached are the clinical documents that were made public for the original Sarepta AC meeting. The pdf file is the "official" document. The word documents are also the final documents, as far as I can tell.

Tomorrow's 9 AM meeting will be used to provide feedback to Ron's updated TL memo. The feedback should focus on the italicized text, as the rest of the document is already public, and does not have factual errors.

Ron is adamant that he wants feedback on his memo before he can make his first slide presentation. I asked him to get ready to make an initial presentation next week.

I will shortly start working on an addendum to our AC cover document. I hope to have that ready early next week.

Eric

MEMORANDUM

(b) (5)



14 pages have been withheld as b(5) immediately following this page

FDA Briefing Document

(b) (5)



103 pages of draft language have been withheld as b(5) immediately following this page

FDACDER0003686

Philips, Howard

From: Unger, Ellis
Sent: Friday, March 18, 2016 5:32 PM
To: Temple, Robert; Jenkins, John K
Subject: Eteplirsen Foreign Inspection - It seems clear it will happen

See below.

From: Choy, Fannie (Yuet)
Sent: Friday, March 18, 2016 4:47 PM
To: Bastings, Eric; Farkas, Ronald
Cc: Dunn, Billy; Unger, Ellis
Subject: FW: Audit Schedule For The Belgian and Italian Sites

fyi Sarepta forwarded an ongoing discussion on site visit. Please see schedule below.

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, March 18, 2016 4:08 PM
To: Bukowczyk, Michelle
Cc: Choy, Fannie (Yuet)
Subject: RE: Audit Scedule For The Belgian and Italian Sites

Dear Michelle,

That's great news – thank you for your flexibility.

As requested, we will provide you the information regarding addresses and hotel recommendations in the next couple of days. In addition, we will arrange for a translator to be present at each of the sites during the audits.

Please feel free to contact me if you have any further requests or questions.

Regards,
Shamim

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



215 First Street, Cambridge, MA 02142

From: Bukowczyk, Michelle [<mailto:Michelle.Bukowczyk@fda.hhs.gov>]
Sent: Friday, March 18, 2016 1:38 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: Audit Proposal For Italian Sites
Importance: High

Dear Shamim,

Thank you for putting this together. It looks great!

We need information from the sites on their addresses and hotel recommendations. Will you please provide me the information as soon as possible so we can make travel arrangements for the investigators?

Is it possible to get a translator at each site? Your company can provide the translator if you wish or we can use a staff member at the sites.

Best Regards,
Michelle

Michelle Bukowczyk
Consumer Safety Officer
BIMO/Biologics Foreign Inspection Coordinator
United States Food and Drug Administration
michelle.bukowczyk@fda.hhs.gov
Phone Number (301)796-4397
Cell (240) 731- 8910



From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Wednesday, March 16, 2016 9:40 PM
To: Bukowczyk, Michelle
Subject: RE: Audit Proposal For Italian Sites

Dear Michelle,

We have been working with Dr. Eugenio Mercuri to come up with a schedule that works with your request and his complex schedule. In particular, he needs to be in the UK for a key EU Commission sponsored conference on Thursday and Friday April 28-29.

He has requested that the inspectors, if possible plan to visit his site in Rome first (see schedule below) on Wednesday, April 27 in the afternoon. The schedule also attempts to accommodate the intent to visit all sites. We tried to break this up by geographic region to make the travel the easiest for the investigators. Please let us know if this schedule will work for the FDA so we can work on locking in these dates with each site as well.

Date	Location	Hospital/Clinic	Clinican	Num. Pts.	Notes
April 25 (Mon)	Leuven, Belgium		Dr. Nathalie Goemans	3	

April 26 (Tue)	Leuven, Belgium		Dr. Nathalie Goemans	3	
April 27 (Wed)	Italy, Rome	Polioclinico Gemelli Universita Cattolica Sacro Curore Roma	Dr. Eugenio Mercuri	0	Fly to Rome from Brussels (morning), see Dr. Mercuri afternoon of 27 th .
April 28 (Thu)	IT, Rome	Ospedale Bambino Gesù	Drssa Adele D Amico	2	
April 29 (Fri)					Travel to North and Middle Italy
April 30 (Sat)					
May 1 (Sun)					
US FDA Inspector #1 Schedule (Middle/Northern Italy)					
May 2 (Mon)	IT, Pisa	Istituto Stella Maris Pisa	Drssa Roberta Battini	1	
May 3 (Tue)	IT, Pavia	Fondazione Mondino Pavia	Drssa Angela Berardinelli	1	
May 4 (Wed)	IT, Torino	Universita di Torino	Profssa Tiziana Mongini	2	
May 5 (Thu)					Travel to Rome
May 6 (Fri)					Travel to US
US FDA Inspector #2 Schedule (Northern Italy)					
May 2 (Mon)	IT, Napoli	Seconda Universita Napoli	Profssa Luisa Politano	1	
May 3 (Tue)	IT, Milan	Istituto Neurologico Besta	Dr Giovanni Baranello	1	
May 3 (Tue)	IT, Milan	Ospedale S Raffaele Milano	Dr Stefano Previtali	1	
May 4 (Wed)	IT, Genoa	Ospedale Giannina Gaslini	Dr Claudio Bruno	1	
May 5 (Thu)					Travel to Rome
May 6 (Fri)					Travel to US

Regards,
Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality

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

e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

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MEMORANDUM

DATE: March 20, 2016

FROM: Ronald Farkas, M.D., Ph.D.
Clinical Team Leader
Division of Neurology Products, CDER, FDA

TO: Members and Invited Guests of the Peripheral and Central Nervous Systems
Drugs Advisory Committee (PCNS AC)

SUBJECT: Clinical Team Leader Memorandum for New Drug Application (NDA) 206488, for
the use of Exondys 51 (eteplirsen) for the treatment of Duchenne muscular
dystrophy in patients with mutations amenable to exon 51 skipping

(b) (5)

eteplirsen

Temple, Robert

From: Bastings, Eric
Sent: Tuesday, March 22, 2016 7:04 PM
To: Temple, Robert
Subject: FW: FDA Security at Sarepta AC meeting: the rhetoric

The nasty stuff is below.

Also see <https://twitter.com/adamfeuerstein/status/692077424834646017>

Eric

From: Bastings, Eric
Sent: Sunday, March 20, 2016 1:16 PM
To: Choi, Moon Hee; Ngo, Diem-Kieu (CDR,USPHS); Peterson, Jayne E; Reese, Cicely
Cc: Dunn, Billy
Subject: FDA Security at Sarepta AC meeting" the rhetoric

Here is a sample of the rhetoric about the Sarepta AC.

Eric

Farkas needs a special prosecutor to prove he is a habitual story teller. Now he needs more than three months to conjure up new revelations and play make believe with that nasty awful, horrible, no good drug Eteplirsen. I mean it likely works and would save a bunch of boy's worldwide from pain and suffering. Even death. I wonder what this maybe opthamologist does in his basement when he gets home for work. If I only could write horror stories! I mean he has to take pleasure in seeing young boys suffer and even die. Effectively, should he block Eteplirsen that is what he is accomplishing. Throw the bum out!

<https://finance.yahoo.com/mbview/searchview/?&bn=8725fb77-7f25-376f-ba90-76e44fcd776&q=farkas&in=b&sm=>

FDASIA - I contacted 2 Senators - Shelby and Nelson - who will attend ADCOM to make sure the 2012 FDASIA law is enforced.

Straight from the void.....

The highest ups in FDA and beyond know what needs to happen with Eteplirsen now and that is approval.

They can't avoid it any longer, no matter the size of the payoffs.

Heads will roll this time if Etep is not given a thumbs up, due to the massive firestorm and scandal that would ensue.

Covering that rear end is the priority now.

Farkas and the others will be directed and will comply.

Plain and simple.

<https://finance.yahoo.com/mbview/searchview/?&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&q=farkas&in=b&sm=>

Farkas and Shkreli made boat load of money shorting biotech stocks. You can bet everything they did is all well planned.

<https://finance.yahoo.com/mbview/searchview/?&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&q=farkas&in=b&sm=>

Yes, Farkas would prefer placebo controlled despite the fact that in DMD, using a placebo would be unethical forcing those receiving placebo to undergo biopsies. You'd probably never be able to convince parents to allow their kids to be Guinea pigs for that sort of study, and this, you'd never be able to run the study that Farkas insists upon. It shouldn't be run, and it's probably impossible to run a full powered placebo controlled study. So, Farkas would prefer that these boys just sit back and enjoy their cruel death rather than allow a possibly more biased, yet informative study none the less. The DNP has a LONG history of being the most dysfunctional department within the FDA. Farkas is a big part of why.

<https://finance.yahoo.com/mbview/searchview/?&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&q=farkas&in=b&sm=>

Farkas and qualifications? Isn't that an oxymoron.

https://finance.yahoo.com/mbview/searchview/:_ylt=AqSxF0OduS7ErrKc6cIt4HreAohG:_ylu=X3oDMTB2ZGV1aW5oBHBvcwM3NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-:_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-:_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=2

A candy sucker after doing the 6 mwt is a motivator. How many crushed suckers have you seen outside of banks where that is commonplace. Farkas has to be a dufus

https://finance.yahoo.com/mbview/searchview/:_ylt=AqSxF0OduS7ErrKc6cIt4HreAohG:_ylu=X3oDMTB2ZGV1aW5oBHBvcwM3NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-:_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-:_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=2

I laughed until it hurt when I read that... Farkas-gate scandal.. That's genius. Maybe it's the same guy by that name who was on Seinfeld many years ago..... All hilarity aside FDA better make this all right and very soon for all involved. The world is and has been watching their words and actions now. So truth/medicine/science/data/efficacy/safety better be the determining factors = AA; not FDA dysfunction/politics and no AA..

https://finance.yahoo.com/mbview/searchview/:_ylt=AqSxF0OduS7ErrKc6cIt4HreAohG:_ylu=X3oDMTB2ZGV1aW5oBHBvcwM3NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-:_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-:_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=2

Farkas was unqualified to write the report since he is not a DMD expert and the FDA assigned the task to an unqualified person. Farkas caused investors to lose more than 60% of their investment.

https://finance.yahoo.com/mbview/searchview/:_ylt=AqSxF0OduS7ErrKc6cIt4HreAohG:_ylu=X3oDMTB2ZGV1aW5oBHBvcwM3NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-

[: _ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-; _ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=2](https://finance.yahoo.com/mbview/searchview/?_ylt=AqSxF0Odu57ErrKc6cIt4HreAohG;_ylu=X3oDMTB2ZGV1aW5oBHBvcwM3NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=2)

you need to antagonize Farkas and his cronies by bombarding them with emails and calls

call him what he really is

thats how you get things done around here

you know how to play the game

its always been your strong suit

https://finance.yahoo.com/mbview/searchview/?_ylt=AqSxF0Odu57ErrKc6cIt4HreAohG;_ylu=X3oDMTB2ZGV1aW5oBHBvcwM3NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=2

Farkas has no expertise, nor handle on DMD, Neurology, nor integrity ...He was in a position of power and influence with the FDA and, lacking both expertise and integrity was the easiest and least expensive influence for BIG Pharma and the Health Insurance Industry to buy off.

He's not stupid...just evil, wicked, mean, bad and nasty - and now he's much richer than he was prior to his brief.

https://finance.yahoo.com/mbview/searchview/?_ylt=AqSxF0Odu57ErrKc6cIt4HreAohG;_ylu=X3oDMTB2ZGV1aW5oBHBvcwM3NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=2

BMRN is on record admitting that they weren't certain that all the kids in their study actually had Exon 51 deletion DMD! How then could anyone use any of their data with any certainty as to its accuracy? Farkas' agenda is holding onto his old world ideology NOT getting safe, effective to kids who have none.

https://finance.yahoo.com/mbview/searchview/?_ylt=AqSxF0Odu57ErrKc6cIt4HreAohG;_ylu=X3oDMTB2ZGV1aW5oBHBvcwM3NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=2

Apparently, Farkas trained as an ophthalmologist, but quit residency after 1 year to join FDA, he never passed his boards. So no, he's not a DMD expert, he's not a neurologist, he's not even a board certified ophthalmologist

https://finance.yahoo.com/mbview/searchview/?_ylt=AvfclZrwy5.1wwfLcVFiFEbeAohG;_ylu=X3oDMTB2YWdpYjkyBHBvcwM4MARzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=3

Farkas the Executioner

https://finance.yahoo.com/mbview/searchview/;_ylt=AvfclZrwy5.1wwfLcVFfEbeAohG;_ylu=X3oDMTB2YWdpYjkyBHBvcwM4MARzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcd776&stb=r&sto=d&lv=e&page=3

Reply to

Farkas the Executioner

by [alt225alt225](#) • Jan 19, 2016 9:30 AM

[starfe11](#) • Jan 19, 2016 9:31 AM

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tell him that in an email

lets shake the him up for a change

https://finance.yahoo.com/mbview/searchview/;_ylt=AvfclZrwy5.1wwfLcVFfEbeAohG;_ylu=X3oDMTB2YWdpYjkyBHBvcwM4MARzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcd776&stb=r&sto=d&lv=e&page=3

Farkas the INCOMPETENT IRRESPONSIBLE.

Don't forget that he gets PAID BY US ALL (tax money). We have the right to demand excellence.

No shame in saying the above -- though, I also believe that he is just playing a (dangerous irresponsible) game.

https://finance.yahoo.com/mbview/searchview/;_ylt=Aoayx.DD5XpxqnrNwpM_In_eAohG;_ylu=X3oDMTB2Zml1dmJvBHBvcwM4MgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcd776&stb=r&sto=d&lv=e&page=4

Handling farkas with a crowbar approach has worked micacles

Has anyone learned anything

The shorts have

It's so funny now

https://finance.yahoo.com/mbview/searchview/;_ylt=Alc4TnM9WRqou9hTokfhQQ7eAohG;_ylu=X3oDMTB2ZzMxNHFoBHBvcwM4MQRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcd776&stb=r&sto=d&lv=e&page=6

Possibly. I think Farkas needs a shrink. One could posture that he is sexist and is railing against:

1. The female dominated advocacy of DMD moms and the FDAISA that brought them to him.
2. His female leader, JW, who created a sorority with DMD moms that he doesn't feel part of.

https://finance.yahoo.com/mbview/searchview/?_ylt=AiYPpf4kDTzxFpyLWxWDg5feAohG;_ylu=X3oDMTB2djNsdXYyBHBvcwM4MwRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=7

I think Farkas would benefit from undergoing a few of these biopsy procedures himself. At the very least, the experience might convince him to treat the outcomes with higher rigor.

https://finance.yahoo.com/mbview/searchview/?_ylt=AiYPpf4kDTzxFpyLWxWDg5feAohG;_ylu=X3oDMTB2djNsdXYyBHBvcwM4MwRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=7

Correct, the resident idiot Farkas at the FDA. A man that was likely fired from his residency and given the choice to resign. The alternative is he quit because he couldn't cut it. This is the man the FDA picks to to diss Etep. We need to ask Woodcock is she a crock of dung too.

https://finance.yahoo.com/mbview/searchview/?_ylt=AiYPpf4kDTzxFpyLWxWDg5feAohG;_ylu=X3oDMTB2djNsdXYyBHBvcwM4MwRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=7

Perhaps you don't understand the farkas, the evil one, effect. You can paint all the rosie pictures you want, but farkas is in charge and his bd gave you his thoughts -- which caused the sell off. So unless farkas changes, unless new bd's are issued, then farkas has the last say and the institutional interpretation was not good which drove it into the 10's

https://finance.yahoo.com/mbview/searchview/?_ylt=AiYPpf4kDTzxFpyLWxWDg5feAohG;_ylu=X3oDMTB2djNsdXYyBHBvcwM4MwRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=7

Exactly. Farkas is going to get peed on.

https://finance.yahoo.com/mbview/searchview/?_ylt=AiYPpf4kDTzxFpyLWxWDg5feAohG;_ylu=X3oDMTB2djNsdXYyBHBvcwM4MwRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=7

grey.Herr Farkas & Co. missed their calling.They would of been guards at AUSCHWITZ.

https://finance.yahoo.com/mbview/searchview/?_ylt=An1KhuyuzKuf1SyG0L6sEJveAohG;_ylu=X3oDMTB2dWQwnZqBHBvcwM4NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=10

Get ahead of the others and threaten Farkas today

https://finance.yahoo.com/mbview/searchview/?_ylt=An1KhuyuzKuf1SyG0L6sEJveAohG;_ylu=X3oDMTB2dWQwdnZqBHBvewM4NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=10

100 congressman against an arrogant egomaniac Eye doctor...I am sure Farkas will justify his position without losing face! BTW, We have a Pediatric Neurologist on the committee, shouldn't he be on the ADCOM BD lead, or is he/she 30 years old and intimidated by a 60 year old EYE GUY..I just don't get the specialist designation and allocation to responsibility. Perhaps the new 3 committee members will be more innovative, AA and FDASIA oriented. That would be nice. Finally, and again, I am repeating myself, let the Pediatric Neurologist take the lead on the new BD..If we get one!

https://finance.yahoo.com/mbview/searchview/?_ylt=AgnG3gBhd9KsrugBbHHggeLeAohG;_ylu=X3oDMTB2bzc2NGQ1BHBvewM4NQRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=11

after reading all of his posti agree -- we should welcome dr farkas, the evil one, to the board. welcome winterlinion or dr farkas which do you prefer.

https://finance.yahoo.com/mbview/searchview/?_ylt=AioGx8ofAB9xNxXtk3AH3creAohG;_ylu=X3oDMTB2Zmhyb3M1BHBvewM4OQRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=13

Some talk that the briefing docs were published to:

- 1). in a fashion to hinder stock prices.
- 2). were written to get back at certain people or ruffle feathers of Janet or trifle with whomever.
- 3). That Farkas wants to see death and suffering of little children.
- 4). FDA is purely trying to flex their muscles.
- 5). Farkas is somehow a rogue reviewer that is now getting an earful for what he wrote, as if something as serious as the briefing documents to the panelists wouldn't have been reviewed and had the approval of management 1 or 2 or 3 levels above him prior to distribution...

I think all of that is loony.

What is plausible and more likely is that Farkas is just bad at his job. Just because you have a PhD or went to medical school doesn't mean your a statistician.

And it doesn't mean you were good at either whatever you "specialized" in whether that be your PhD topic. One of my chemistry professors with a PhD in chemistry was one of the worst chemist I knew. She would often get corrected in her Level-101 chemistry lecture by her 18 and 19 year old students daily.

And going to medical school and being certified in a speciality doesn't mean you have broad knowledge of the medical field... Nor does it mean your even good at the field you specialized in.

And most importantly it doesn't mean you have common sense.

I don't think Farkas is the sharpest crayon in the FDA. The only way he'll get an "earful" for such a #\$\$%\$ job on the briefing docs that were already approved by his boss's boss, is if he and the FDA get so severely embarrassed during the AdCom when all the errors are highlighted.

https://finance.yahoo.com/mbview/searchview/?_ylt=AioGx8ofAB9xNxXtk3AH3creAohG;_ylu=X3oDMTB2Zmhyb3M1BHBvcwM4OQRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=13

I wouldn't be totally surprised if Farkas or a family member had a large short position. This just seems to set a new low for government incompetency. Objective criticism is one thing, but the briefing doc reads like a partisan manifesto. Imagine if a piece of garbage like that was submitted to a scientific publication.

https://finance.yahoo.com/mbview/searchview/?_ylt=AptHSDZuuhpvZoXhNzZWQWbeAohG;_ylu=X3oDMTB2MHI3a3ZpBHBvcwM4OARzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=14

I filed complaint with the SEC, named Farkas and Dunn as responsible for the document, pointed out the falsifications in the Doc, triple witching day etc....

https://finance.yahoo.com/mbview/searchview/?_ylt=AvX4tZqhOLmscroyKJ1k.mTeAohG;_ylu=X3oDMTB2dWQWdnZqBHBvcwM4NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=15

Conrad, she may be our strongest ally at this point, in de-Farkas-ization. And she may be able to get it done while out of the spotlight.

https://finance.yahoo.com/mbview/searchview/?_ylt=Ao6i43zs5nCG4qf_qFcLS_PeAohG;_ylu=X3oDMTB2b25kdm9pBHBvcwM4NwRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=16

stocktrooth you are hilarious!!!! i will stop sending my deaththreats to Farkas... i bet that bumped the date back two weeks....didn't think about that....thanks for your perspective and humor!!!!

https://finance.yahoo.com/mbview/searchview/?_ylt=AiSoLePkZ3.sPbu7XWhOCfbaohG;_ylu=X3oDMTB2dWQWdnZqBHBvcwM4NgRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=16

Maybe we should try to arrange a meeting between kunkle, and yes that is his name, and lucifer aka farkas; otherwise, a lot of children will get farkased (my new name for the f word).

https://finance.yahoo.com/mbview/searchview/?_ylt=AkOiba4baVzXWJqEXKN.1N3eAohG;_ylu=X3oDMTB2b25kdm9pBHBvcwM4NwRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=17

Just guessing here, Thousands of kids dying because the FDA Farkas drags his feet and delays ALL EXONS would get my attention. He might as well just tell them to die and stop whining. He can't put two and two together so he makes things up.

https://finance.yahoo.com/mbview/searchview/;_ylt=AkOiba4baVzXWJqEXKN.1N3eAohG;_ylu=X3oDMTB2b25kdm9pBHBvcwM4NwRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=17

Yes, they poo-pooed safety in the etepliresen analysis, but when it comes to themselves they're worried sick over it. Run and hide, Farkas. Run and hide! A bully and yet a coward. As usual.

https://finance.yahoo.com/mbview/searchview/;_ylt=AkMYNaqTkWn5Lggg_ClvJrjeAohG;_ylu=X3oDMTB2bzc2NGQ1BHBvcwM4NQRzZWMDTWVkaWFNc2dCb2FyZHNYSFJVbHQ-;_ylg=X3oDMTBhYWM1a2sxBGxhbmcDZW4tVVM-;_ylv=3?&q=farkas&in=b&inf=&sm=&bn=8725fb77-7f25-376f-ba90-76e44fcfd776&stb=r&sto=d&lv=e&page=17

Philips, Howard

From: Unger, Ellis
Sent: Tuesday, March 22, 2016 5:52 PM
To: Temple, Robert
Subject: FW: revised eteplirsen memo
Attachments: UPDATED CDTL MEMO ETEPLIRSEN 21 to EB EU.doc

From: Farkas, Ronald
Sent: Tuesday, March 22, 2016 5:09 PM
To: Bastings, Eric; Unger, Ellis
Subject: revised eteplirsen memo

Eric and Ellis,

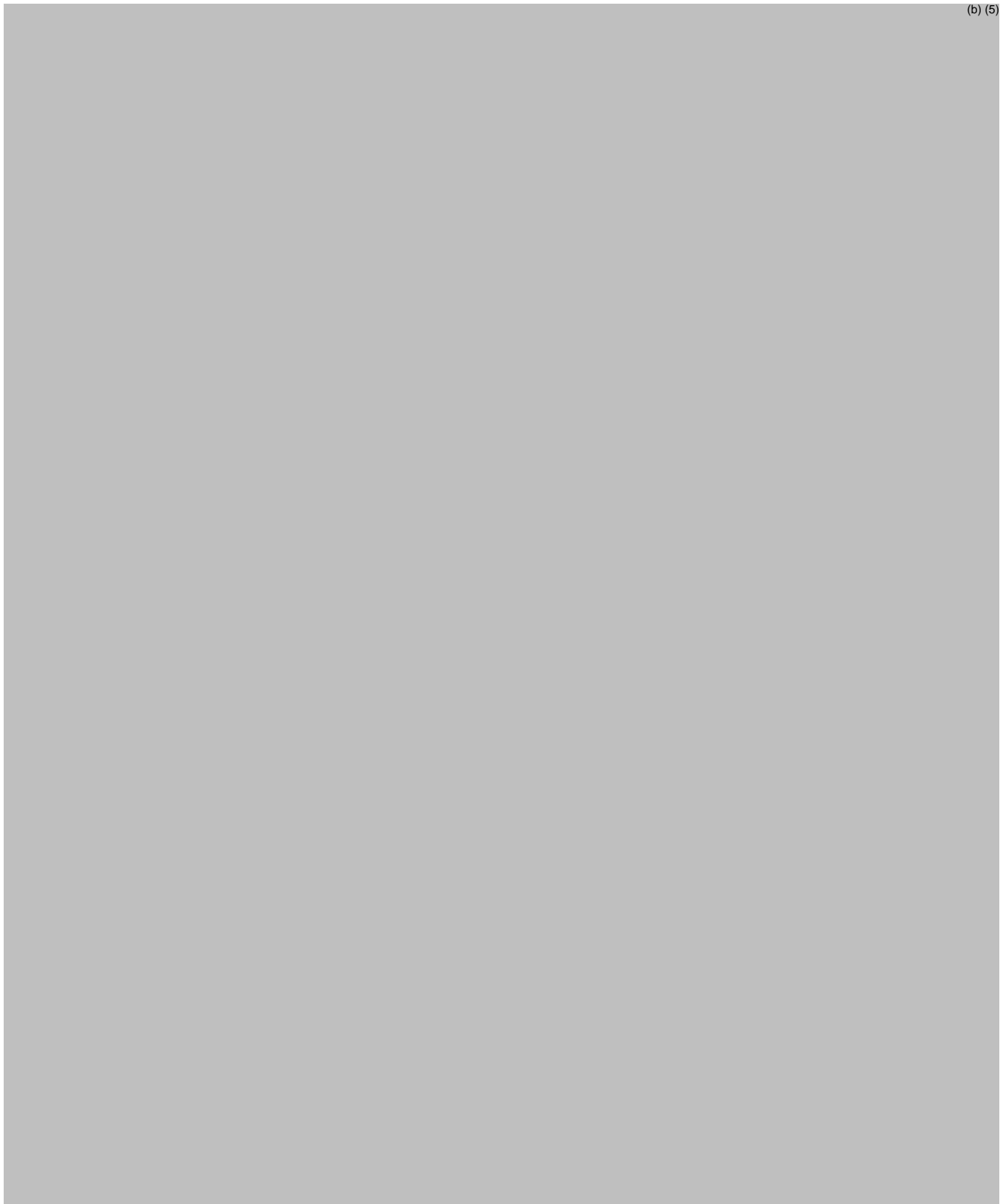
There are some pretty extensive revisions in this version, not so much in the responses to the applicant's objections, and more in some of the new commentary and analyses.

Thanks

Ron

MEMORANDUM

(b) (5)



74 pages have been withheld as b(5) immediately following this page

Philips, Howard

From: Bastings, Eric
Sent: Tuesday, March 29, 2016 4:48 AM
To: Temple, Robert; Unger, Ellis
Cc: Farkas, Ronald; Dunn, Billy; Breder, Christopher D
Subject: Eteplirsen cover memo
Attachments: Eteplirsen April 25 AC Cover 0329.doc

Ellis, Bob,

Here is the revised version of the AC cover memo.

This has been reviewed by Ron, who provided some comments and responses to the “key inaccuracies”.

This document does not take into consideration the new Sarepta briefing documents.

I will have a look at them and see if anything in our memo needs to be changed in response. If you see something on your end, let me know.

The plan, however, should be to address FDA comments to the new Sarepta briefing document in our addendum, which we will release around mid-April, and which will include analysis from the CINRG database, and also findings on the source documents of the control kids.

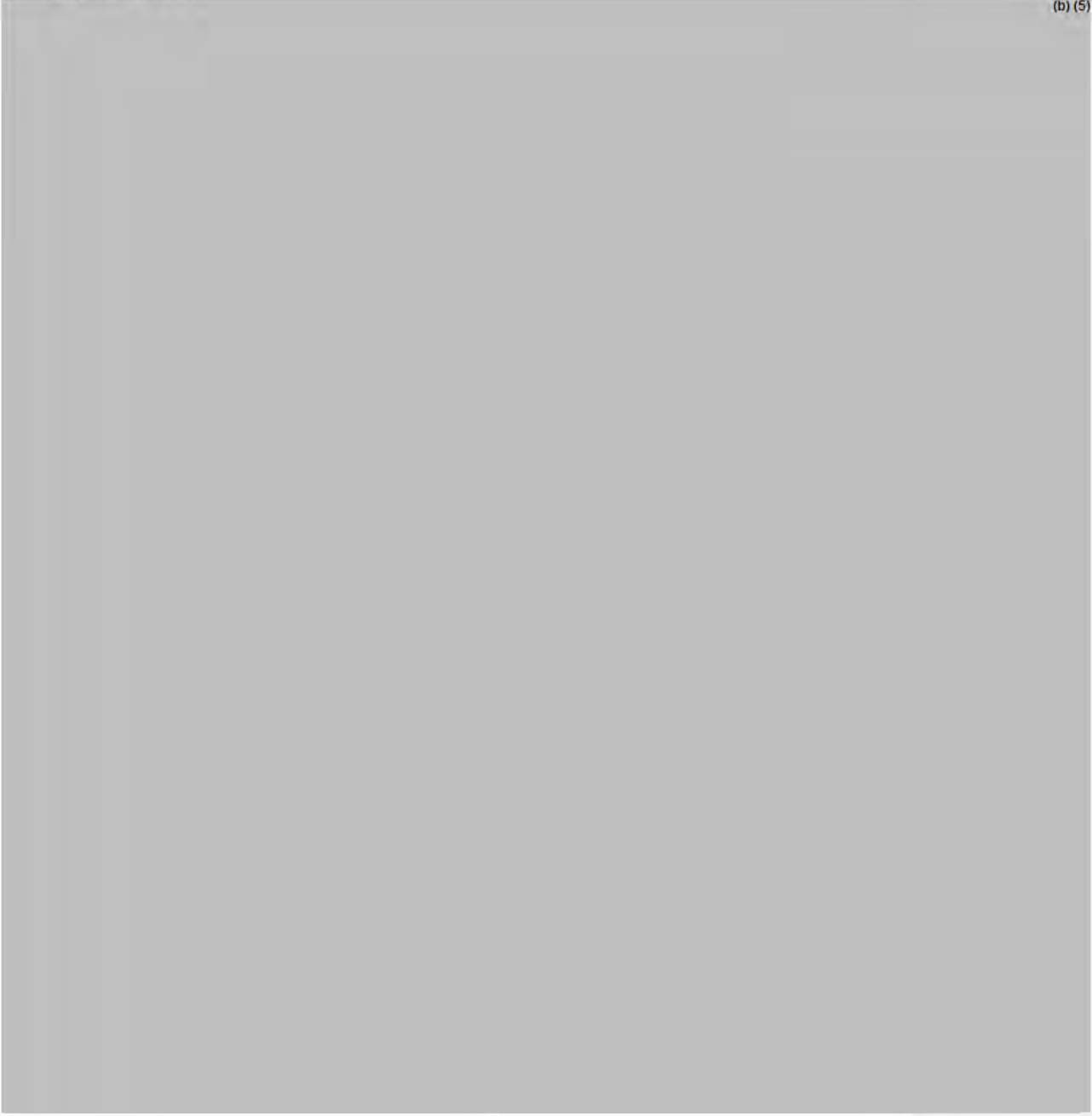
I will be standing by to consider your edits and comments.

Thanks.

Eric

MEMORANDUM

(b) (5)



35 pages of draft language have been withheld as b(5) immediately following this page

MEMORANDUM

(b) (5)



28 pages of draft language have been withheld as b(5) immediately following this page

Philips, Howard

From: Farkas, Ronald
Sent: Thursday, March 31, 2016 11:08 AM
To: Unger, Ellis
Cc: Temple, Robert; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet)
Subject: RE: Revised eteplirsen memo
Attachments: UPDATED CDTL MEMO changes accepted_3-30-16_unger.doc

Ellis,

Great, thanks, I agreed with all your suggestions [REDACTED] (b) (5)
[REDACTED], and appreciate that you added the figure legends. There were two areas of text you highlighted as unclear, and it seemed that the best way to fix those was to delete the unclear text because the surrounding text was sufficient. I also deleted the figure showing [REDACTED] (b) (5) because the text description was sufficient (with a few words added) and the figure had the problem you noticed [REDACTED] (b) (5)
[REDACTED]).

Hopefully the attached will be the final version unless anyone finds other problems.

Thanks

Ron

From: Unger, Ellis
Sent: Wednesday, March 30, 2016 6:34 PM
To: Farkas, Ronald
Cc: Temple, Robert; Bastings, Eric; Dunn, Billy
Subject: RE: Revised eteplirsen memo

Ron,

I went through your revised memo carefully, and made some suggested edits – most of which I think you'll agree with. See what you think.

Ellis

From: Farkas, Ronald
Sent: Tuesday, March 29, 2016 11:07 PM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy
Subject: Revised eteplirsen memo

This version of the memo contains edits based on the recent suggestions from Ellis, and also has a fair amount of new content, including about the source documents we recently received from the natural history patients, which appear to be highly relevant to problems with data reliability.

As I was just finishing I accidentally overwrote the tracked-changes version, so I'm sending now the only version I have, without changes tracked, so please accept my apologies.

I'm likely to be driving all day Friday, so it would be good if any comments could be provided as soon as possible, so that the memo can be finalized tomorrow or Thursday at the latest, as it's my understanding that it needs to go to the AC staff by Friday.

Thanks

Ron

MEMORANDUM

(b) (5)



71 pages of draft language have been withheld as b(5) immediately following this page

Philips, Howard

From: Choi, Moon Hee
Sent: Tuesday, April 05, 2016 9:05 AM
To: Unger, Ellis
Cc: Ngo, Diem-Kieu (CDR,USPHS); Temple, Robert; Dunn, Billy; Bastings, Eric; Choy, Fannie (Yuet); Peterson, Jayne E; Reese, Cicely
Subject: RE: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Dear Dr. Unger,

I want to let you know that the CDER Vote Memo for the April 25th PCNS Advisory Committee will be moving forward as ACOMS and OCHA were consulted regarding Mr. Dupree's participation for the postponed January 22nd meeting and it was agreed that Mr. Dupree should remain cleared to participate.

Thank you.

Moon Hee V. Choi, Pharm.D.
Designated Federal Officer, NDAC & PCNS
Food and Drug Administration (FDA)
Office of Executive Programs (OEP)
Division of Advisory Committee and Consultant Management (DACCM)
White Oak Building 31, Room 2417
10903 New Hampshire Avenue
Silver Spring, MD 20993
Telephone: (301) 796-2894
Fax: (301) 847-8533
Email: Moonhee.Choi@fda.hhs.gov

From: Unger, Ellis
Sent: Friday, April 01, 2016 8:16 AM
To: Choy, Fannie (Yuet)
Cc: Choi, Moon Hee; Ngo, Diem-Kieu (CDR,USPHS); Temple, Robert; Dunn, Billy; Bastings, Eric
Subject: RE: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Hi Fannie,

I'm not willing to sign this vote memo with Benjamin Dupree as the patient representative, given that we've learned he has a family member who owns stock in Sarepta – the company whose product is being discussed at this AC meeting. His participation as a voting (or non-voting) member of the Committee represents a blatant conflict of interest in my view. (Should the AC vote in favor of approval, Sarepta stock could easily double in value.) I understand that our rules do not prohibit his participation, but that does not mean that we are obliged to select him.

It is important to have patient representation on the Committee. I suggest they quickly find a different patient representative – one who has no known conflicts of interest.

Ellis

From: Choy, Fannie (Yuet)
Sent: Thursday, March 31, 2016 3:45 PM
To: Unger, Ellis
Cc: Choy, Fannie (Yuet)
Subject: FW: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Dr. Unger

Please review and sign off the Vote memo when you have a moment.

Thank you
Fannie

From: Choi, Moon Hee
Sent: Thursday, March 31, 2016 2:35 PM
To: Choy, Fannie (Yuet)
Cc: Ngo, Diem-Kieu (CDR,USPHS)
Subject: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Hi Fannie,

Attached you will find the CDER Vote Memo for the Apr 25 PCNS meeting. Can you please have Dr. Unger sign (electronic signature is ok) and get it back to me?

Thank you.

Moon

Philips, Howard

From: Unger, Ellis
Sent: Thursday, April 07, 2016 5:15 PM
To: Temple, Robert
Subject: FW: Revised cover memo
Attachments: Sarepta cover memo (tracked changes)_4-7-16 jkj eb.doc

From: Bastings, Eric
Sent: Thursday, April 07, 2016 2:57 PM
To: Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald
Subject: Revised cover memo

Ellis,

Here is the revised cover memo. I think I addressed all of John's comments/questions, with one exception: [REDACTED] (b) (5)
[REDACTED]. Lisa L vehemently opposed to its use, and vetting this won't happen in my lifetime.

I leave it up to you and John how you want to address that.

Eric

MEMORANDUM

(b) (5)

21 pages of draft language have been withheld as b(5) immediately following this page

Temple, Robert

From: Unger, Ellis
Sent: Friday, April 08, 2016 2:59 PM
To: Farkas, Ronald; Bastings, Eric
Cc: Temple, Robert; Dunn, Billy
Subject: RE: Revised cover memo

There is basically no correlation here. As Eric and Bob have pointed out, of the 4 patients whose 6MW distances were best preserved had, 2 had very low levels of dystrophin, and 2 had the highest levels.

If dystrophin level simply reflects the amount of muscle mass remaining, then I've completely misunderstood Western blot. This is supposed to be % of normal dystrophin within muscle. Right? In other words, this is indexed to muscle mass through another muscle protein. Right?

From: Farkas, Ronald
Sent: Friday, April 08, 2016 2:45 PM
To: Unger, Ellis; Bastings, Eric
Cc: Temple, Robert; Dunn, Billy
Subject: RE: Revised cover memo
Importance: High

Yes, there is confounding between the years you've had the baseline amount of dystrophin (since birth, to an approximation), and the much fewer years you might have had the increased dystrophin level from eteplirsen. If the little bit of extra dystrophin from eteplirsen is having an effect, than the trace levels present prior to treatment will have a large confounding effect.

I should also add I've had a longstanding concern that a false-positive correlation between dystrophin levels and function could be obtained if the dystrophin levels were simply reflecting the amount of muscle that was remaining.

Thanks

Ron

From: Farkas, Ronald
Sent: Friday, April 08, 2016 2:38 PM
To: Unger, Ellis; Bastings, Eric
Cc: Temple, Robert; Dunn, Billy
Subject: RE: Revised cover memo
Importance: High

Conceptually, yes, we want to look at the relationship between eteplirsen, dystrophin, and function, but I'm afraid that this plot isn't going to help to clarify things. "Change in 6MWD" is not really the right variable because enrolled patients were from age 7 to 11 years, and age is strongly correlated to decline in 6MWD (we've included new graphs in the revised memos because we realized it's important to compare patients of similar age). If we were to even start to try to do this analysis the right way, we'd have to account for the effect of age, and also the effect of selecting the older kids at an age when some other kids would have already lost ambulation; it would have to be based on "percent predicted decline".

I also agree with Eric that the sample size is too small to see a poor correlation (even if done correctly) as evidence against efficacy.

Chris and I looked at dystrophin levels vs NSAA, which you might imagine has a less age-dependent effect (kind of same slope independent of age), and saw no relationship at all, as I recall – we included the two kids that lost ambulation early because they hadn't reached a floor-effect for NSAA.

**Actually, another potential problem with this is the confounding between baseline dystrophin and eteplirsen-induced dystrophin. I'd have to think through this a little more, though. Anyway, I think it's not a very good idea to include this in the memo.

Thanks

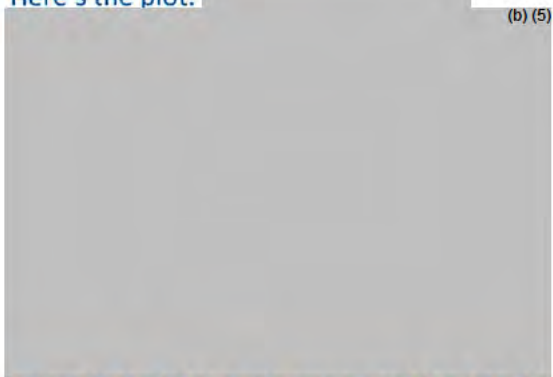
Ron

From: Unger, Ellis
Sent: Friday, April 08, 2016 1:53 PM
To: Bastings, Eric
Cc: Temple, Robert; Dunn, Billy; Farkas, Ronald
Subject: RE: Revised cover memo

In retrospect (on maybe not, since this isn't quite final), the critical correlation here is between preservation of walking ability (Δ 6MWD) and dystrophin protein (by Western blot).

If production of dystrophin protein is "reasonably likely to predict clinical benefit," then there should be some semblance of a correlation.

Here's the plot. (b) (5)



I think this plot is quite important (and so does Bob). Others?

From: Bastings, Eric
Sent: Friday, April 08, 2016 1:31 PM
To: Unger, Ellis
Cc: Temple, Robert; Dunn, Billy; Farkas, Ronald
Subject: RE: Revised cover memo

Ellis,

What do you think about Ron's comment?

I don't think strongly this has to be in the memo.

Eric

From: Farkas, Ronald
Sent: Friday, April 08, 2016 12:12 PM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy
Cc: Temple, Robert
Subject: RE: Revised cover memo

I'm not sure we really need to talk about the correlation between quantification of overall dystrophin levels by Western blot versus immunofluorescence because Western blot is the more quantitative method and we have the Western blot data.

It might be seen as misguided to look for a correlation between Western blot, which quantifies dystrophin, and percent positive fibers, which describes localization in the tissue. Yes, might be reasonable to think that the two would be correlated if the drug worked well, but not clear to me that lack of correlation necessarily provides evidence that the drug is not working at all. It might not be unreasonable to propose that the drug caused, for whatever reason, a patchy increase in dystrophin in some kids, and a more diffuse increase across cells in other kids, so that the correlation was weak.

From: Bastings, Eric
Sent: Friday, April 08, 2016 12:00 PM
To: Unger, Ellis; Dunn, Billy; Farkas, Ronald
Cc: Temple, Robert
Subject: RE: Revised cover memo

I'm fine with it, but would like to know what Ron thinks.

Eric

From: Unger, Ellis
Sent: Friday, April 08, 2016 11:53 AM
To: Dunn, Billy; Bastings, Eric; Farkas, Ronald
Cc: Temple, Robert
Subject: RE: Revised cover memo

So you guys were OK with the addition of the (b) (5) and my (b) (5)

From: Dunn, Billy
Sent: Friday, April 08, 2016 10:02 AM
To: Bastings, Eric; Unger, Ellis; Farkas, Ronald
Cc: Temple, Robert
Subject: RE: Revised cover memo

I have been trying not to gum up the works, but I have added two suggestions on page 9 concerning our CINRG analysis. Please take a look.

From: Bastings, Eric
Sent: Friday, April 08, 2016 8:12 AM
To: Unger, Ellis; Farkas, Ronald
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Revised cover memo

Thanks, Ellis.

I made a couple of edits, and need Ron's input for the "other database" comment.

Eric

From: Unger, Ellis
Sent: Friday, April 08, 2016 12:21 AM
To: Bastings, Eric; Farkas, Ronald
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Revised cover memo

All,

This was significantly improved. I accepted your edits (Eric) and John's edits. I made a number of new edits of my own, and the vast number of them had no effect on meaning. I did not track them.

But in 3 or 4 places I used track changes because I wanted to draw your attention to my edits so you could consider them and make sure you agree.

Ron – Dr. Jenkins was willing to review your memo as we had had a specific concern. Because we did not (have a specific concern), he did not review it.

Thanks,

Ellis

From: Bastings, Eric
Sent: Thursday, April 07, 2016 2:57 PM
To: Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald
Subject: Revised cover memo

Ellis,

Here is the revised cover memo. I think I addressed all of John's comments/questions, with one exception: (b) (5)
(b) (5) Lisa L vehemently opposed to its use, and vetting this won't happen in my lifetime.

I leave it up to you and John how you want to address that.

Eric

Temple, Robert

From: Bastings, Eric
Sent: Friday, April 08, 2016 3:40 PM
To: Unger, Ellis; Farkas, Ronald; Temple, Robert; Dunn, Billy
Subject: RE: Revised cover memo

I can go with that. That carries the point. Let's finalize it.

Eric

From: Unger, Ellis
Sent: Friday, April 08, 2016 3:34 PM
To: Farkas, Ronald; Temple, Robert; Bastings, Eric; Dunn, Billy
Subject: RE: Revised cover memo

It's not too few. If the patients who walked the best had high levels of dystrophin, we'd be impressed. How about this text:

(b) (5)

From: Farkas, Ronald
Sent: Friday, April 08, 2016 3:31 PM
To: Unger, Ellis; Temple, Robert; Bastings, Eric; Dunn, Billy
Subject: RE: Revised cover memo

So are we agreed that we won't include an analysis that we know can only be negative because there are too few patients?

From: Unger, Ellis
Sent: Friday, April 08, 2016 3:27 PM
To: Farkas, Ronald; Temple, Robert; Bastings, Eric; Dunn, Billy
Subject: RE: Revised cover memo

One of the take home messages, not stated, is that there are too few patients. I suspect that, for at least some on the committee, their take home message for FDA will be that 12 patients are just too few to conclude anything.

From: Farkas, Ronald
Sent: Friday, April 08, 2016 3:24 PM
To: Temple, Robert; Unger, Ellis; Bastings, Eric; Dunn, Billy
Subject: RE: Revised cover memo
Importance: High

I very strongly advise against including this figure and the accompanying text. The analysis is not scientifically sound, and the negative result is not interpretable. I can see only negative consequences –such as making us look unreasonable to

be expecting a correlation with such few patients (it is too few patients. we've gone through this with (b) (5) - you can't see a correlation unless you have more data) or, perhaps worse, opening a can of worms of post-hoc analyses that the sponsor somehow makes look positive.

Thanks

Ron

From: Temple, Robert
Sent: Friday, April 08, 2016 3:16 PM
To: Unger, Ellis; Bastings, Eric; Dunn, Billy; Farkas, Ronald
Subject: RE: Revised cover memo

Looks good to me. The arrows are the point.

From: Unger, Ellis
Sent: Friday, April 08, 2016 3:12 PM
To: Temple, Robert; Bastings, Eric; Dunn, Billy; Farkas, Ronald
Subject: RE: Revised cover memo

See if you all are OK with this.

From: Temple, Robert
Sent: Friday, April 08, 2016 3:00 PM
To: Bastings, Eric; Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald
Subject: RE: Revised cover memo

The line isw not what's important. What is important is what Eric just noted. So take out the line.

From: Bastings, Eric
Sent: Friday, April 08, 2016 2:17 PM
To: Unger, Ellis
Cc: Temple, Robert; Dunn, Billy; Farkas, Ronald
Subject: RE: Revised cover memo

I don't know what to make of that information. Seems like 2 of the patients with the lowest amount of dystrophin and two with the highest had the lowest amount of decline (circa -100 m or less). It is pretty scattered.

The line (and r), though, suggests some correlation. Are there enough data points to make that sort of analysis? Also, what is the p value?

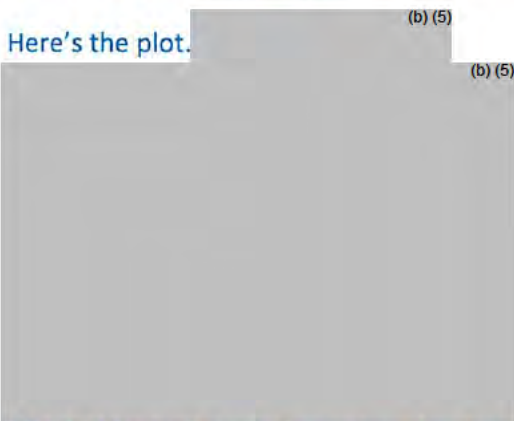
Eric

From: Unger, Ellis
Sent: Friday, April 08, 2016 1:53 PM
To: Bastings, Eric
Cc: Temple, Robert; Dunn, Billy; Farkas, Ronald
Subject: RE: Revised cover memo

In retrospect (on maybe not, since this isn't quite final), the critical correlation here is between preservation of walking ability (Δ 6MWD) and dystrophin protein (by Western blot).

If production of dystrophin protein is "reasonably likely to predict clinical benefit," then there should be some semblance of a correlation.

Here's the plot.



I think this plot is quite important (and so does Bob). Others?

From: Bastings, Eric
Sent: Friday, April 08, 2016 1:31 PM
To: Unger, Ellis
Cc: Temple, Robert; Dunn, Billy; Farkas, Ronald
Subject: RE: Revised cover memo

Ellis,

What do you think about Ron's comment?

I don't think strongly this has to be in the memo.

Eric

From: Farkas, Ronald
Sent: Friday, April 08, 2016 12:12 PM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy
Cc: Temple, Robert
Subject: RE: Revised cover memo

I'm not sure we really need to talk about the correlation between quantification of overall dystrophin levels by Western blot versus immunofluorescence because Western blot is the more quantitative method and we have the Western blot data.

It might be seen as misguided to look for a correlation between Western blot, which quantifies dystrophin, and percent positive fibers, which describes localization in the tissue. Yes, might be reasonable to think that the two would be correlated if the drug worked well, but not clear to me that lack of correlation necessarily provides evidence that the drug is not working at all. It might not be unreasonable to propose that the drug caused, for whatever reason, a patchy increase in dystrophin in some kids, and a more diffuse increase across cells in other kids, so that the correlation was weak.

From: Bastings, Eric
Sent: Friday, April 08, 2016 12:00 PM
To: Unger, Ellis; Dunn, Billy; Farkas, Ronald
Cc: Temple, Robert
Subject: RE: Revised cover memo

I'm fine with it, but would like to know what Ron thinks.

Eric

From: Unger, Ellis
Sent: Friday, April 08, 2016 11:53 AM
To: Dunn, Billy; Bastings, Eric; Farkas, Ronald
Cc: Temple, Robert
Subject: RE: Revised cover memo

So you guys were OK with the addition of the (b) (5) and my (b) (5)

From: Dunn, Billy
Sent: Friday, April 08, 2016 10:02 AM
To: Bastings, Eric; Unger, Ellis; Farkas, Ronald
Cc: Temple, Robert
Subject: RE: Revised cover memo

I have been trying not to gum up the works, but I have added two suggestions on page 9 concerning our CINRG analysis. Please take a look.

From: Bastings, Eric
Sent: Friday, April 08, 2016 8:12 AM
To: Unger, Ellis; Farkas, Ronald
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Revised cover memo

Thanks, Ellis.

I made a couple of edits, and need Ron's input for the "other database" comment.

Eric

From: Unger, Ellis
Sent: Friday, April 08, 2016 12:21 AM
To: Bastings, Eric; Farkas, Ronald
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Revised cover memo

All,

This was significantly improved. I accepted your edits (Eric) and John's edits. I made a number of new edits of my own, and the vast number of them had no effect on meaning. I did not track them.

But in 3 or 4 places I used track changes because I wanted to draw your attention to my edits so you could consider them and make sure you agree.

Ron – Dr. Jenkins was willing to review your memo is we had had a specific concern. Because we did not (have a specific concern), he did not review it.

Thanks,

Ellis

From: Bastings, Eric
Sent: Thursday, April 07, 2016 2:57 PM
To: Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald
Subject: Revised cover memo

Ellis,

Here is the revised cover memo. I think I addressed all of John's comments/questions, with one exception: (b) (5)
(b) (5) Lisa L vehemently opposed to its use, and vetting this won't happen in my lifetime.

I leave it up to you and John how you want to address that.

Eric

Philips, Howard

From: Temple, Robert
Sent: Friday, April 08, 2016 4:54 PM
To: Farkas, Ronald; Bastings, Eric; Dunn, Billy; Unger, Ellis
Subject: RE: potential for being taken out of context

But we probably believe that restoration of dystrophin to Beckeroid levels or >10%, if not undermined by clinical data, WOULD be a reasonably likely surrogate, wouldn't we? The point here is that the tiny levels achieved here, even if you believe them, had no impact.

From: Farkas, Ronald
Sent: Friday, April 08, 2016 4:35 PM
To: Bastings, Eric; Dunn, Billy; Unger, Ellis; Temple, Robert
Subject: potential for being taken out of context

If read out of context, this may say something we probably don't want to say:

(b) (5)

We might consider that the applicant could come forward with evidence from outside the eteplirsen drug development program that shows there is a correlation between dystrophin and maintenance of ambulation.

Thanks

Ron

Philips, Howard

From: Temple, Robert
Sent: Friday, April 08, 2016 3:14 PM
To: Farkas, Ronald; Bastings, Eric; Unger, Ellis; Dunn, Billy
Subject: RE: Revised cover memo

But more dystrophin had no impact at all, showing that the “1%,” which some have suggested was “enough” really did not show anything at all.

From: Farkas, Ronald
Sent: Friday, April 08, 2016 3:00 PM
To: Temple, Robert; Bastings, Eric; Unger, Ellis; Dunn, Billy
Subject: RE: Revised cover memo

Bob,

Yes, if the drug made a lot of dystrophin (or even, I think, 10% dystrophin), you’d expect to see a good correlation with positive fibers. I just think it’s clear to everyone now, including the committee, that the drug did not make a lot of dystrophin. I think the question has shifted to if eteplirsen made 1% dystrophin, and if such low levels might give a small benefit (some experts have always said “any amount more dystrophin is better”).

Thanks

Ron

From: Temple, Robert
Sent: Friday, April 08, 2016 2:38 PM
To: Farkas, Ronald; Bastings, Eric; Unger, Ellis; Dunn, Billy
Subject: RE: Revised cover memo

You all follow this more than I do, but the immunofluorescence is being offered as evidence of massive dystrophin synthesis. The figure shows pretty nicely that the two do not relate.

From: Farkas, Ronald
Sent: Friday, April 08, 2016 12:12 PM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy
Cc: Temple, Robert
Subject: RE: Revised cover memo

I’m not sure we really need to talk about the correlation between quantification of overall dystrophin levels by Western blot versus immunofluorescence because Western blot is the more quantitative method and we have the Western blot data.

It might be seen as misguided to look for a correlation between Western blot, which quantifies dystrophin, and percent positive fibers, which describes localization in the tissue. Yes, might be reasonable to think that the two would be correlated if the drug worked well, but not clear to me that lack of correlation necessarily provides evidence that the drug is not working at all. It might not be unreasonable to propose that the drug caused, for whatever reason, a patchy increase in dystrophin in some kids, and a more diffuse increase across cells in other kids, so that the correlation was weak.

From: Bastings, Eric
Sent: Friday, April 08, 2016 12:00 PM
To: Unger, Ellis; Dunn, Billy; Farkas, Ronald

Cc: Temple, Robert
Subject: RE: Revised cover memo

I'm fine with it, but would like to know what Ron thinks.

Eric

From: Unger, Ellis
Sent: Friday, April 08, 2016 11:53 AM
To: Dunn, Billy; Bastings, Eric; Farkas, Ronald
Cc: Temple, Robert
Subject: RE: Revised cover memo

So you guys were OK with the addition of the (b) (5) and my (b) (5)

From: Dunn, Billy
Sent: Friday, April 08, 2016 10:02 AM
To: Bastings, Eric; Unger, Ellis; Farkas, Ronald
Cc: Temple, Robert
Subject: RE: Revised cover memo

I have been trying not to gum up the works, but I have added two suggestions on page 9 concerning our CINRG analysis. Please take a look.

From: Bastings, Eric
Sent: Friday, April 08, 2016 8:12 AM
To: Unger, Ellis; Farkas, Ronald
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Revised cover memo

Thanks, Ellis.

I made a couple of edicts, and need Ron's input for the "other database" comment.

Eric

From: Unger, Ellis
Sent: Friday, April 08, 2016 12:21 AM
To: Bastings, Eric; Farkas, Ronald
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Revised cover memo

All,

This was significantly improved. I accepted your edits (Eric) and John's edits. I made a number of new edits of my own, and the vast number of them had no effect on meaning. I did not track them.

But in 3 or 4 places I used track changes because I wanted to draw your attention to my edits so you could consider them and make sure you agree.

Ron – Dr. Jenkins was willing to review your memo is we had had a specific concern. Because we did not (have a specific concern), he did not review it.

Thanks,

Ellis

From: Bastings, Eric
Sent: Thursday, April 07, 2016 2:57 PM
To: Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald
Subject: Revised cover memo

Ellis,

Here is the revised cover memo. I think I addressed all of John's comments/questions, with one exception: [REDACTED] (b) (5)
[REDACTED]. Lisa L vehemently opposed to its use, and vetting this won't happen in my lifetime.

I leave it up to you and John how you want to address that.

Eric

ehpluseu

Temple, Robert

From: Unger, Ellis
Sent: Monday, April 11, 2016 3:26 PM
To: Temple, Robert
Subject: Fw: potential for being taken out of context
Attachments: Sarepta cover memo (final 04-09).doc

Sent from my BlackBerry.

From: Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Sent: Saturday, April 9, 2016 11:50 AM
To: Bastings, Eric; Temple, Robert
Cc: Farkas, Ronald; Dunn, Billy
Subject: RE: potential for being taken out of context

Thanks Eric.

I agree with all of your edits.

But I took one last read (for once - not late in the evening), and I made some additional edits – all are self-explanatory.

Although small, some edits are substantive. (For example, I don't call out (b) (4))

Rather than saying (b) (5) I say it was the only study to assess a clinical endpoint.

(b) (5)

Finally, see what I think is a critical addition in the middle of page 11:

(b) (5)

I'm happy with it now.

Take a look.

Ellis

From: Bastings, Eric
Sent: Saturday, April 09, 2016 7:51 AM
To: Temple, Robert; Unger, Ellis
Cc: Farkas, Ronald; Dunn, Billy
Subject: RE: potential for being taken out of context

Ellis, Bob,

I made a few edits, which are hope will be the final ones.

Can you see if we can declare this the final version?

Thanks.

Eric

From: Farkas, Ronald

Sent: Friday, April 08, 2016 6:49 PM

To: Temple, Robert; Bastings, Eric; Dunn, Billy; Unger, Ellis

Subject: RE: potential for being taken out of context

Bob,

Yes, that's my point, the sentence, out of context, seems to say we might doubt that. We might want to be more specific that we are talking about the low levels in the eteplirsen-treated patients.

(b) (5)

From: Temple, Robert

Sent: Friday, April 08, 2016 4:54 PM

To: Farkas, Ronald; Bastings, Eric; Dunn, Billy; Unger, Ellis

Subject: RE: potential for being taken out of context

But we probably believe that restoration of dystrophin to Beckeroid levels or >10%, if not undermined by clinical data, WOULD be a reasonably likely surrogate, wouldn't we? The point here is that the tiny levels achieved here, even if you believe them, had no impact.

From: Farkas, Ronald

Sent: Friday, April 08, 2016 4:35 PM

To: Bastings, Eric; Dunn, Billy; Unger, Ellis; Temple, Robert
Subject: potential for being taken out of context

If read out of context, this may say something we probably don't want to say:

[Redacted content]

(b) (5)

We might consider that the applicant could come forward with evidence from outside the eteplirsen drug development program that shows there is a correlation between dystrophin and maintenance of ambulation.

Thanks

Ron

MEMORANDUM

DATE: April 8, 2016

FROM: Billy Dunn, MD and Eric Bastings, MD, Division of Neurology Products
Ellis Unger, MD and Robert Temple, MD, Office of Drug Evaluation-I
Office of New Drugs, Center for Drug Evaluation and Research, FDA

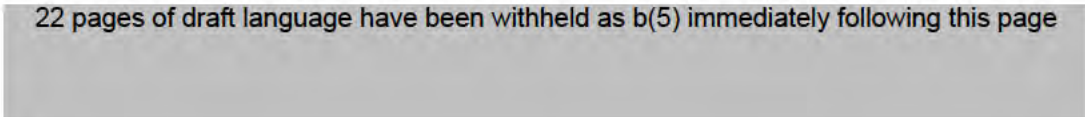
TO: Members and Invited Guests of the Peripheral and Central Nervous Systems
Drugs Advisory Committee (PCNS AC)

SUBJECT: Briefing Memo for New Drug Application (NDA) 206488, for the use of eteplirsen
for the treatment of Duchenne muscular dystrophy in patients with mutations
amenable to exon 51 skipping

(b) (5)



22 pages of draft language have been withheld as b(5) immediately following this page



FDACDER0004132

Philips, Howard

From: Bastings, Eric
Sent: Thursday, April 14, 2016 12:53 PM
To: Unger, Ellis; Farkas, Ronald; Jin, Kun; Dunn, Billy; Bhattaram, Atul; Breder, Christopher D; Temple, Robert
Cc: Choy, Fannie (Yuet)
Subject: RE: Draft slides, will send updated version before noon

Regrading the fact that eteplirsen patients continue to attempt performing functional tests at times when controls stop trying, the 6MWT data show the same thing with the Italian and Belgian controls, with only eteplirsen patients walking distances below 200 meters. All controls go from above 200 to zero.

(b) (5)



From: Zhong, Jinglin
Sent: Thursday, April 14, 2016 12:01 PM
To: Unger, Ellis; Farkas, Ronald; Bastings, Eric; Jin, Kun; Diggs, Felicia
Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Dunn, Billy; Ling, Xiang
Subject: RE: Draft slides, will send updated version before noon

Hi, team, here is the final slides. I was busy with all the editing and did not have time to finish updating the line pattern and add the imputation for the 2 etep patients.

I apologize if I miss any of your editing.

<< File: CINRG_analysis_final.ppt >>

Jinglin

From: Unger, Ellis

Sent: Thursday, April 14, 2016 11:46 AM

To: Zhong, Jinglin; Farkas, Ronald; Bastings, Eric; Jin, Kun

Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Dunn, Billy; Ling, Xiang

Subject: RE: Draft slides, will send updated version before noon

You could. This pattern is not apparent in the run time plot, however.

From: Zhong, Jinglin

Sent: Thursday, April 14, 2016 11:30 AM

To: Unger, Ellis; Farkas, Ronald; Bastings, Eric; Jin, Kun

Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Dunn, Billy; Ling, Xiang

Subject: RE: Draft slides, will send updated version before noon

(b) (5)

From: Unger, Ellis

Sent: Thursday, April 14, 2016 11:19 AM

To: Zhong, Jinglin; Farkas, Ronald; Bastings, Eric; Jin, Kun

Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Dunn, Billy; Ling, Xiang

Subject: RE: Draft slides, will send updated version before noon

Hi Jinglin,

(b) (5)

FDACDER0004156

Thanks!

Ellis

From: Zhong, Jinglin
Sent: Thursday, April 14, 2016 10:51 AM
To: Farkas, Ronald; Bastings, Eric; Jin, Kun
Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Unger, Ellis; Dunn, Billy; Ling, Xiang
Subject: RE: Draft slides, will send updated version before noon

Ron,

Jialu is the one worked on KM curves. I only read part of the report and has not touched the LOA data yet. I know Jialu has a lot of questions about the data and the plot. She is offline now. She will be back soon.

Jinglin

From: Farkas, Ronald
Sent: Thursday, April 14, 2016 10:44 AM
To: Zhong, Jinglin; Bastings, Eric; Jin, Kun
Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Unger, Ellis; Dunn, Billy; Ling, Xiang
Subject: RE: Draft slides, will send updated version before noon

Jinglin,

Great, thanks, slides look great. I took an initial look and have a few questions:

Thanks

Ron

From: Zhong, Jinglin

Sent: Thursday, April 14, 2016 10:27 AM

To: Bastings, Eric; Jin, Kun; Farkas, Ronald

Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Unger, Ellis; Dunn, Billy; Ling, Xiang

Subject: Draft slides, will send updated version before noon

Hello, team,

Finally here is the draft slides from the stat team. I will working on updating [REDACTED] (b) (5).

The changes will be [REDACTED] (b) (5)

Please review the draft slides. We appreciate any comments and suggestion to improve the slides.

Thanks!

Jinglin

<< File: CINRG_analysis_drat.ppt >>

Philips, Howard

From: Ling, Xiang
Sent: Thursday, April 14, 2016 2:16 PM
To: Jin, Kun
Cc: Unger, Ellis; Bastings, Eric; Farkas, Ronald; Dunn, Billy; Bhattaram, Atul; Breder, Christopher D; Temple, Robert; Choy, Fannie (Yuet)
Subject: RE: Draft slides, will send updated version before noon

Here is the result.

		LOA (6MWD<200m)				
	N	Month 12	Month 24	Month 36	Month 48	Total
Eteplirsen	12	2	0	1	3	6 (50%)
Control (Italian and Belgian)	13	1	3	5	3	12/13(92%)

Thanks,
Xiang

From: Jin, Kun
Sent: Thursday, April 14, 2016 1:28 PM
To: Ling, Xiang
Cc: Unger, Ellis; Bastings, Eric; Farkas, Ronald; Dunn, Billy; Bhattaram, Atul; Breder, Christopher D; Temple, Robert; Choy, Fannie (Yuet)
Subject: RE: Draft slides, will send updated version before noon

Hi Xiang,

Do you have the data to look at this? Thanks,

Kun

From: Unger, Ellis
Sent: Thursday, April 14, 2016 12:56 PM
To: Bastings, Eric; Farkas, Ronald; Jin, Kun; Dunn, Billy; Bhattaram, Atul; Breder, Christopher D; Temple, Robert
Cc: Choy, Fannie (Yuet)
Subject: RE: Draft slides, will send updated version before noon

Good point. And if LOA were defined as 6MWD < 200 m, I wonder what fractions of the eteplirsen and control patients would be considered to have experienced "LOA?"

From: Bastings, Eric
Sent: Thursday, April 14, 2016 12:53 PM
To: Unger, Ellis; Farkas, Ronald; Jin, Kun; Dunn, Billy; Bhattaram, Atul; Breder, Christopher D; Temple, Robert

Cc: Choy, Fannie (Yuet)

Subject: RE: Draft slides, will send updated version before noon

Regrading the fact that eteplirsen patients continue to attempt performing functional tests at times when controls stop trying, the 6MWT data show the same thing with the Italian and Belgian controls, with only eteplirsen patients walking distances below 200 meters. All controls go from above 200 to zero.

<< OLE Object: Picture (Device Independent Bitmap) >>

From: Zhong, Jinglin

Sent: Thursday, April 14, 2016 12:01 PM

To: Unger, Ellis; Farkas, Ronald; Bastings, Eric; Jin, Kun; Diggs, Felicia

Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Dunn, Billy; Ling, Xiang

Subject: RE: Draft slides, will send updated version before noon

Hi, team, here is the final slides. I was busy with all the editing and did not have time to finish updating the line pattern and add the imputation for the 2 etep patients.

I apologize if I miss any of your editing.

<< File: CINRG_analysis_final.ppt >>

Jinglin

From: Unger, Ellis

Sent: Thursday, April 14, 2016 11:46 AM

To: Zhong, Jinglin; Farkas, Ronald; Bastings, Eric; Jin, Kun

Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Dunn, Billy; Ling, Xiang

Subject: RE: Draft slides, will send updated version before noon

You could. This pattern is not apparent in the run time plot, however.

From: Zhong, Jinglin

Sent: Thursday, April 14, 2016 11:30 AM

To: Unger, Ellis; Farkas, Ronald; Bastings, Eric; Jin, Kun

Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Dunn, Billy; Ling, Xiang

Subject: RE: Draft slides, will send updated version before noon

(b) (5)

From: Unger, Ellis

Sent: Thursday, April 14, 2016 11:19 AM

To: Zhong, Jinglin; Farkas, Ronald; Bastings, Eric; Jin, Kun

Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Dunn, Billy; Ling, Xiang

Subject: RE: Draft slides, will send updated version before noon

Hi Jinglin,

(b) (5)

Thanks!

Ellis

From: Zhong, Jinglin

Sent: Thursday, April 14, 2016 10:51 AM

To: Farkas, Ronald; Bastings, Eric; Jin, Kun

Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Unger, Ellis; Dunn, Billy; Ling, Xiang

Subject: RE: Draft slides, will send updated version before noon

Ron,

Jialu is the one worked on KM curves. I only read part of the report and has not touched the LOA data yet. I know Jialu has a lot of questions about the data and the plot. She is offline now. She will be back soon.

Jinglin

From: Farkas, Ronald
Sent: Thursday, April 14, 2016 10:44 AM
To: Zhong, Jinglin; Bastings, Eric; Jin, Kun
Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Unger, Ellis; Dunn, Billy; Ling, Xiang
Subject: RE: Draft slides, will send updated version before noon

Jinglin,

Great, thanks, slides look great. I took an initial look and have a few questions:



Thanks

Ron

From: Zhong, Jinglin
Sent: Thursday, April 14, 2016 10:27 AM
To: Bastings, Eric; Jin, Kun; Farkas, Ronald
Cc: Bhattaram, Atul; Zhang, Jialu; Choy, Fannie (Yuet); Hung, Hsien Ming J; Breder, Christopher D; Unger, Ellis; Dunn, Billy; Ling, Xiang
Subject: Draft slides, will send updated version before noon

Hello, team,

Finally here is the draft slides from the stat team. I will working on updating  (b) (5)

The changes will be  (b) (5)

Please review the draft slides. We appreciate any comments and suggestion to improve the slides.

Thanks!

Jinglin

<< File: CINRG_analysis_drat.ppt >>

Philips, Howard

From: Temple, Robert
Sent: Monday, April 18, 2016 1:06 PM
To: Blount, Aprile
Subject: FW: Revised eteplirsen slides, with script
Attachments: Eteplirsen revised 4 17 send.pptx.html

[This is the one I need.](#)

From: Farkas, Ronald
Sent: Sunday, April 17, 2016 8:10 PM
To: Bastings, Eric; Dunn, Billy; Unger, Ellis; Temple, Robert; Breder, Christopher D
Subject: Revised eteplirsen slides, with script

There are a lot of revisions throughout.

Thanks

Ron

Philips, Howard

From: Unger, Ellis
Sent: Monday, April 18, 2016 6:36 PM
To: Farkas, Ronald
Cc: Bastings, Eric; Dunn, Billy; Temple, Robert; Breder, Christopher D
Subject: RE: Revised eteplirsen slides, with script
Attachments: Ron - suggestions 4-18-16_unger.doc

Ron,

The slides are immensely better! Here are my comments.

Since there is no track changes in PowerPoint, I copied the text to Word and used track changes there so you could easily see my suggestions.

Ellis

From: Farkas, Ronald
Sent: Sunday, April 17, 2016 8:10 PM
To: Bastings, Eric; Dunn, Billy; Unger, Ellis; Temple, Robert; Breder, Christopher D
Subject: Revised eteplirsen slides, with script

There are a lot of revisions throughout.

Thanks

Ron

Slide 26

- Study 201/202 tested doses only modestly higher than 20 mg/kg/wk, in ~~only~~ a small number of patients (12)
 - 30 mg/kg/wk in 4 patients
 - 50 mg/kg/wk in 4 patients
 - Placebo in 4 patients
- Dystrophin measured at ~~week-Week~~ 12, as in Study 28, and at also at ~~Weeks~~ 24 and 48 ~~weeks~~
 - These three time points referred to in briefing material and this presentation as the “1st 3 biopsies”

Slide 27

- Study 201/202 investigators reported dystrophin increased at ~~week-Week~~ 24, but not at ~~week-Week~~ 12
 - ~~Different~~ from robust effect on dystrophin reported at ~~week-Week~~ 12 in Study 28
 - Consistency of findings of great concern in science; raises questions that should be explored
 - High dystrophin levels reported in all patients, seemingly to 25 to 50% of normal or higher (Mendell et al., Ann Neurol 2013)
- With conclusion of likely effective dystrophin levels in all patients, end of exploratory studies

30

- Detailed review of the dystrophin data from Study 28 and the first 3 biopsies of Study 201/202 confirmed FDA concerns about problems with assay reliability and consistency of findings across and within studies
 - Western blot bands oversaturated
 - Problems with the way data was recorded, not just interpreted
 - Data that is not reliably recorded cannot be improved by re-reading

31

Instead of the expected levels of 25 to 50% dystrophin, a very low level, $0.93 \pm 0.84\%$, was detected, by WB, the most accurate method of quantification used by the applicant

37

- Applicant reported 17% dystrophin positive fibers for eteplirsen-treated patients, and 1% in the poorly-matched controls
 - Uncertainty how much of this difference might have been due to drug, versus other differences between samples
- It also remains difficult to find consistency in the pPercent pPositive fFiber counts, even with the improved method of reading by 3 blinded readers

39

- Percent pPositive fFibers did not consistently increase at Wweek 24 according to the blinded re-analysis
- In patients treated with placebo for 24 weeks, then eteplirsen for 24 weeks, percent positive fibers did not increase

42

- **0.93 ± 0.84%** of normal dystrophin levels, as measured by Western blot, after long-term treatment with eteplirsen, and **17%** of muscle fibers with at least some detectable amount
 - Not clear how much or perhaps whether these values represent an increase over the trace dystrophin levels that naturally occur in DMD
 - Consistency of findings is key to science, but there is no independent confirmation of findings
 - Ratios presented by the applicant appear to be “apples to oranges” due to poorly matched controls

49 GREAT!

Younger half-brother (II) wheelchair-bound at age 9
Older half-brother (I) normal walking ability at age 15

52

- The clinical endpoints were essentially all negative, and did not provide support for efficacy

You might need to say more. The 1° endpoint was dystrophin production, which they thought (at the time) was positive.

54

I would not underline. It's distracting. You are not talking to children here.

56

DMD experts have noted that physical function may be affected by being in an efficacy study

57

58

No need to underline “necessary.”

59

- The decision to ask a patient to attempt to perform a functional test such as 6MWT, versus deeming the patient unable, is based on the judgment and attitudes of the investigator, patient and caregivers about the patient's ambulatory abilities

PREVIOUS FEEDBACK ALREADY SENT!!!!

60 I think you can make the box a bit smaller, which might give you enough room on the slide to note, somehow, that although there were 2 patients like this, your box includes only one example. As it is now, it's a bit confusing, because you're talking about 2 patients, and the table appears to show two examples, side-by-side.

61

- Supportive treatment, including steroids, can have ~~has~~ important effects on slowing functional decline, and there were some differences between eteplirsen-treated patients and external controls
 - e.g. eteplirsen patients treated with steroids for about a year longer, which can extend ambulation
- The key point is that experts in DMD have observed that seemingly small differences in supportive care or steroid use may have large effects on age of loss of ambulation [underlining is distracting]

62 I'd get rid of the red squares.

63

- Differences in which patients stay and which leave an observational study
- Patients who are not motivated to volunteer for drug studies, or are not qualified to participate in such studies, may remain in a natural history cohort.
- Patients who have progressed more rapidly may be preferentially over-represented in observational natural history studies if because they may no longer meet eligibility requirements for drug efficacy studies

65

- p-values, sensitivity analyses, etc. can be misleading because they only tell you data are different, not why they are different [no underlining]

This would be a place to show some of the CINRG data, for example, markedly long rise times in eteplirsen patients vs. CINRG patients.

67

The applicant has shown these 6-minute walk data as a function of time on study, but showing them by age is more meaningful. These figures show 6MWT based on patient age because loss of ambulation is correlated with ~~to~~ age in DMD, and important for comparing similar patients

I'd leave the X's and question marks OFF this first iteration of the graph.

68

"X" = control patients walking by able to perform the 10m walk/run, but given zero value for 6MWT

"?" = control patients retrospectively assigned zero by asking if patient was ambulatory at Year year 4

71

- Contrary to what is suggested by some of the applicant's figures, there is no evidence of a major difference in age (or likely future age) of loss of ambulation ~~in-between~~ the eteplirsen patients and controls

72 don't underline

73

≈25% of exon 51 boys walking at 16 years (it's not "approximately 25%, it's 25%)

≈15% walking at 18 years (I don't think you need this, and I'm not sure the figure is correct.)

Data recently provided to FDA for detailed review

don't underline

75

Placebo-patients from the control arms~~s??~~ of recent studies of drisapersen are shown; each line is 1 year of data for each patient

Control armS of studies, or control arm of study? (both should be singular or both should be plural.)

76

You'll need to mention (in words) why they weren't a good match.

77

- Many patients over 12 years ~~have a slow path of decline~~continue to do well (glass "half full")

80

No apparent correlation ~~of-between~~ dystrophin levels and change in 6MWT

82

Number slide. Fix font size on "measured"

83

84

I think I would omit this slide. You've already shown the generally similar slope (last slide) and mean data (next slide). What's the real point?

85

I would replace 85 and 865 with a single slide. It needs a title: Mean NSAA scores in eteplirsen vs. external controls

~~Lower baseline score in controls can be seen more clearly in the plot of mean values~~

Eteplirsen:

- Higher scores at baseline
- Similar slope (change in score with time)
- Error bars show substantial overlap – small Ns

| 86 omit

87

| There is little reason to believe that age at loss of ambulation for these patients will exceed the typical range of untreated patients with DMD natural history

90

- | • Higher values for eteplirsen may reflect differences s in assessment, not function

92

- | • Analysis of the ~~The~~ externally controlled portion of Study 201/202 ~~must be analyzed as appropriate for~~ keep in mind the limitations of an externally-controlled study as described in FDA Guidances such as ICH E10

93

- | • There is no reliable way to determine whether the modest differences between eteplirsen-treated patients and external controls resulted from an effect of eteplirsen or from other differences, known or unknown, between the groups at baseline or during conduct of the study
- | • There is no reliable clinical evidence of efficacy for eteplirsen

95

- | • There is little evidence suggesting that this magnitude-type of dystrophin expression could have a measurable affect on disease progression

| 96 I think I'd roll 96 and 97 into one conclusion slide. You might also want to say something about the utility of a placebo-controlled trial.

Temple, Robert

From: Bastings, Eric
Sent: Tuesday, April 19, 2016 11:35 AM
To: Dunn, Billy; Farkas, Ronald; Temple, Robert; Unger, Ellis
Cc: Freed, Lois M
Subject: Wow

Neurology Today

Four-Year Eteplirsen Results Show 10 of 12 Children with Duchenne Muscular Dystrophy Are Still Walking
VANCOUVER—Ten of 12 children with Duchenne muscular dystrophy (DMD) were still walking four years after treatment began with the investigational drug eteplirsen, compared with only one of 13 historical controls with DMD, researchers reported here at the AAN Annual Meeting on Tuesday

4/19/2016

[Four-Year Eteplirsen Results Show 10 of 12 Children with Duchenne Muscular Dystrophy Are Still Walking](#)

BY DAN HURLEY

VANCOUVER—Ten of 12 children with Duchenne muscular dystrophy (DMD) were still walking four years after treatment began with the investigational drug eteplirsen, compared with only one of 13 historical controls with DMD, researchers reported here at the AAN Annual Meeting on Tuesday.

Eteplirsen, an antisense oligomer, is designed to skip the mutation in exon 51 of the dystrophin gene in order to allow production of the protein, at least in partly functional form. The oligomer is infused weekly intravenously.

During the first stage of the clinical trial, which lasted for 24 weeks, the 12 children were randomized to eteplirsen 50 mg/kg, eteplirsen 30 mg/kg, or placebo. The primary endpoint was an assessment of dystrophin in skeletal muscle as measured by Western blot and immunofluorescence. The randomized controlled phase was followed by an open-label extension in which all 12 patients received eteplirsen 30 mg/kg or 50mg/kg.

At 36 months, the 12 eteplirsen-treated patients demonstrated a statistically significant advantage by being able to walk 151 meters more than the 13 external controls ($p < 0.01$) during the six-minute walk test (6MWT) and experienced a lower incidence of loss of ambulation. The findings of the study, led by Jerry R. Mendell, MD, FAAN, chair of pediatric research and professor of pediatrics and neurology at Nationwide Children's Hospital and Ohio State University in Columbus, were released in the February issue of *Annals of Neurology*.

The four-year results — along with a letter signed by 36 neurologists and other scientists in support of the drug — are expected to be weighed carefully by the US Food and Drug Administration (FDA) Peripheral and Central Nervous System Drugs Advisory Committee when it meets again on April 25.

Sarepta, the drug's manufacturer, is seeking accelerated approval for eteplirsen for patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which represents about 13 percent of all DMD patients.

In a briefing document released in January, the FDA took issue with the original three-year study data, however, based mainly on three points: the tiny amount of functioning dystrophin detected in the treated children's

muscles; the comparability of the treated children to the historical controls; and the fact that all 10 of the treated children who were still walking four years after treatment had nevertheless shown substantial declines in walking distance.

The FDA also questioned whether the 13 historical controls had received the same intensity of physical therapy and steroid treatment. "Performance on the six-minute walk test could be influenced by motivation and coaching," the FDA said in its briefing document, adding that "open-label trials are susceptible to bias on the part of investigators, patients, and parents."

In addition, the FDA stated that the clinical course of the 12 patients treated with eteplirsen "appears to be within the expected natural history of DMD." Treated children, it stated, "experienced a sequential worsening of functional abilities and muscle weakness, as demonstrated by changes in rise times from the floor and the evolution of North Star Ambulatory Assessment scores."

Commenting on the FDA response to the study, Stanley F. Nelson, MD, professor of human genetics and co-director of the Center for Duchenne Muscular Dystrophy at the David Geffen School of Medicine at the University of California, Los Angeles (UCLA), who was one of the scientists to sign the letter to the FDA, said: "We felt perplexed that the data look good, yet have not been met with a clear path forward for approval. The data are highly supportive of the drug having a positive effect with good safety."

The new four-year data regarding age at loss of ambulation now provide even more compelling data for accelerated approval based on an irreversible morbidity, he pointed out.

Melissa J. Spencer, PhD, a professor of neurology and co-director of the Center for Duchenne Muscular Dystrophy at UCLA, who also signed the letter to the FDA about the drug, said whether or not the FDA advisory committee recommends accelerated approval following its April 25 meeting, the ongoing phase 3 trial will likely be continued as any DMD patient amenable to exon 51 skipping can get the drug through an academic medical center.

"The thinking is that maintenance of muscle mass that is remaining can improve a patient's quality of life," even for an older patient who can no longer walk, she said.

Objective: DMD, a rare, degenerative, X-linked genetic disease results in progressive muscle loss and premature death, occurring in ~1:3500-5000 males worldwide. DMD is primarily caused by frameshift-causing whole-exon mRNA deletions that prevent production of dystrophin protein. Eteplirsen, a PMO, is designed to induce production of internally-shortened dystrophin in patients amenable to exon 51-skipping. **Methods:** In a 24-week double-blind placebo-controlled study, twelve 12 boys aged 7-13 years were randomized to weekly intravenous infusions of 30/50 mg/kg eteplirsen or placebo, rolling-over to an ongoing open-label extension study (1:1 30/50 mg/kg). Clinical outcome measures included 6MWT and dystrophin expression. Routine safety assessments and cardiac monitoring were conducted. External control (EC) data were obtained from the DMD Italian Network and the Leuven Neuromuscular Research Center. A cohort (N=13) comparable to the eteplirsen-treated boys was defined based on age at baseline, corticosteroid use, and genotype. 3 year longitudinal data were used for comparative analysis of 6MWT performance. **Results:** At Year 3, a statistically-significant treatment benefit of 151 meters on 6MWT was observed in eteplirsen-treated patients compared with EC ($p<0.01$). 2/12 (16.6[percent]) eteplirsen patients lost ambulation by Year 1 with no additional losses observed, compared with 6/13 (46[percent]) EC at Year 3. Muscle biopsy analysis demonstrated exon 51-skipping in consented eteplirsen-treated patients (N=11) by RT-PCR and statistically significant increases ($p<0.001$) of dystrophin intensity and [percent] dystrophin-positive fibers by immunohistochemistry over untreated DMD controls (N=9). Western blot confirmed dystrophin production in 9/11 patients. No deaths,

discontinuations due to AEs, or treatment-related SAEs were reported. LVEF on ECHO was stable over 3 years. AEs were generally mild and unrelated to study-drug. **Conclusions:** After 3 years of eteplirsen-treatment, DMD patients had a mean 6MWT that was 151m higher ($p<0.01$) than the comparable external cohort and de novo dystrophin was detected using 3 complementary methods in nearly all eteplirsen-treated patients.

Disclosure: Dr. Mendell has nothing to disclose. Dr. Goemans has nothing to disclose. Dr. Rodino-Klapac has nothing to disclose. Dr. Sahenk has received research support from Sarepta Therapeutics. Dr. Lowes has received personal compensation for activities with Sarepta Pharmaceuticals, Eli Lilly, and Pfizer as a consultant. Dr. Alfano has nothing to disclose. Dr. Berry has nothing to disclose. Dr. Peterson has nothing to disclose. Dr. Lewis has nothing to disclose. Dr. Shontz has nothing to disclose. Dr. Shao has received personal compensation for activities with Sarepta Therapeutics as an employee. Dr. Duda has received personal compensation for activities with Sarepta Therapeutics as an FTE. Dr. Donoghue has received personal compensation for activities with Sarepta Therapeutics as an FTE. Dr. Schnell has received personal compensation for activities with Sarepta Therapeutics as a full time employee. Dr. Dworzak has received personal compensation for activities with Sarepta Therapeutics as an FTE. Dr. Wentworth has nothing to disclose. Dr. EM has received personal compensation for activities with Sarepta Therapeutics. Dr. Mercuri has nothing to disclose. Dr. Italian Network has nothing to disclose.

Philips, Howard

From: Blount, Aprile
Sent: Wednesday, April 20, 2016 6:23 PM
To: Choy, Fannie (Yuet)
Cc: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald
Subject: Correct version eteplirsen AC slides
Attachments: HistoricCntrlTrials Final_PCNS AC Mtg25Apr2016.ppt

Sorry, I missed RT's emails with corrections. Here's the final version.

From: Blount, Aprile
Sent: Wednesday, April 20, 2016 6:13 PM
To: Choy, Fannie (Yuet)
Cc: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald
Subject: RE: updated eteplirsen AC slides

Here they are.

From: Choy, Fannie (Yuet)
Sent: Wednesday, April 20, 2016 6:05 PM
To: Blount, Aprile
Subject: FW: updated eteplirsen AC slides

Sounds like you have the slides for me 😊

From: Temple, Robert
Sent: Wednesday, April 20, 2016 5:59 PM
To: Bastings, Eric; Farkas, Ronald; Unger, Ellis; Dunn, Billy; Rao, Ashutosh; Bhattaram, Atul; Jin, Kun; Breder, Christopher D
Cc: Choy, Fannie (Yuet); Blount, Aprile
Subject: RE: updated eteplirsen AC slides

Mine are all done, so send away.

From: Bastings, Eric
Sent: Wednesday, April 20, 2016 5:57 PM
To: Farkas, Ronald; Unger, Ellis; Dunn, Billy; Temple, Robert; Rao, Ashutosh; Bhattaram, Atul; Jin, Kun; Breder, Christopher D
Cc: Choy, Fannie (Yuet)
Subject: RE: updated eteplirsen AC slides

We can send Bob's slides tonight, if they are ready, and send the main presentation tomorrow.

I'll let the AC staff know.

Eric

From: Farkas, Ronald
Sent: Wednesday, April 20, 2016 5:49 PM
To: Unger, Ellis; Bastings, Eric; Dunn, Billy; Temple, Robert; Rao, Ashutosh; Bhattaram, Atul; Jin, Kun; Breder, Christopher D

Cc: Choy, Fannie (Yuet)

Subject: RE: updated eteplirsen AC slides

Ash is out of town – some of these changes are for his slides. Can we wait till mid-day tomorrow to send to the AC staff so he can see edits?

From: Unger, Ellis

Sent: Wednesday, April 20, 2016 5:31 PM

To: Farkas, Ronald; Bastings, Eric; Dunn, Billy; Temple, Robert; Rao, Ashutosh; Bhattaram, Atul; Jin, Kun; Breder, Christopher D

Cc: Choy, Fannie (Yuet)

Subject: RE: updated eteplirsen AC slides

FRIST THIRD OR SO.....

Slides (b) and 6 ... change (b) (5) to “could increase” ??

Slide 10, I'd remove “ (b) (5) ”

Slide 13 – need to define BMD

18 Control samples from different muscle groups used - biceps, quadriceps, deltoid and data combined

21 For (b) (5) -most new drugs, it is usual...

22 Study 28 investigators reported dystrophin levels of 0 to 5% of normal (b) (5) in untreated patients

24 in all patients at (b) (5) Week 48

27 well done!

28, get rid of (b) (5). Also—change (b) (5) to “...was reported by WB, the most...”

31, would put “~” in front of the 1 (now 1% IS approximate)

33 I'd delete (b) (5)

From: Farkas, Ronald

Sent: Wednesday, April 20, 2016 2:34 PM

To: Unger, Ellis; Bastings, Eric; Dunn, Billy; Temple, Robert; Rao, Ashutosh; Bhattaram, Atul; Jin, Kun; Breder, Christopher D

Cc: Choy, Fannie (Yuet)

Subject: updated eteplirsen AC slides

Ellis,

I've tried to address issues raised at the run-through yesterday. This version does not have (b) (5)

. The script is also not updated, but will start to work on that now.

Thanks

Ron



U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Historically Controlled Trials

Robert Temple, MD
Deputy Center Director For Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration

PCNS AC Meeting
April 25, 2016

FDACDER0004176



Overview

Brief discussion of history of FDA use of historically controlled studies and concerns associated with this design.

N.B. Will not specifically address eteplirsen data (Study 201/202). That will come in subsequent presentations.



Historical Control

Section 505(d) of the FD & C Act, defining standards for drug approval, calls for substantial evidence of effectiveness, meaning evidence “consisting of adequate and well-controlled investigations, including clinical investigations. . . on the basis of which it could fairly & responsibly be concluded. . . that the drug will have the effect it. . . is represented to have.”

Adequate and well-controlled studies were first described in regulations in 1970, now included in 21 CFR 314.126, and have always included as one kind of adequate & well-controlled study the “Historical Control.”



Historical Control - Regulation

(v) Historical Control: The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

Note that a baseline control trial, where a single-arm treatment is compared with what would have been expected in the absence of an intervention, is a kind of historical control.



Historical Control – ICH E-10

Renames “historical control” as one of a kind“ external control” and notes several kinds of external control groups:

- Population treated earlier (historical control)
- Population treated contemporaneously at another institution
- A group treated outside the study within same institution
- Baseline control, where the patient’s course is compared with the “expected” course, based on general knowledge of specific experience, or, sometimes, with a prior period of observation.

The design works most clearly when effect is dramatic and rapid: general anesthesia, cardioversion, tumor shrinkage.



Historical Control - ICH E-10 (cont)

The “inability to control bias is a major and well-recognized limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable.”

Really two distinct aspects of bias: bias before the trial; bias during and after the trial.

1. Bias before the trial – patient selection. But this is really two issues.
 - Non-comparability of the groups; i.e., they may differ in important characteristics that may influence outcome.
 - Selection bias – the control patients are worse, (sicker or destined to have worse outcomes than the treated patients).



Historical Control - ICH E-10 (cont)

Non-comparability can go in either direction, favoring or disfavoring the treatment. The guidance points out, however, that “it is well-documented that untreated historical-control groups tend to have worse outcomes than an apparently similarly chosen control group in a randomized study, possibly reflecting a selection bias.”



ICH E-10 Selection Bias

Classic Analysis

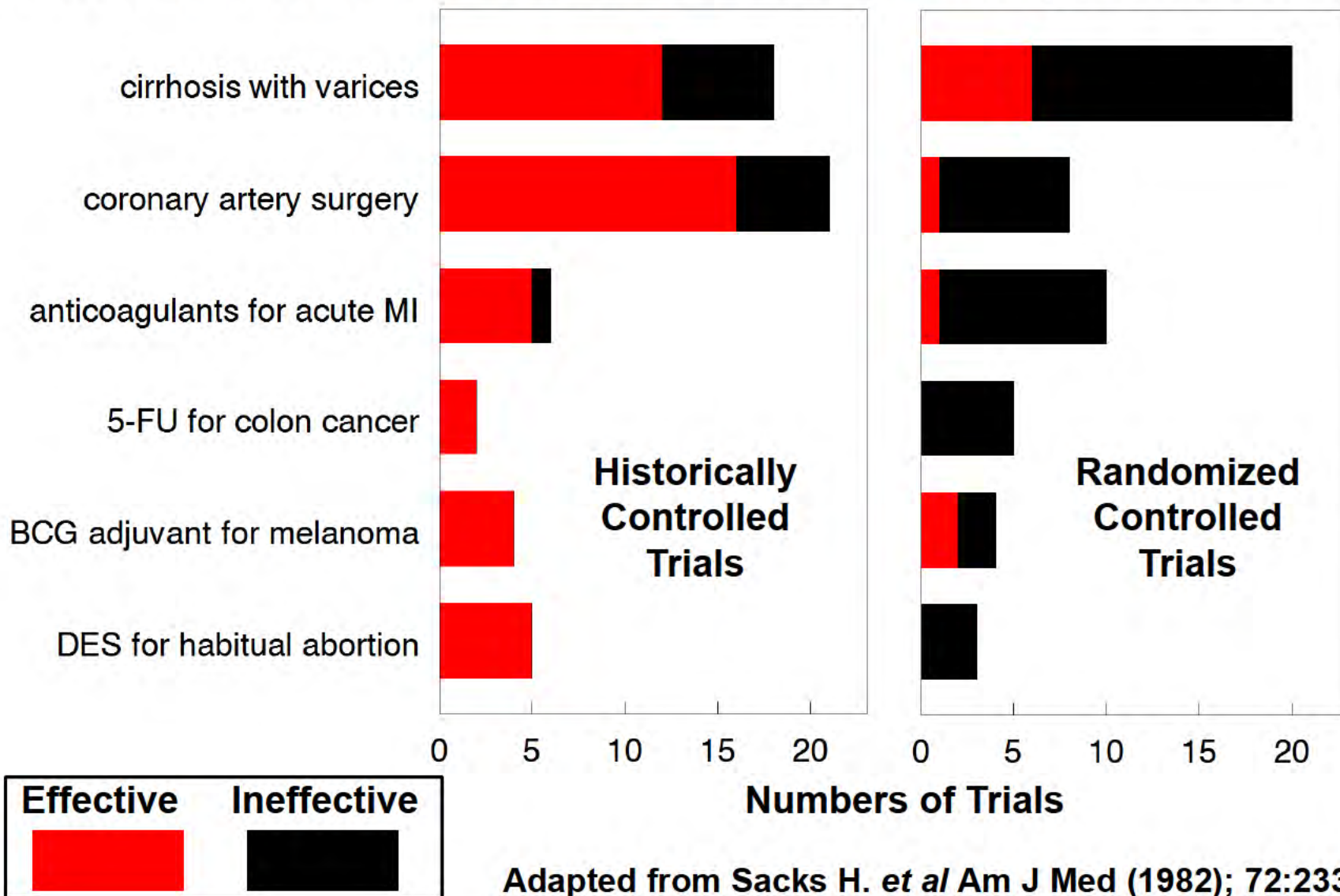
Sacks, Chalmers, Smith. Am. J Med (1982); 72: 233-240.

Compared RCTs and HCTs for same disease, finding results regularly more favorable for HCTs.

In following figure, it is clear that results of RCTs are regularly less positive than HCTs (10/50 favorable for RCTs vs 44/56 favorable for HCTs).

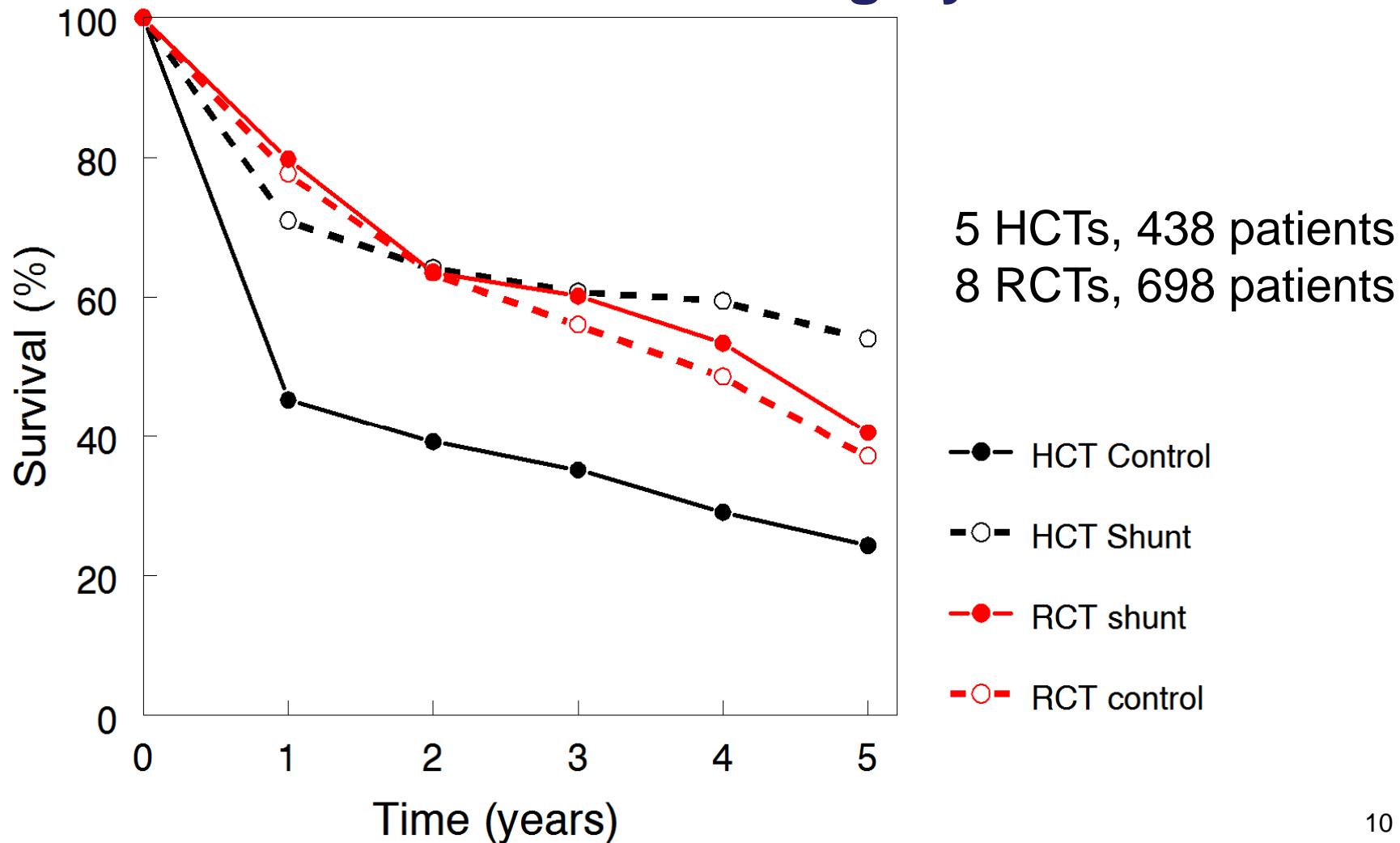


Conclusions on RCTs and HCTs on 6 Therapeutic Questions





Survival of Treated and Control Groups in Clinical Trials of Shunt Surgery for Cirrhosis:





Selection Bias

It seems likely that the historical control untreated patients were sicker and that the surgical candidates in the HCT's were in better shape. In the RCTs they appeared very similar. Selection bias in this case (patients different at baseline) is the only real source of potential bias, as mortality is objective, but the finding was very powerful.

ICH E-10 specifically notes that selection of the control retrospectively, i.e., with results known and in hand, poses a particular problem.



ICH E-10

Other Bias

2. Bias during and after the trial.

Apart from selection bias, the lack of blinding and the investigators' knowledge of treatment in patients getting the test treatment (and those getting the control treatments if they are being newly analyzed) can also allow bias to affect endpoints if they are subjective. Most endpoints, even those seemingly objective, have subjective (judgment) elements, including presence of absence of AMI, cause of hospitalization, and most other endpoints. You will later hear a discussion of subjectivity of ability to ambulate. Importantly, expectation bias and motivation can affect symptoms and performance.



ICH E-10 Other Bias

Another potential source of bias is choice of endpoint (when there are several possibilities), including whether to use a composite endpoint, time-to-event or cumulative events, decisions about which patients to include, etc. These problems can be seen in RCTs as well, but expectations for a prospective statistical analysis plan are higher for RCTs; indeed, they are a virtual requirement.



ICH E-10 Bottom Line(s)

The overall tone is skeptical about use of external controls for most situations, as is our adequate and well-controlled studies regulation, but both accept them as credible in particular situations. ICH E-10 urges:

- Selection of a control group for which there is detailed information (demographic, baseline state, concomitant medications, and study course).
- Try to assure similar Rx, other than test drug, and similar observations in the treatment and control groups.
- Use of multiple external control groups.
- Consideration of blinded endpoint reassessment in treatment and external control group.



ICH E-10 Bottom Line(s) (cont)

ICH E-10 also suggests that the main credible use of external controls is when there is an ethical difficulty in doing the RCT. The suggested remedy is to randomize the earliest studies: “The concurrently controlled trial can detect extreme effects very rapidly and, in addition, can detect modest, but still valuable, effects that would not be credibly demonstrated by an externally controlled trial.”

ICH E-10 again notes that external control trials are most likely to be persuasive when the effect is very large.



A Few More Examples

A. Fulminant Hepatitis B

Gocke. Fulminant hepatitis treated with serum containing antibody to Australia antigen. NEJM (1971): 284; 919, letter to the editor.

- Nine consecutive cases of acute fulminant hepatitis B; all fatal despite exchange Tx, steroids, support.
- Eight hepatic coma patients given usual Rx plus anti-Australia antigen serum; 5/8 survived.

Considered reaching a conclusion that the treatment was effective, BUT realized it could be better care, earlier Rx, so urged a RCT in severe hepatitis.



Examples (cont)

Hepatitis RCT

Acute Hepatic Failure Study Group: Failure of specific immunotherapy in fulminant Type B hepatitis. *Ann Int Med* (1977); 86: 272-277.

30 centers, 53 patients

Survival: placebo vs hepatitis B immune globulin (HBIG)

Placebo 9/28 (32%)

HBIG 7/25 (28%)



Examples (cont)

Renal Artery Denervation

B. Widely publicized renal artery denervation device was studied in three trials:

Open-label single-arm study (Symplicity HTN-1 Trial) found an average 3-year fall in BP of 33/19 mmHg

RCT (device vs no device) with no sham control, i.e., open label (Symplicity HTN-2) found at 6 months a change of -32/12 vs 1/0 in the control.

RCT with sham control (Symplicity HTN-3) found at 6 months a change of -14 mmHg (denervation) vs -12 mmHg (sham), $p=0.26$.



Examples

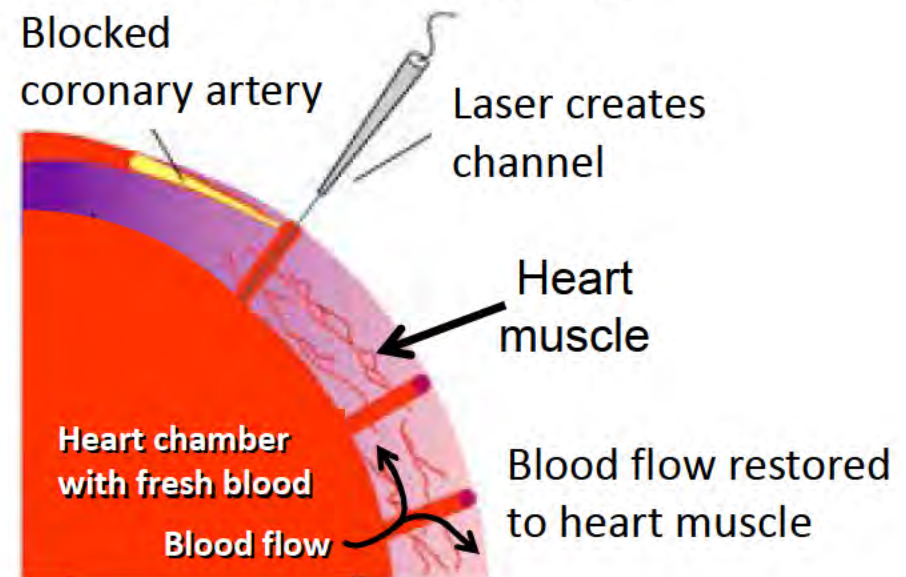
Transmyocardial Laser Revascularization (TMLR).

Dr. Unger has provided 3 slides illustrating a case with a motivationally dependent endpoint, exercise ability, using both a baseline control and a randomized control.

Uncontrolled (Baseline-Controlled) Studies of Transmyocardial Laser Revascularization (TMLR)

- Many cardiac centers experimented with TMLR in the 1990s.
- Patients with coronary artery disease, severe angina, and no treatment options (poor candidates for bypass surgery/angioplasty)

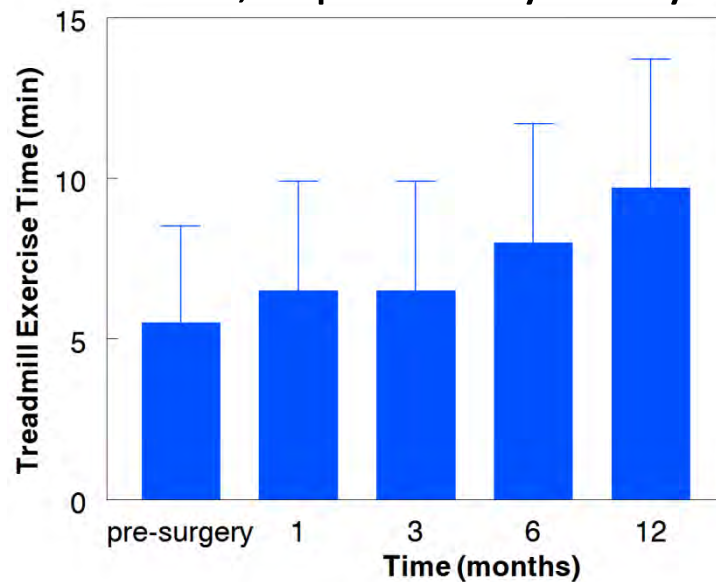
Procedure: open-heart surgery; use laser to create channels through the heart muscle, allowing blood to flow to the muscle directly from the inside the heart.



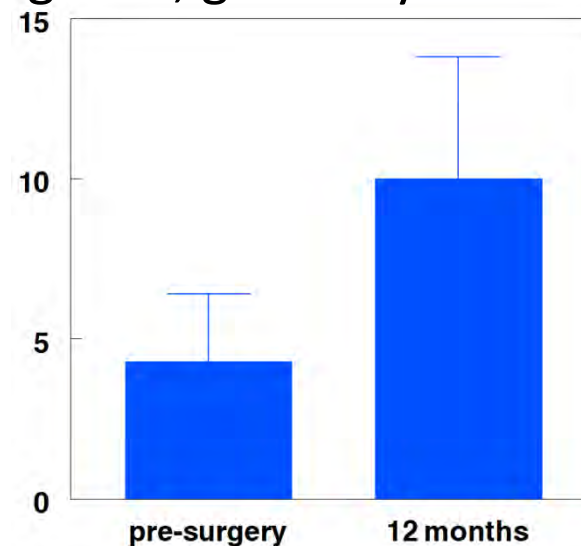
- No way to conduct a placebo-controlled trial to assess efficacy
- One cannot give patients SHAM open-heart surgery!

Many Centers: Extraordinary Results on Exercise

- Observed treatment effects were based on historical comparisons
- Typical results, reported by many investigators, generally small studies:



Ann Thorac Surg 1999;67:432-6



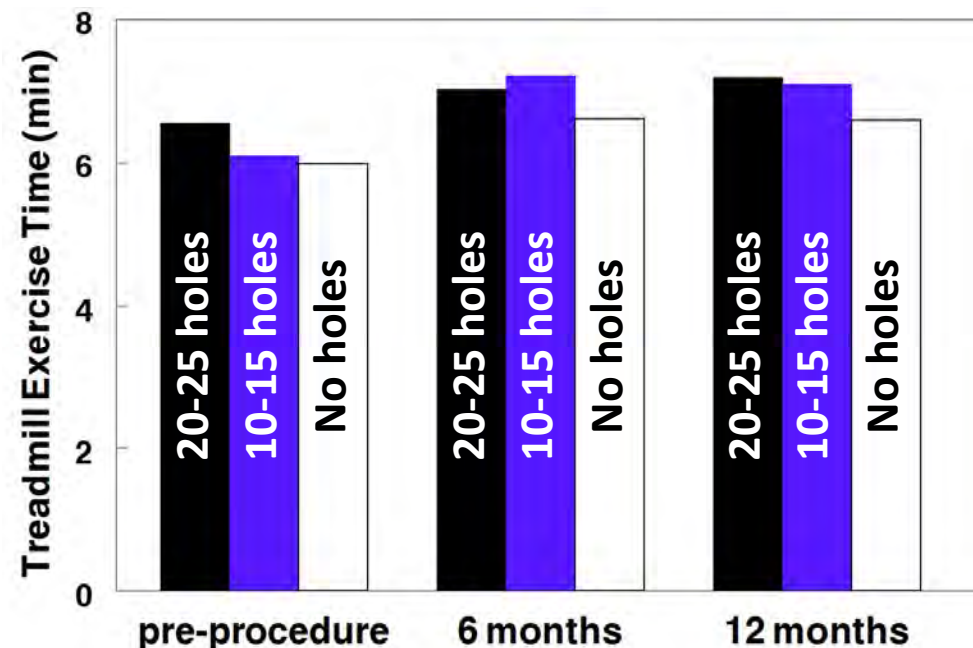
J Thorac Cardiovasc Surg 1996;111:791-9

- Marked increases in exercise time, sustained for a year in sick patients, seemed fantastic – too good (and long-lasting) to be “placebo” effect.
- Many were not willing to attribute the improvement to chance or expectation bias, i.e., they believed that the procedure worked.

***Many patients underwent this operation for angina.

Double-Blind Placebo-Controlled Trial: No Effect of TMLR on Exercise

- With new catheters, laser revascularization could be conducted through arteries, without need for open-heart surgery
- Multicenter, double-blind, placebo-controlled trial in 298 subjects
- Compared “low-dose” and “high dose” laser treatments to a sham procedure, under sedation



Results:

- No improvement in exercise time after 6 or 12 months
- Effects of TMLR on exercise, observed in many uncontrolled studies, was probably due to expectation bias – patients with few options; many hopes from a radical procedure.



But We Do Use Them, As Contemplated in Regulations

- I. Obvious case: tumor response in oncology and, not commonly, cures.
 - a. Some treatments of some leukemias and lymphomas give a cure rate.

It is certain that cannot happen absent therapy, so effect is demonstrated.

- b. The first 3 treatments for metastatic testicular cancer, cis-platinum, ifosfamide, and etoposide, were all based on success rates (1 year tumor-free survival in patients with metastatic disease) > 90% for cis-platinum, and about 10% for ifosfamide and etoposide in cis-platinum failures.

Given the unequivocal expected 1-year tumor-free survival of 0%, this was a straightforward use of a baseline control, single-arm design.



Uses of Historical Controls

2. Stone Cases

Many years ago (late 70's, early 80's) drugs for stone disease were approved based on a comparison of monthly stone rates in patients for the months preceding treatment compared with rates in treatment. Differences were large (would we do that today? Not sure). Premise: patients had a disease that would not spontaneously change.

3. Many orphan diseases (described in various NORD publications) use these designs.

Alglucosidase ALFA for Pompe disease (2006).

Endpoint: 1 year ventilator free survival in 18 treated patients vs 62 historical controls.



Orphans (cont)

- Lomitapide was approved to reduce LDL cholesterol in patients with homozygous familial hypercholesterolemia (2012) based on treatment of 29 patients for 26 weeks in a single-arm trial. The 40% fall in LDL was plainly a change that would not occur spontaneously in this genetic disorder.
- Pasireotide diaspertate was approved (2012) for the treatment of Cushing Disease based on two-arm trial comparing two doses in 162 patients. It was considered unethical to leave patients untreated and the endpoint, one that clearly would not have occurred spontaneously, was normalization of mean urinary free cortisol.
- Deferiprone was approved (2011) for treatment of transfusional iron overload associated with thalassemia syndromes. Evidence of effectiveness came from a 236 patient pooled analysis using a historical control and showing reduced ferritin.



Orphans

- A number of approvals of anti-infectives (anti-fungals, especially) where there was no needed comparison to existing therapy, have compared treatment with literature-based natural history. Isavuconazonium for invasive mucormycosis was approved on this basis.



Uses of Historical Controls

The cases cited are typically ones involving well-defined diseases with VERY predictable outcomes, thought not to be susceptible to effects of treatments other than the test drug and thought to be relatively non-variable from one patient to the next.

There are, however, cases in which there can be debate about how predictable the course of the disease is in the absence of treatment and, thus, whether historical control approaches can be considered and would be well-supported, as stressed in ICH E-10.

Philips, Howard

From: Temple, Robert
Sent: Wednesday, April 20, 2016 6:05 PM
To: Blount, Aprile
Subject: FW: AC Questions
Attachments: image001.png.html

OK, send them if you haven't already.

From: Bastings, Eric
Sent: Wednesday, April 20, 2016 5:54 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

Yes, you can send them to Fannie, and copy the group.

Thanks.

Eric

From: Temple, Robert
Sent: Wednesday, April 20, 2016 5:13 PM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

I'm just looking at my slides. If they are OK, who do I send them to for forwarding? Fanny?

From: Bastings, Eric
Sent: Wednesday, April 20, 2016 5:10 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

Yes. I sent it earlier.

Eric

From: Unger, Ellis
Sent: Wednesday, April 20, 2016 5:01 PM
To: Bastings, Eric; Temple, Robert; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

Did you produce a tracked changes version with all of Bob's edits? I don't have one.

From: Bastings, Eric
Sent: Wednesday, April 20, 2016 5:00 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Farkas, Ronald

Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

OK. So it will read

DISCUSSION: Discuss the strengths and weaknesses of the clinical evidence of efficacy provided by Study 201/202, with particular consideration of the design of the study, sample size, statistical methods, general concerns regarding a comparison to a historical control group, specific concerns with respect to the comparability of these two groups (in particular, how motivational factors and differences in assessment of physical performance outcomes may have affected the 6-minute walk endpoint and other endpoints), and any other issues that you think may be important.

Last call for any other change.

Eric

From: Unger, Ellis
Sent: Wednesday, April 20, 2016 4:39 PM
To: Bastings, Eric; Temple, Robert; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

Here's what Bob proposes (additions underlined):

DISCUSSION: Discuss the strengths and weaknesses of the clinical evidence of efficacy provided by Study 201/202, with particular consideration of the design of the study, sample size, statistical methods, general concerns regarding a comparison to a historical control group, ^{(b) (5)} specific concerns with respect to the comparability of these two groups ^{(b) (5)} (in particular, motivational factors ^{(b) (5)} ^{(b) (5)} and any other issues that you think may be important.

I think some of this is problematic. ^{(b) (5)}

I propose:

DISCUSSION: Discuss the strengths and weaknesses of the clinical evidence of efficacy provided by Study 201/202, with particular consideration of the design of the study, sample size, statistical methods, general concerns

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From: Bastings, Eric
Sent: Wednesday, April 20, 2016 4:09 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

I included all of Bob's edits, and agree with them, with this exception of the one below, which I had trouble merging into the question, beside adding "and".



Please let me know if you have any other edit.

Also, as the concept of "single (not highly persuasive) study plus confirmatory evidence is now included, we will need to stand ready to explain what we mean by that. I suppose, in this case, this refers to the situation described on page 11 of the Evidence guidance, i.e., the following:

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Thanks.

Eric

From: Bastings, Eric
Sent: Wednesday, April 20, 2016 3:40 PM
To: Mazur, Julia; Unger, Ellis
Cc: Temple, Robert; Choy, Fannie (Yuet); Dunn, Billy
Subject: RE: AC Questions

Thanks. I will merge this into the latest draft and circulate the final version.

Eric

From: Mazur, Julia
Sent: Wednesday, April 20, 2016 3:34 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farchione, Tiffany; Choy, Fannie (Yuet)
Cc: Temple, Robert
Subject: AC Questions

Attached are Dr. Temple's AC Question notes.

Julia A. Mazur
Project Specialist
CDER/OND/ODEI
WO Building 22, Room 4217
(240)402-9492

Philips, Howard

From: Temple, Robert
Sent: Wednesday, April 20, 2016 5:11 PM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions
Attachments: image001.png.html

Looks good.

From: Bastings, Eric
Sent: Wednesday, April 20, 2016 5:00 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

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Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

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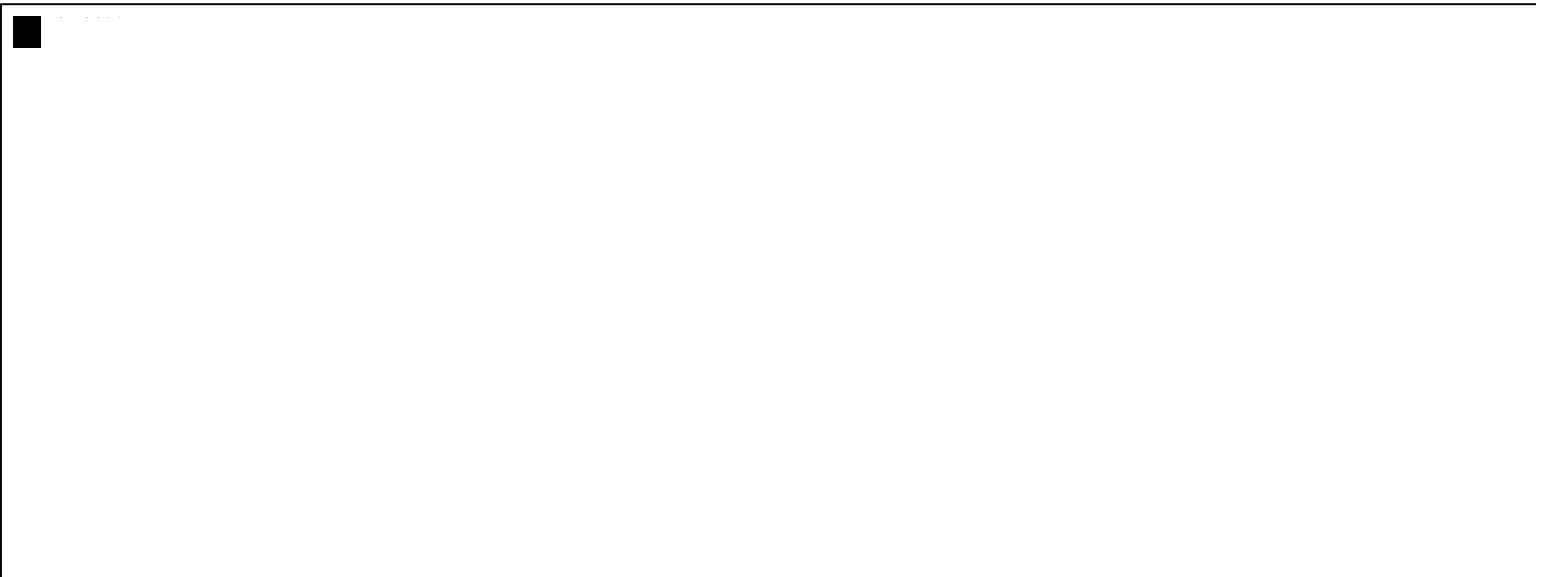
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Sent: Wednesday, April 20, 2016 4:09 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions

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Sent: Wednesday, April 20, 2016 3:40 PM
To: Mazur, Julia; Unger, Ellis
Cc: Temple, Robert; Choy, Fannie (Yuet); Dunn, Billy
Subject: RE: AC Questions

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From: Mazur, Julia
Sent: Wednesday, April 20, 2016 3:34 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farchione, Tiffany; Choy, Fannie (Yuet)
Cc: Temple, Robert
Subject: AC Questions

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Project Specialist
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WO Building 22, Room 4217
(240)402-9492

Philips, Howard

From: Temple, Robert
Sent: Wednesday, April 20, 2016 4:53 PM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions
Attachments: image001.png.html

I added

It should read (slight change from what I had):

(b) (5)

(b) (5)

Seem OK?
From: Bastings, Eric
Sent: Wednesday, April 20, 2016 4:09 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
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Subject: AC Questions

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Philips, Howard

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Sent: Wednesday, April 20, 2016 4:09 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Farkas, Ronald
Cc: Choy, Fannie (Yuet)
Subject: RE: AC Questions
Attachments: Sarepta AC 0425 Questions 0420 eb_eu rf eb_EU rt eb .doc

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Subject: AC Questions

Attached are Dr. Temple's AC Question notes.

Julia A. Mazur
Project Specialist
CDER/OND/ODEI
WO Building 22, Room 4217
(240)402-9492

AC QUESTIONS

(b) (5)



6 pages have been withheld as b(5) immediately following this page

Temple, Robert

From: Choy, Fannie (Yuet)
Sent: Friday, April 22, 2016 12:45 PM
To: Farkas, Ronald; Bastings, Eric; Breder, Christopher D
Cc: Dunn, Billy; Unger, Ellis; Temple, Robert; Bhattaram, Atul; Zhong, Jinglin; Zhang, Jialu; Jin, Kun; Ling, Xiang
Subject: FW: NEUROLOGY MS ID# NEUROLOGY/2015/709162
Attachments: revised_manuscript.docx

fyi

-----Original Message-----

From: Craig McDonald [mailto:cmmcdonald@ucdavis.edu]
Sent: Friday, April 22, 2016 12:17 PM
To: Choy, Fannie (Yuet)
Subject: FW: NEUROLOGY MS ID# NEUROLOGY/2015/709162

Fannie,
The Bello article (attached) has now been accepted for publication and is in press.
Craig McDonald

Craig M. McDonald, MD
Professor and Chair
Department of Physical Medicine & Rehabilitation
Professor of Pediatrics
Director MDA Neuromuscular Disease Clinics
UC Davis Health System
Office: 916-734-2923
Pager: (b) (6)
email: cmmcdonald@ucdavis.edu

On 4/22/16 7:04 AM, "squimby@neurology.org" <squimby@neurology.org> wrote:

>NEUROLOGY MS ID#: NEUROLOGY/2015/709162

>MS TITLE: DMD genotypes and loss of ambulation in the CINRG Duchenne

>Natural History

>Study.

>Luca Bello, Lauren P. Morgenroth, Heather Gordish-Dressman, Eric P.

>Hoffman, Craig

>M. McDonald, and Sebahattin Cirak

>

>

>22 April 2016

>

>

>Dear Dr. Cirak:

>

>We are pleased to accept your paper for publication in NEUROLOGY.

>-----

>IMPORTANT NOTE: Your paper and its findings are embargoed. News media

>must not

>publicize the paper until 4PM EST the day of online publication. This

>includes

>processes that your institutional public relations department must follow

>to release

>any article information. The consequences for embargo break are serious,

>see here:

><http://www.neurology.org/site/misc/auth2.xhtml#EMBARGO>

>-----

>The corresponding author will receive a "Welcome to Production" letter

>within one

>business day after your paper has been transmitted to our publisher,

>Wolters Kluwer.

>Approximately two weeks later, the corresponding author will be notified

>via email

>that copyediting is complete and that the composed proof will be ready

MS ID#: NEUROLOGY/2015/709162

DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study.

Luca Bello^{1,2}, MD; Lauren P. Morgenroth¹, MS, CGC; Heather Gordish-Dressman¹, PhD;
Eric P. Hoffman¹, PhD; Craig M. McDonald³, MD; Sebahattin Cirak^{1,4*}, MD; on behalf of
the CINRG investigators^{1,3,5-22}.

1. Children's National Health System, Washington, DC, USA
2. Department of Neuroscience, University of Padova, Padova, Italy
3. University of California Davis Medical Center, Sacramento, CA, USA
4. Institute of Human Genetics, University Children's Hospital, and Center of Molecular Medicine, University of Cologne (Köln), Köln, Germany
5. Sundaram Medical Foundation and Apollo Children's Hospital, Chennai, India
6. Holland Bloorview Kids Rehab Hospital, Toronto, Canada
7. Alberta Children's Hospital, Calgary, Canada
8. Queen Silvia Children's Hospital, Göteborg, Sweden
9. Royal Children's Hospital, Melbourne, Australia
10. Hadassah Hebrew University Hospital, Jerusalem, Israel
11. Instituto de Neurociencias Fundacion Favaloro, Buenos Aires, Argentina
12. Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh, Pittsburgh, PA; Department of Veterans Affairs Medical Center, Pittsburgh, PA, USA
13. Washington University, St. Louis, MO, USA

14. Children's Hospital of Richmond at VCU, Richmond, VA, USA
15. University of Tennessee, Memphis, TN, USA
16. Children's Hospital at Westmead, Sydney, Australia
17. University of Alberta, Edmonton, Canada
18. Child Neurology and Psychiatry Department, IRCCS C. Mondino, University of Pavia, Italy and Neuromuscular Omnicentre (NEMO), Fondazione Serena Onlus, Niguarda Ca' Granda Hospital, Milan, Italy
19. Texas Children's Hospital, Houston, TX, USA
20. University of Minnesota, Minneapolis, MN, USA
21. Mayo Clinic, Rochester, MN, USA
22. University of Puerto Rico, San Juan, PR, USA

* to whom correspondence should be addressed:

Dr. Sebahattin Cirak, MD

Emmy-Noether Group leader

Institute of Human Genetics

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Kerpener Str. 34

50931 KÖLN, Germany

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e-mail: sebahattin.cirak@uk-koeln.de

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Figures: 2

Supplemental data: table_e-1.docx, table_e-2.docx, coinvestigators.docx, strobeckklist.pdf, online_references.docx, manuscript_track_changes.docx

Search terms: [185] Muscle disease, [227] Pediatric, [58] Natural history study

Author contributions: LB contributed to study design, analyzed and interpreted data, and drafted the manuscript. LPM contributed to study design, analyzed and interpreted data, and critically revised the manuscript for intellectual content. HGD contributed to study design, performed statistical analyses, and critically revised the manuscript for intellectual content. EPH contributed to study design and critically revised the manuscript for intellectual content. CMM contributed to the overall CINRG DMD study design and critically revised the manuscript for intellectual content. SC designed the study and critically revised the manuscript for intellectual content.

Financial disclosures: LB reports no disclosures. LPM reports no disclosures. HGD reports no disclosures. EPH reports that he is co-founder and CEO of ReveraGen BioPharma, co-founder and Vice President of AGADA BioSciences,

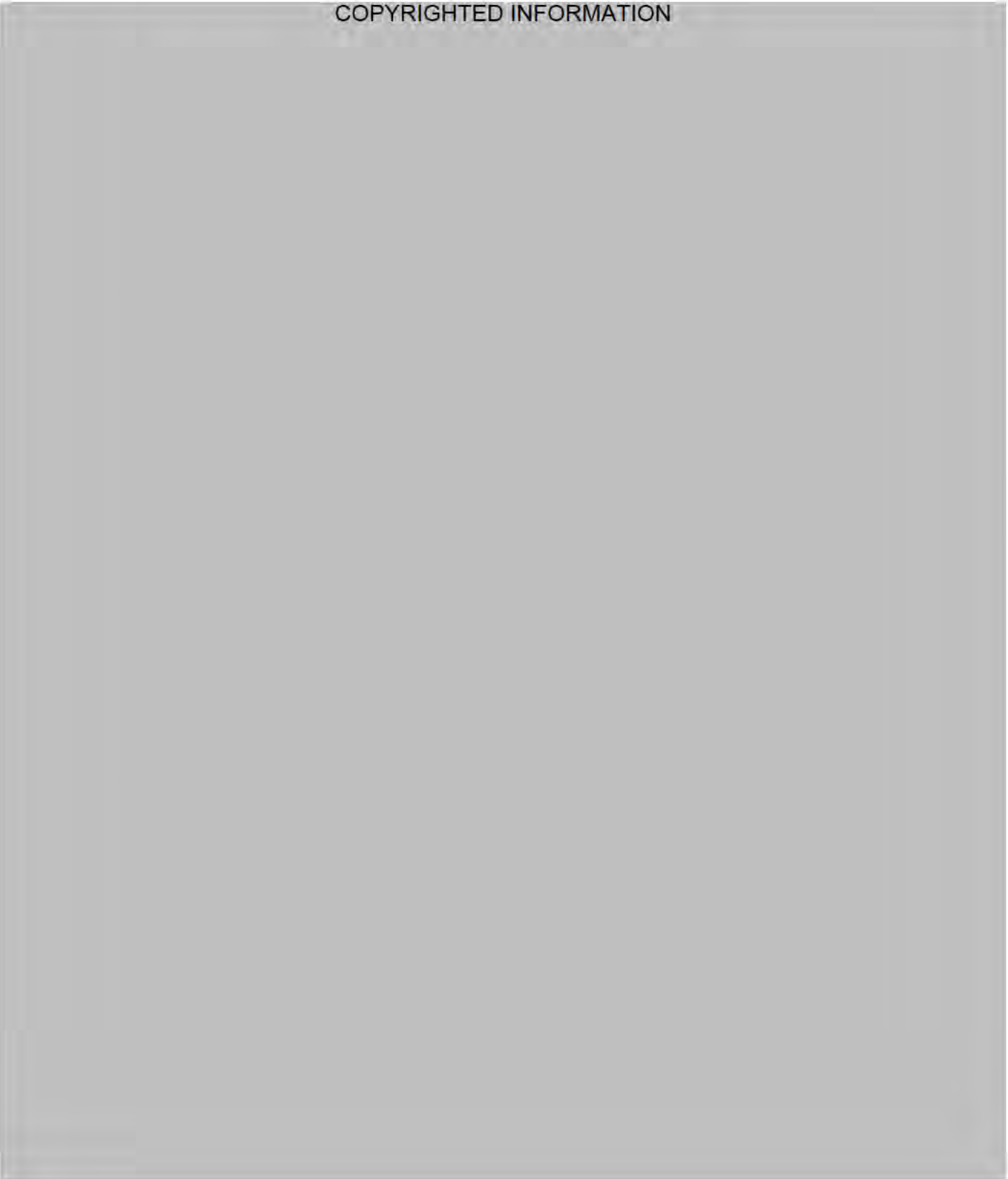
and received grants from National Institutes of Health, during the conduct of the study.

CMM has served as a consultant for clinical trials for PTC Therapeutics, Prosensa, Sarepta, Eli Lilly, Pfizer, Halo Therapeutics, Cardero, and Mitokyne, outside the submitted work; serves on external advisory boards related to Duchenne muscular dystrophy for PTC Therapeutics and Eli Lilly; and reports grants from US Dept of Education/NIDRR, US NIH/NIAMS, US Dept of Defense, and Parent Project Muscular Dystrophy US, during the conduct of the study; grants from Parent Project Muscular Dystrophy US, outside the submitted work. SC reports a sponsored research agreement with Sarepta Therapeutics.

Funding: U.S. Department of Education/NIDRR (#H133B031118, #H133B090001); U.S. Department of Defense (#W81XWH-12-1-0417); National Institutes of Health/NIAMS (#R01AR061875); Italian Ministry of Education PhD grant awarded to LB for the 28th Cycle of the Doctorate School of Medical, Clinical, and Experimental, Science at the University of Padova, Italy. SC is supported by the German Research Foundation (DFG) and MDA Developmental Grant.

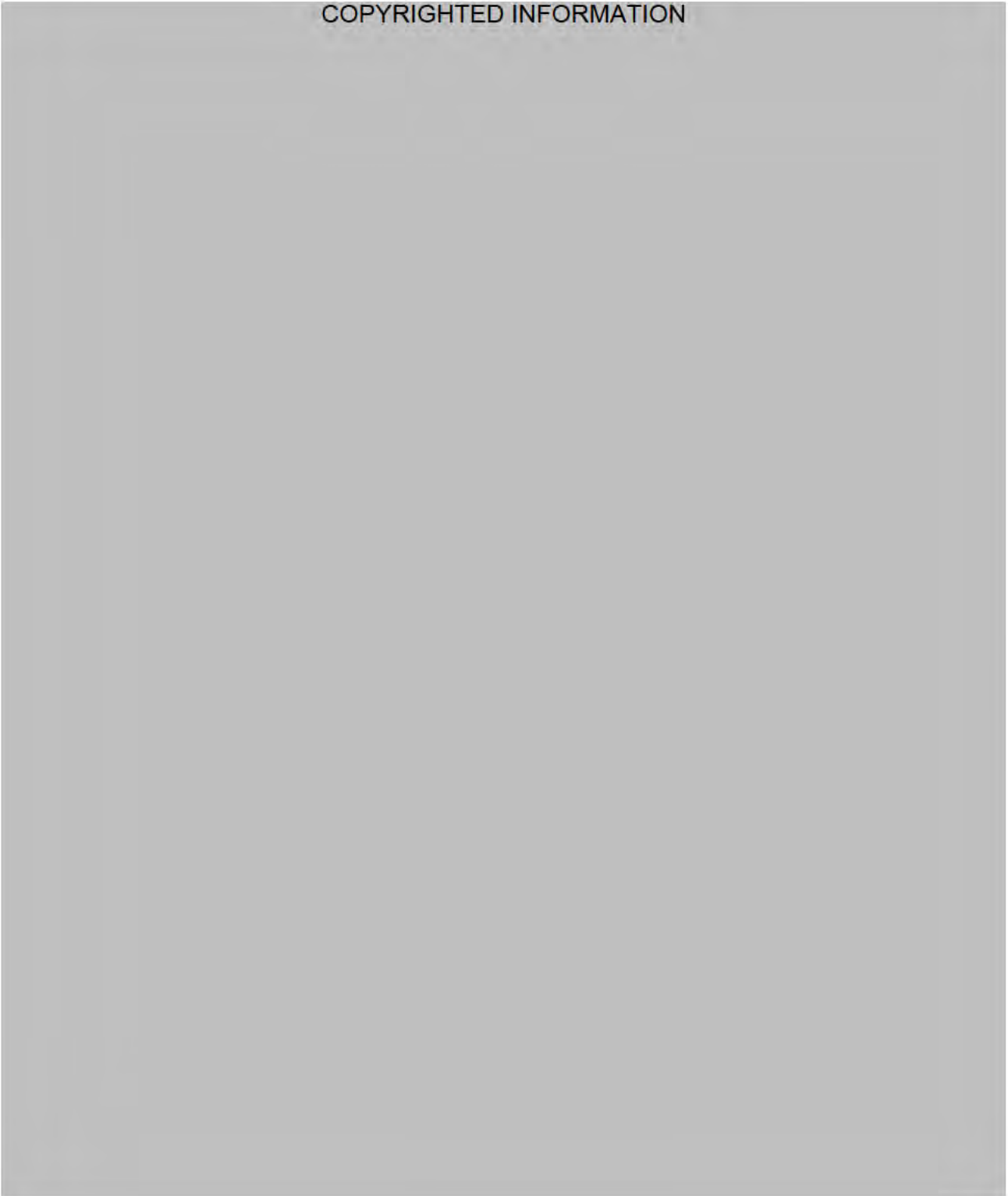
ABSTRACT

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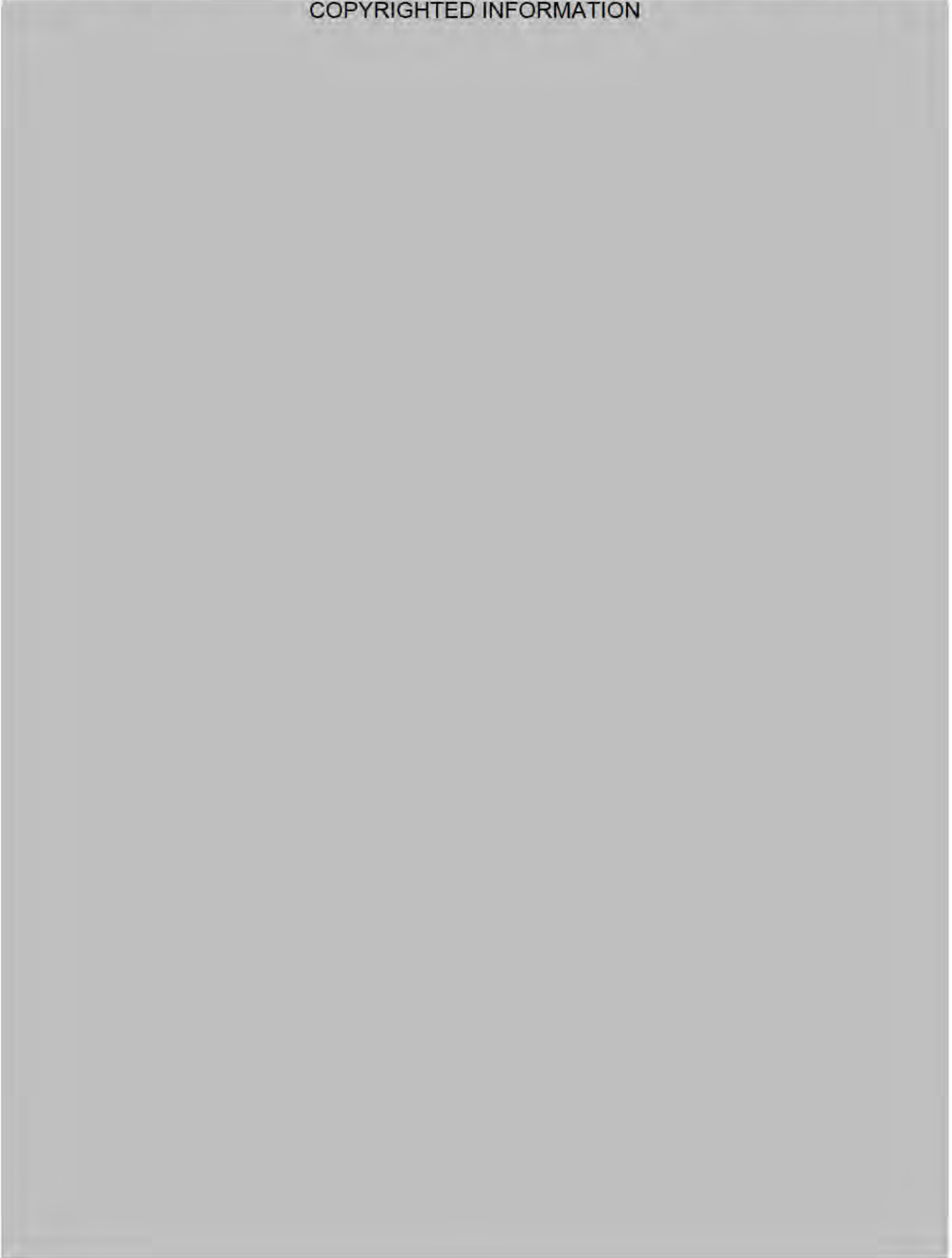


INTRODUCTION

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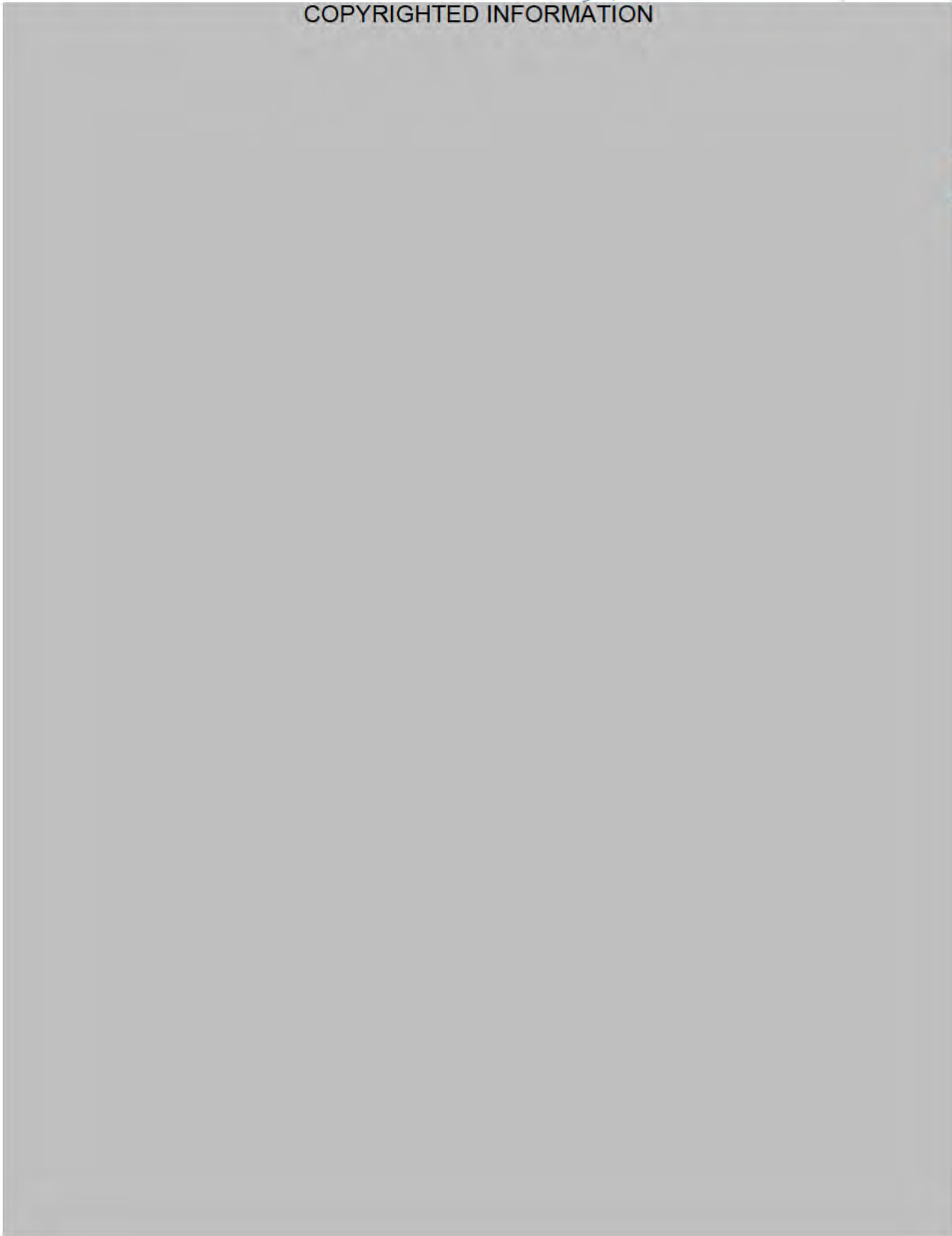
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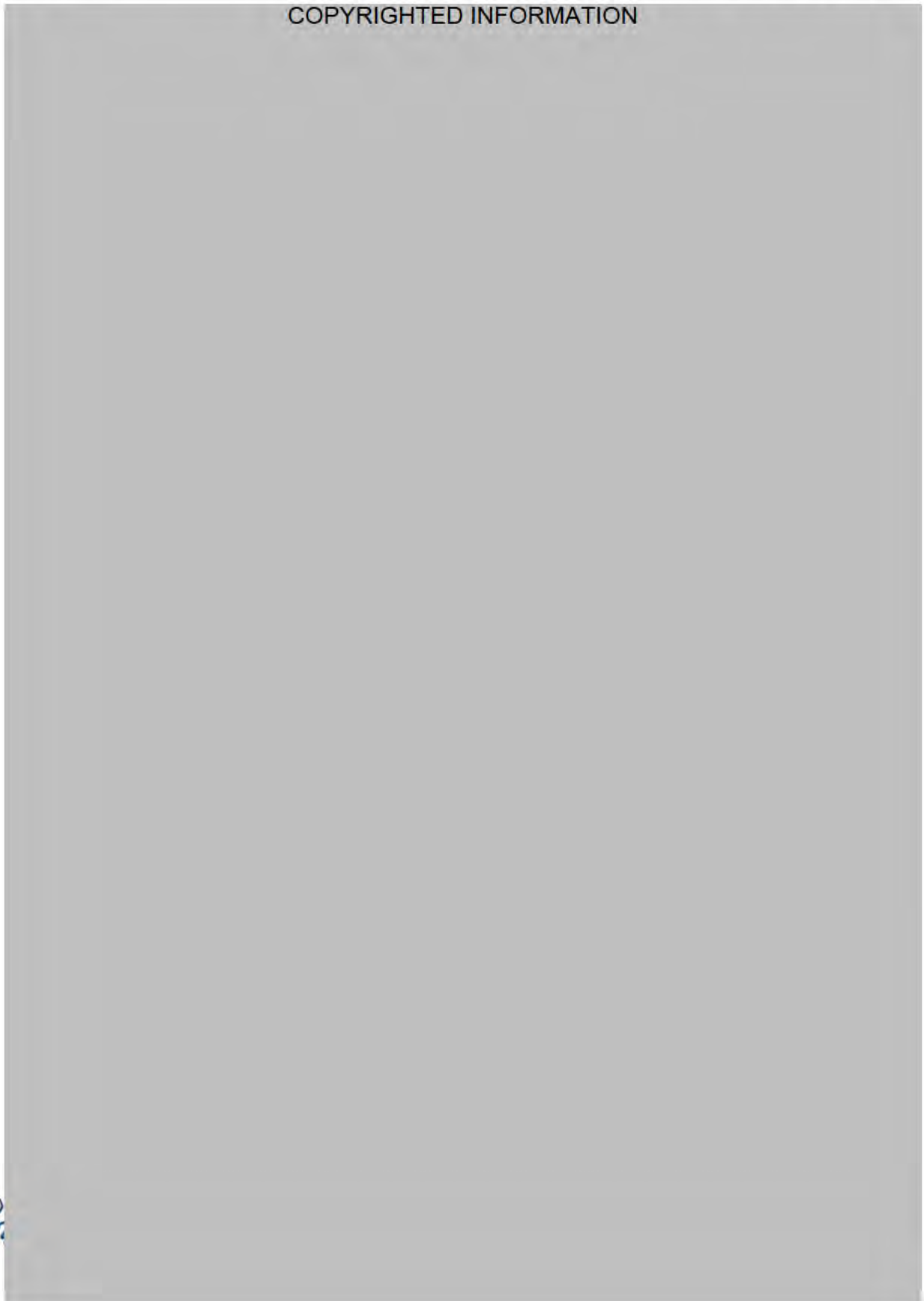
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RESULTS

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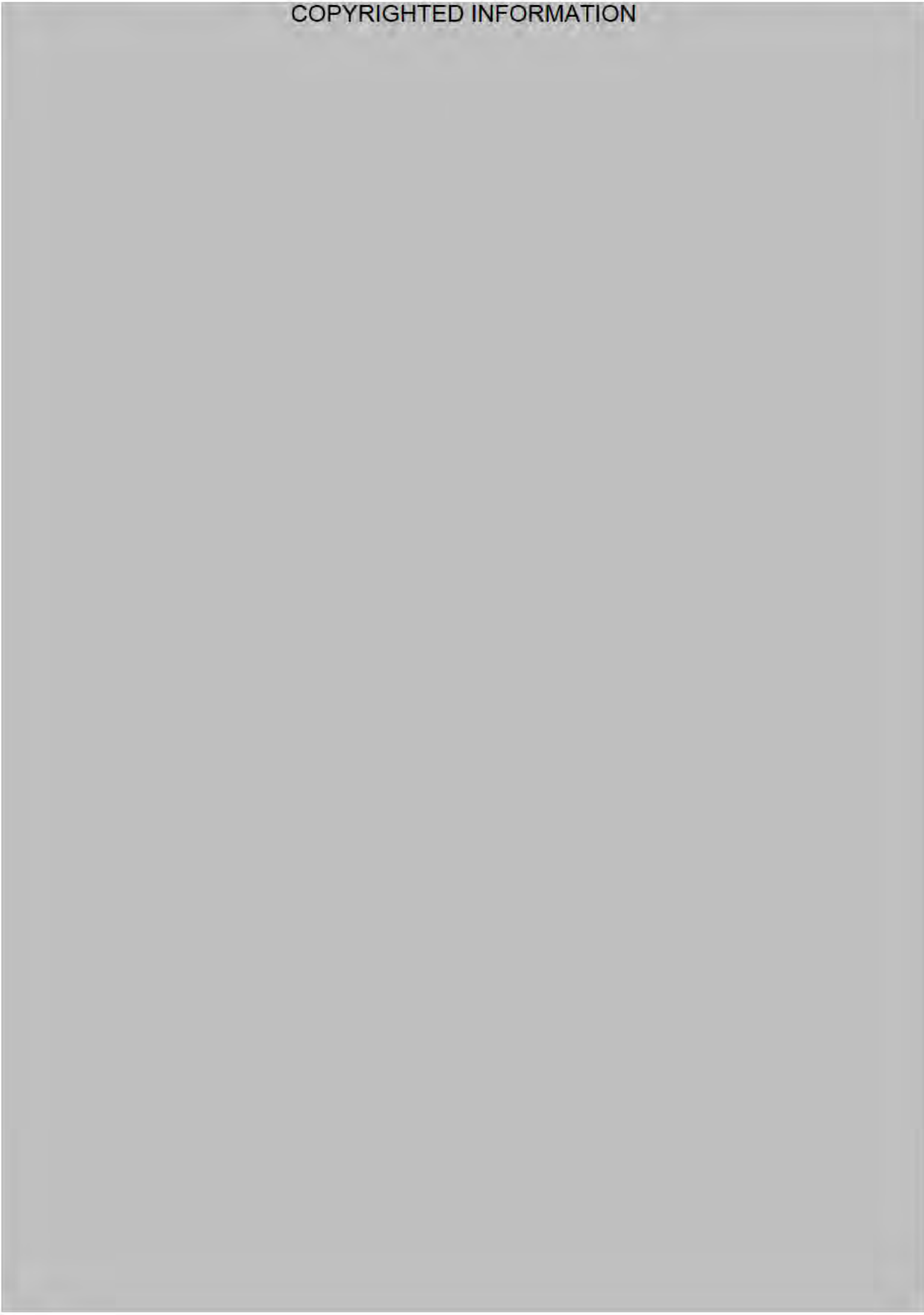


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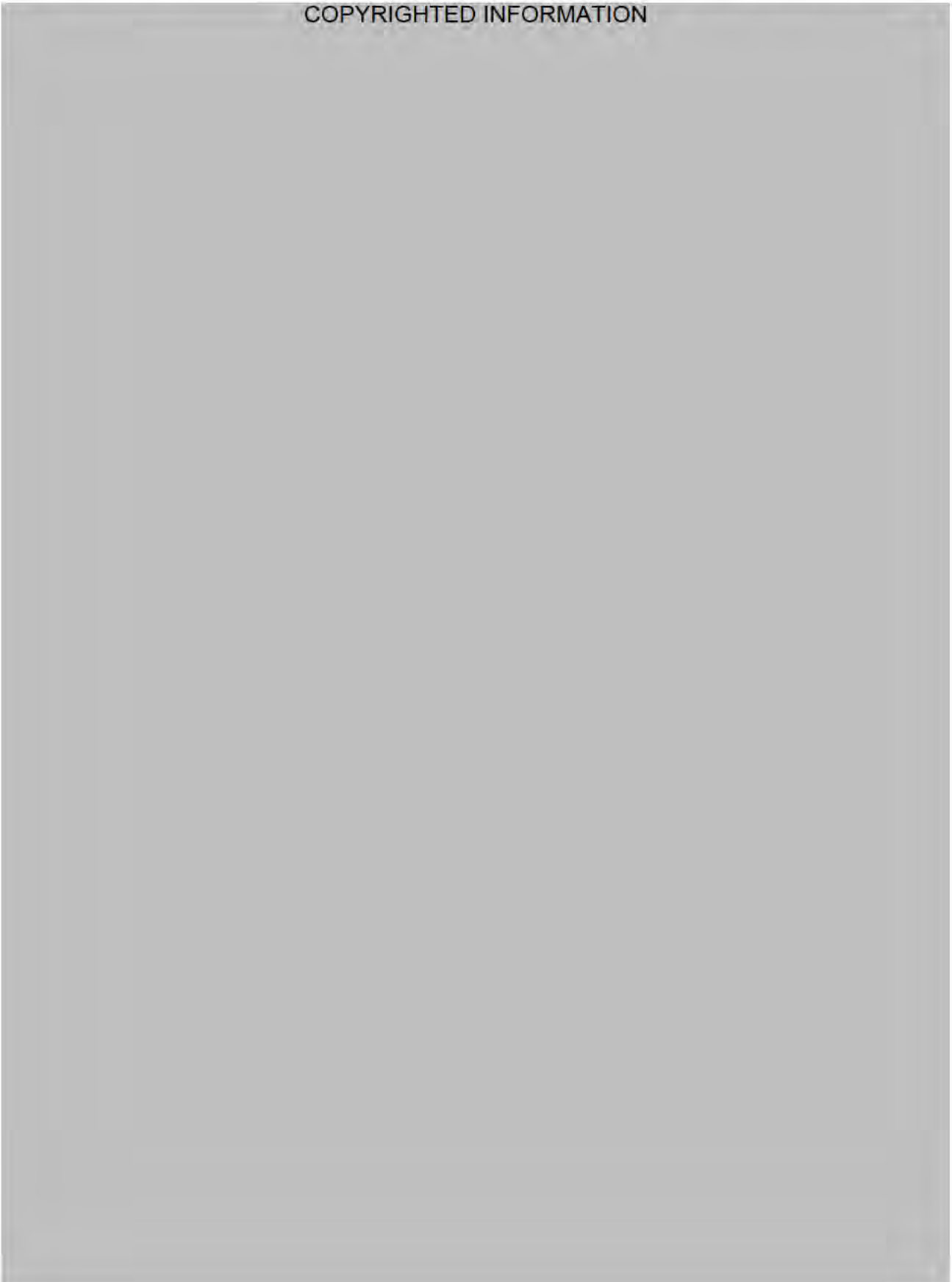


You know
this now?

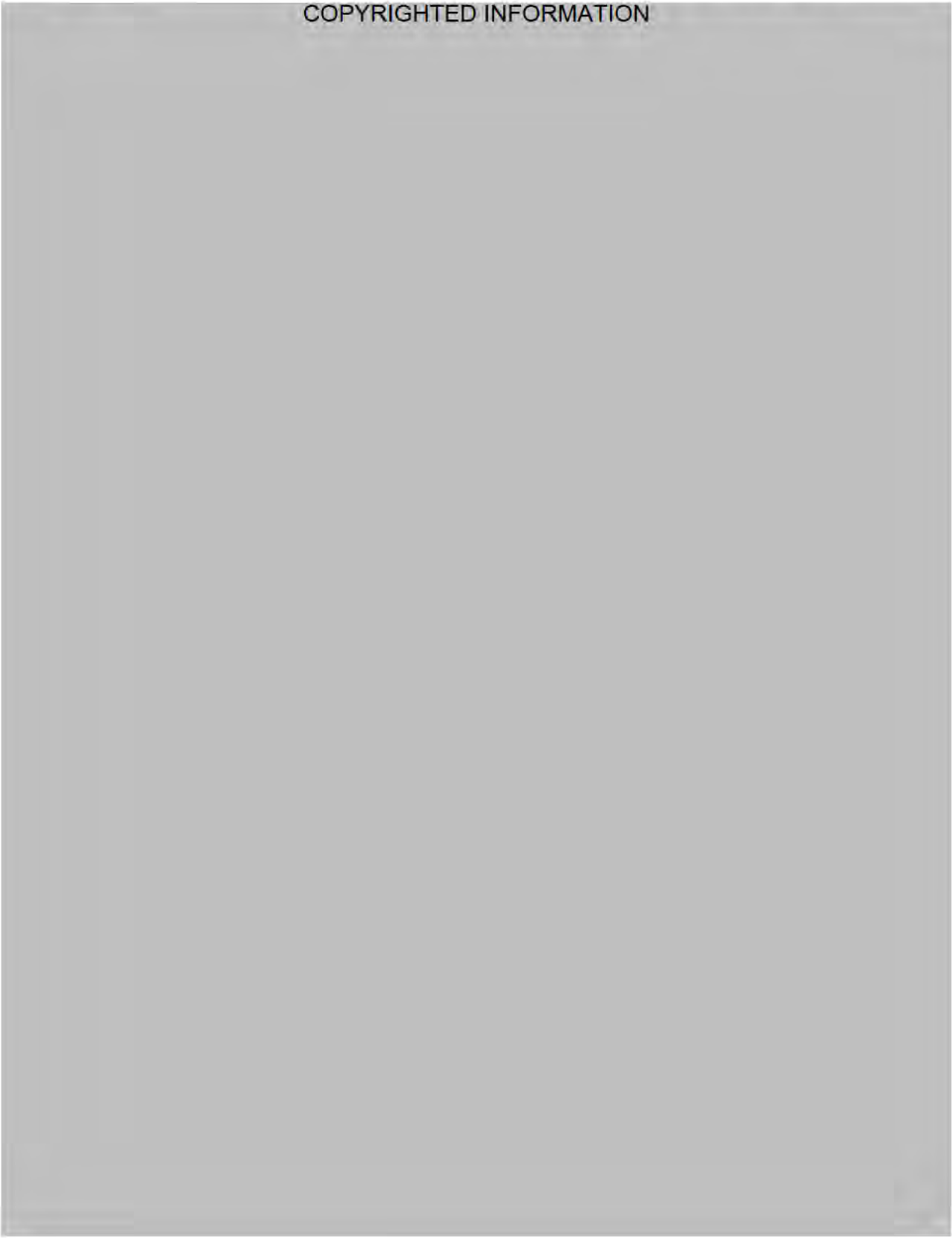
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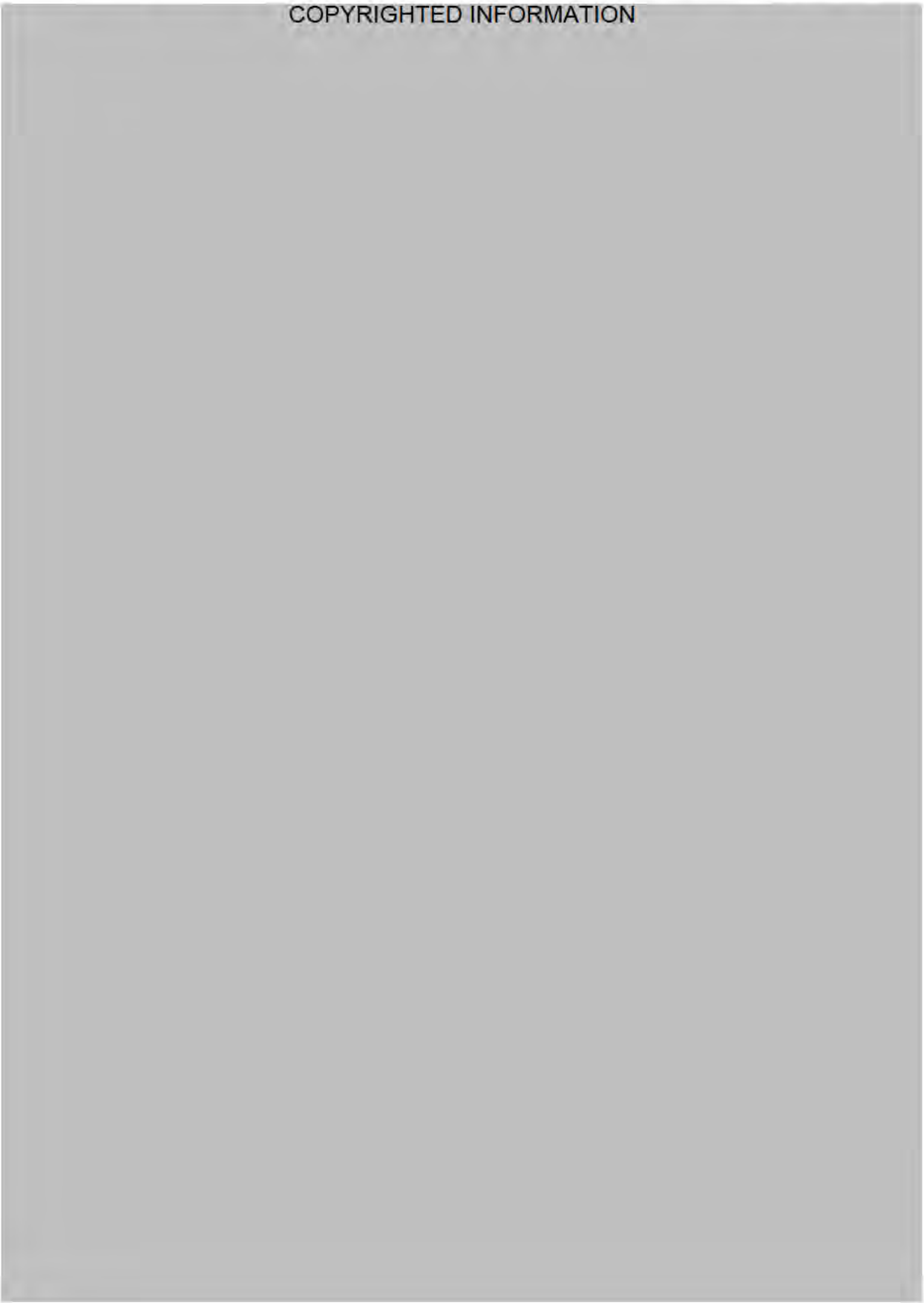
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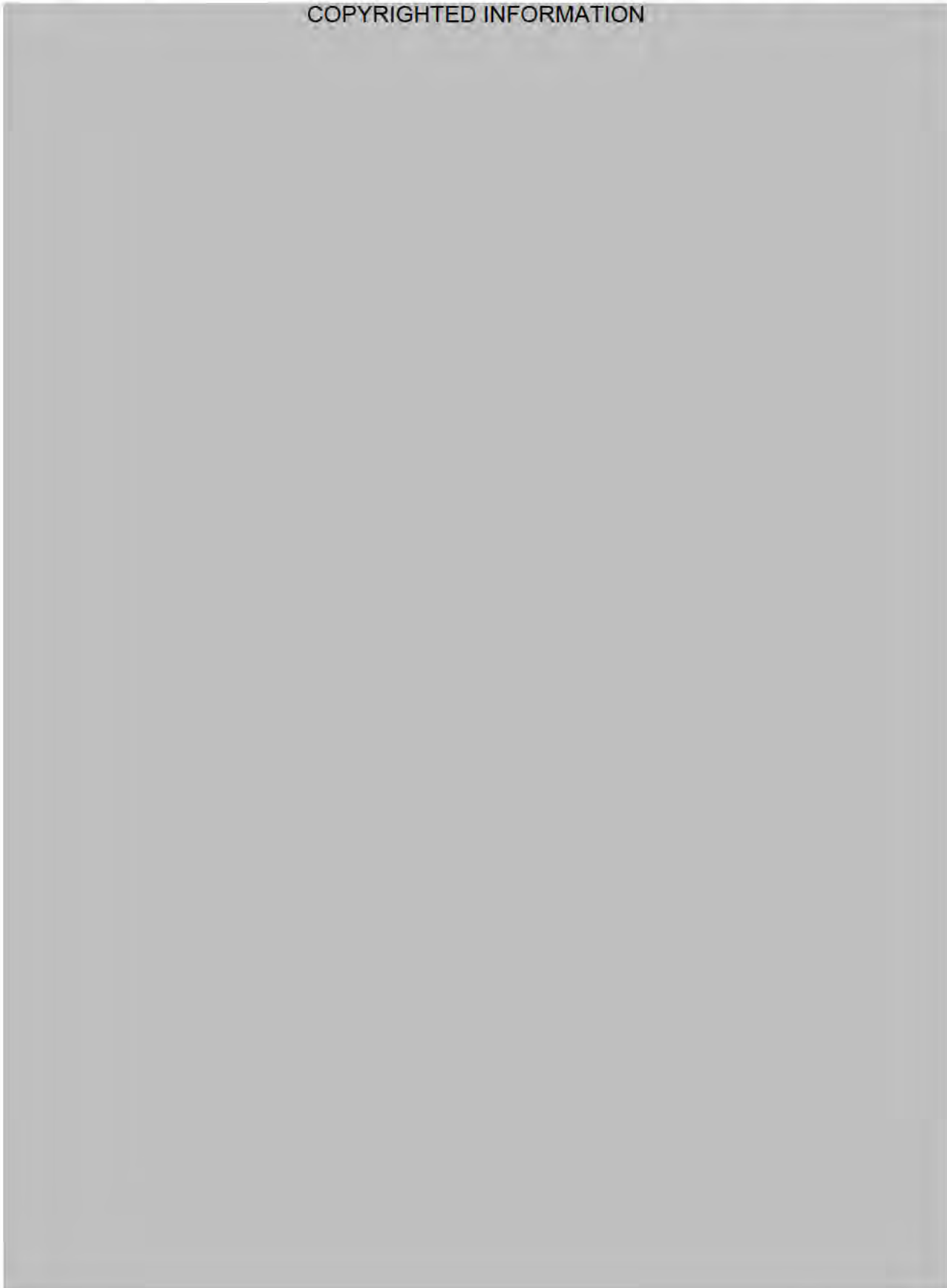
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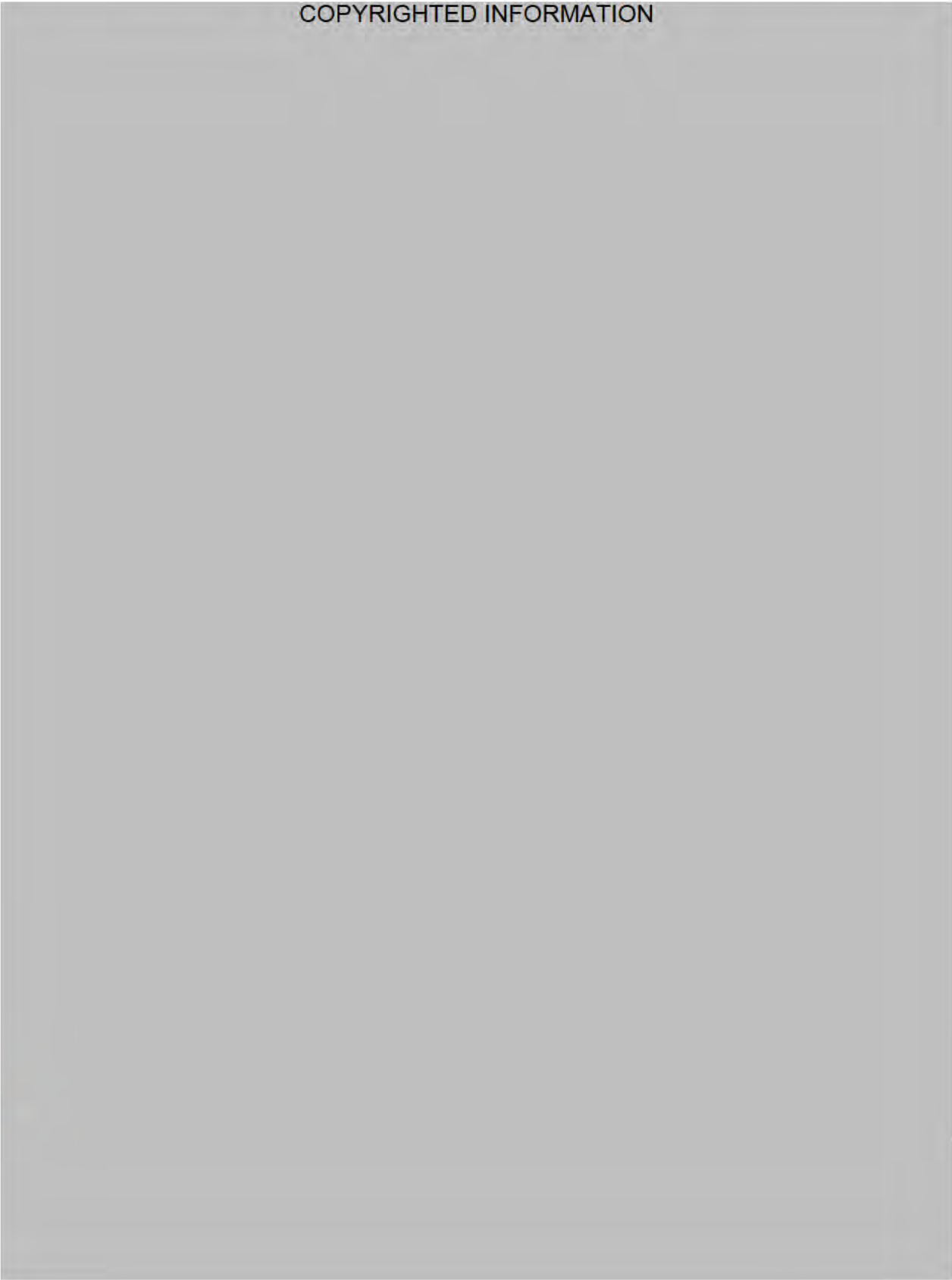
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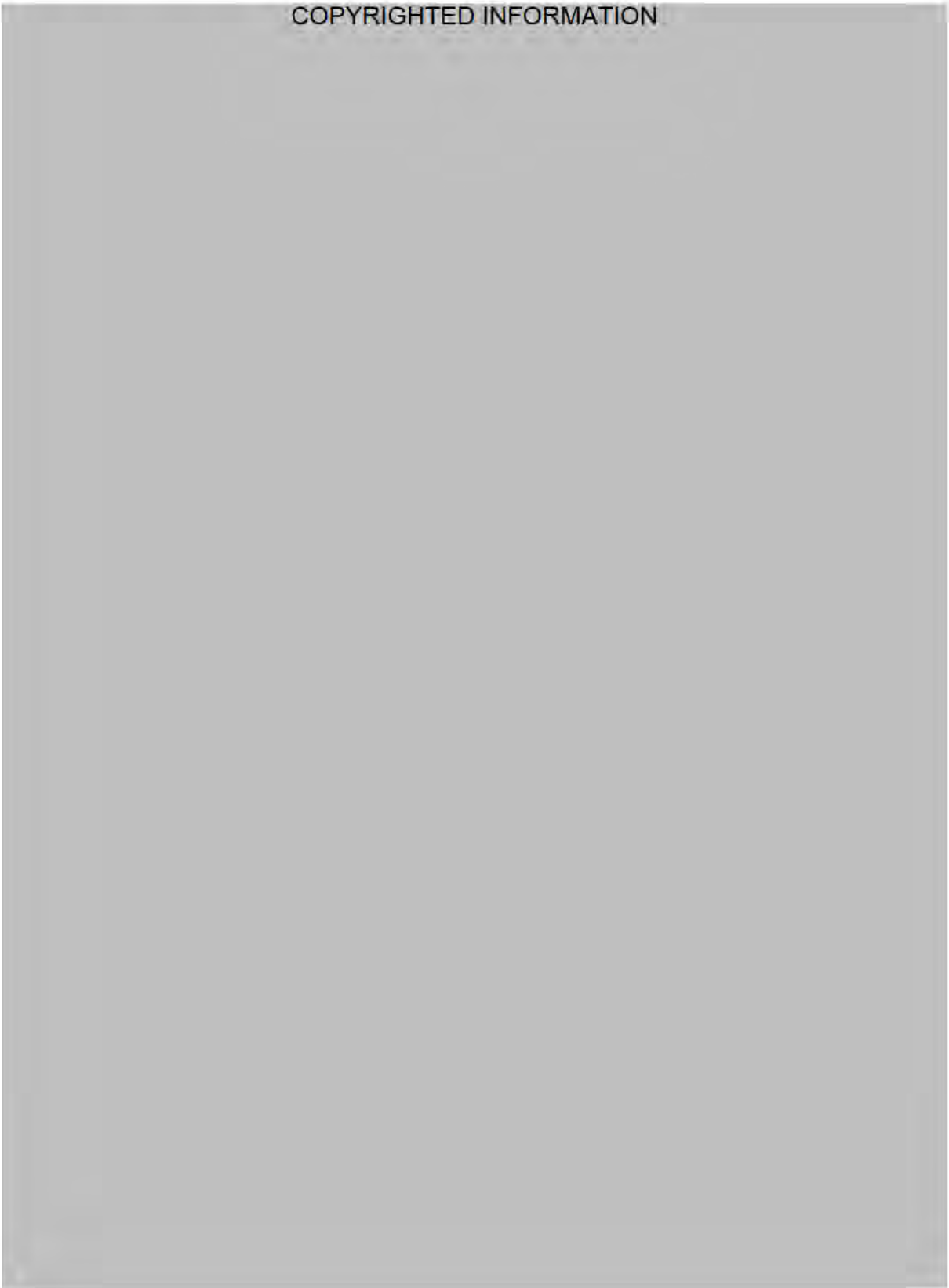
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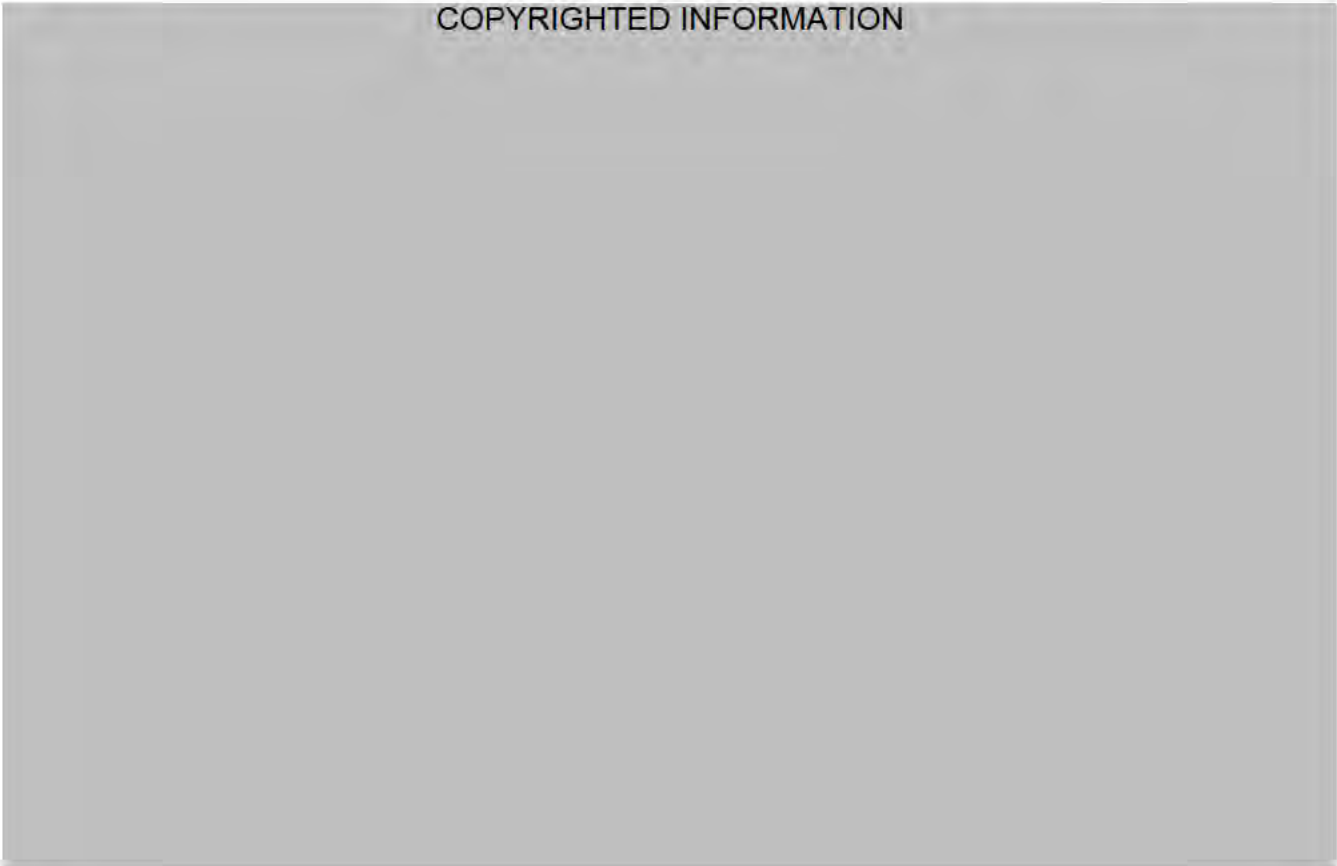
what
that
mean

ACKNOWLEDGEMENTS

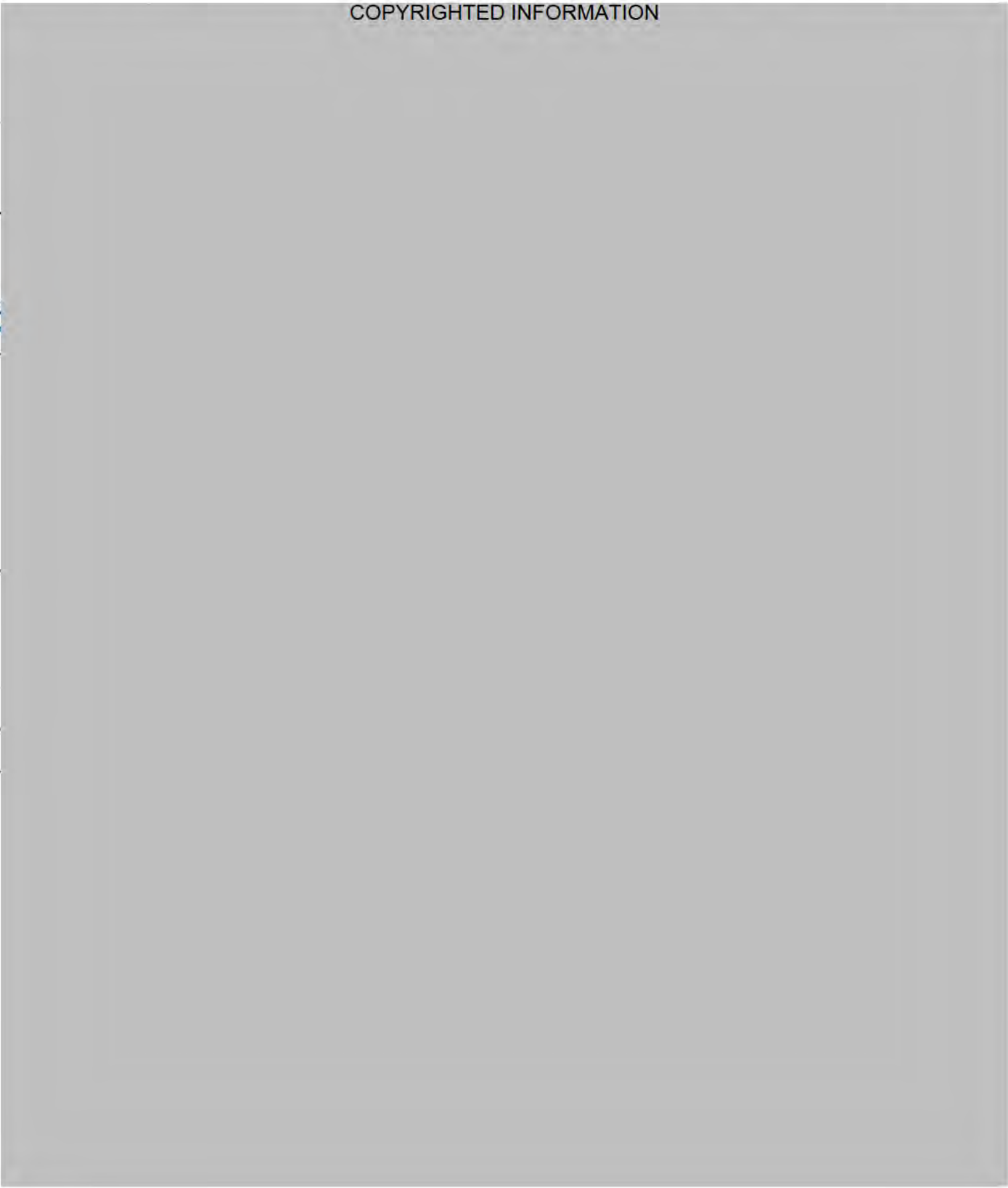
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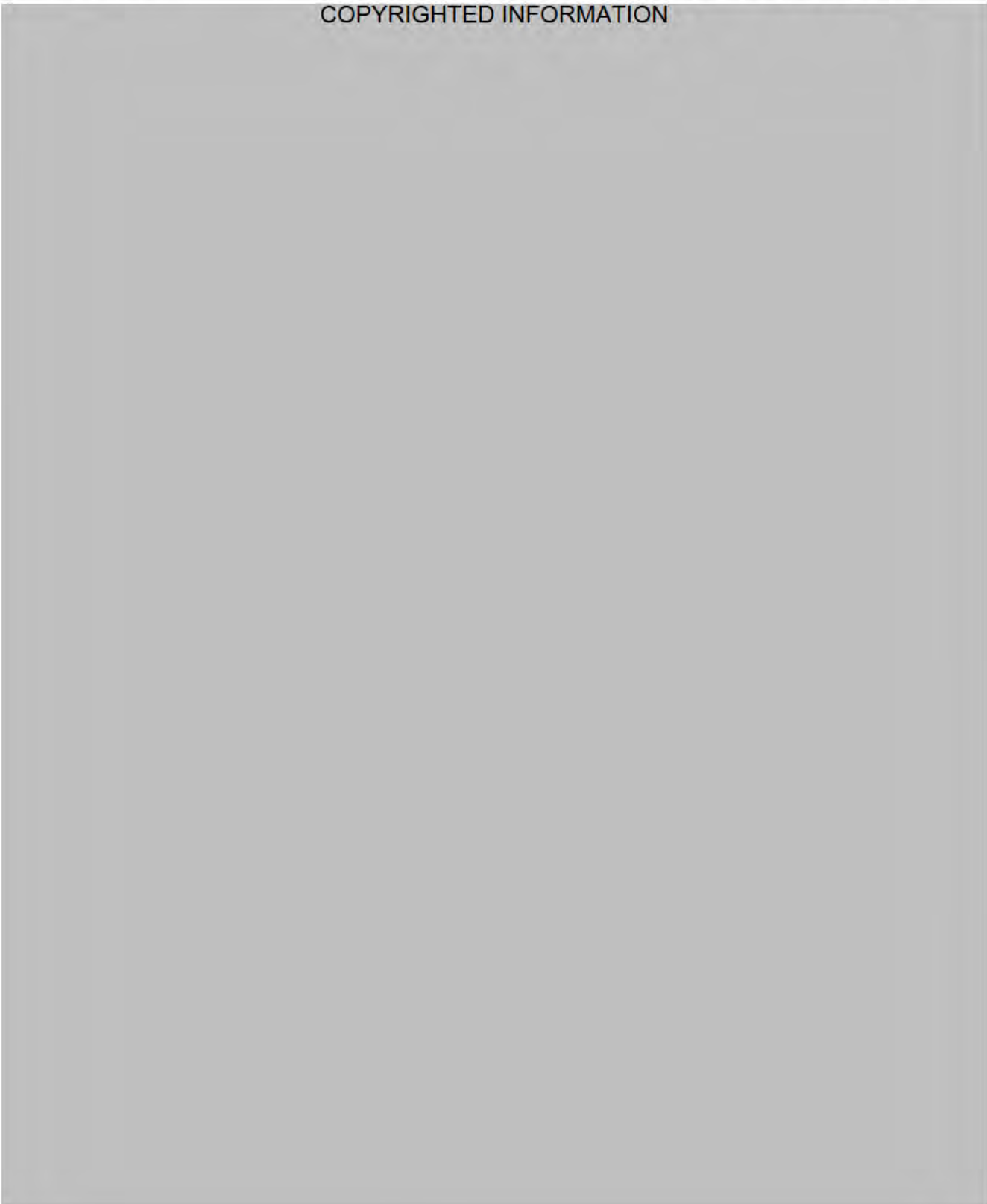
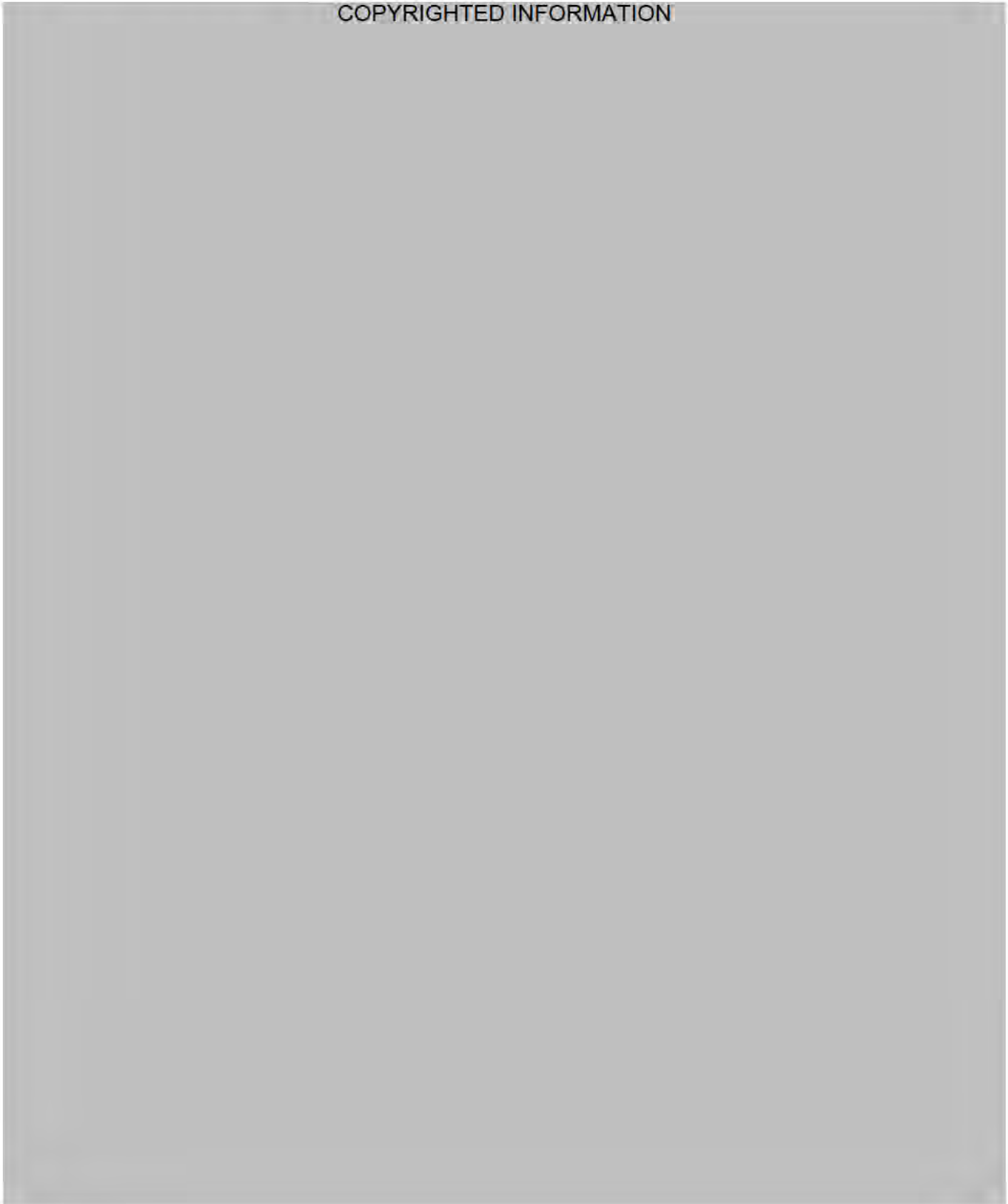
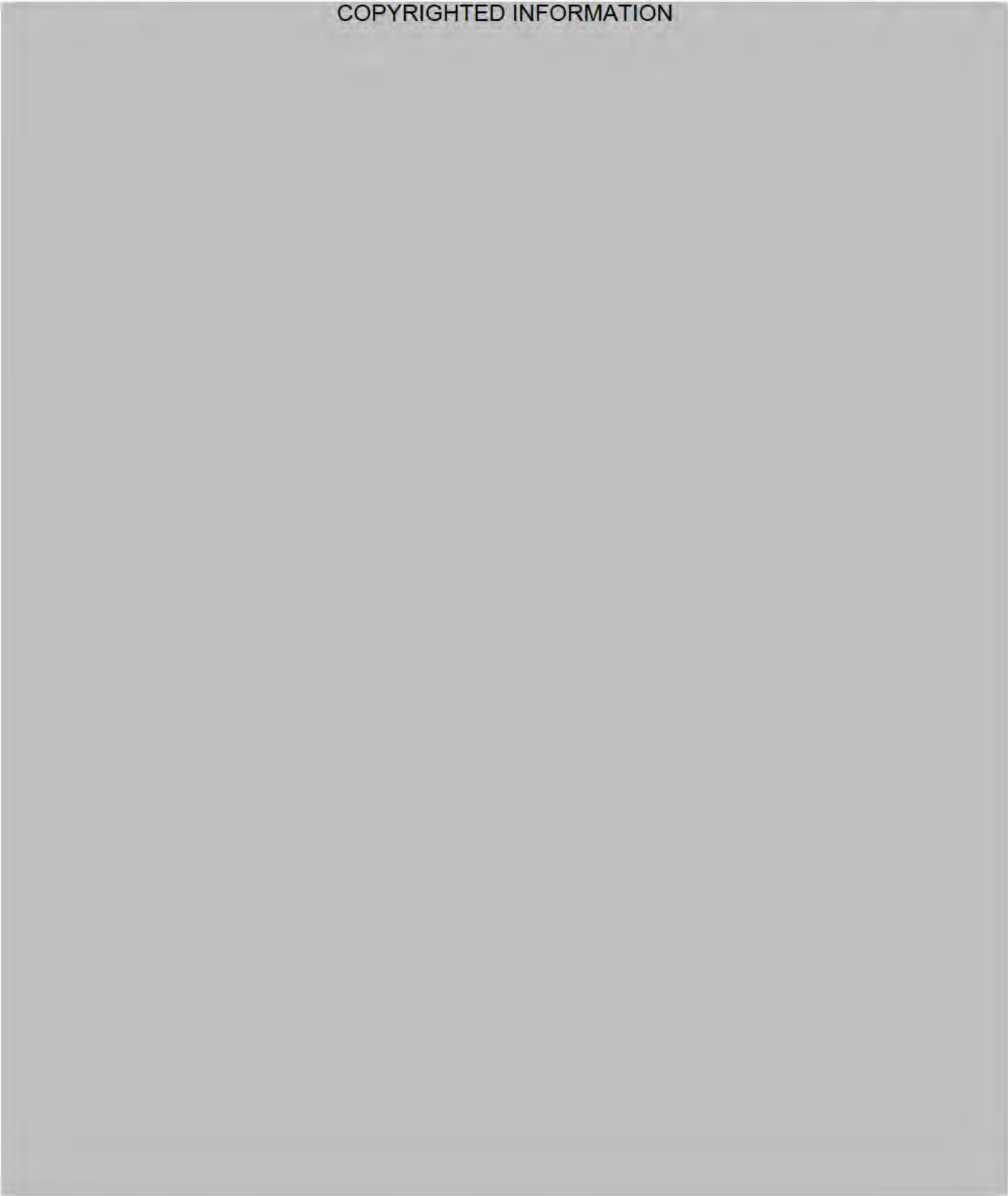


FIGURE LEGENDS

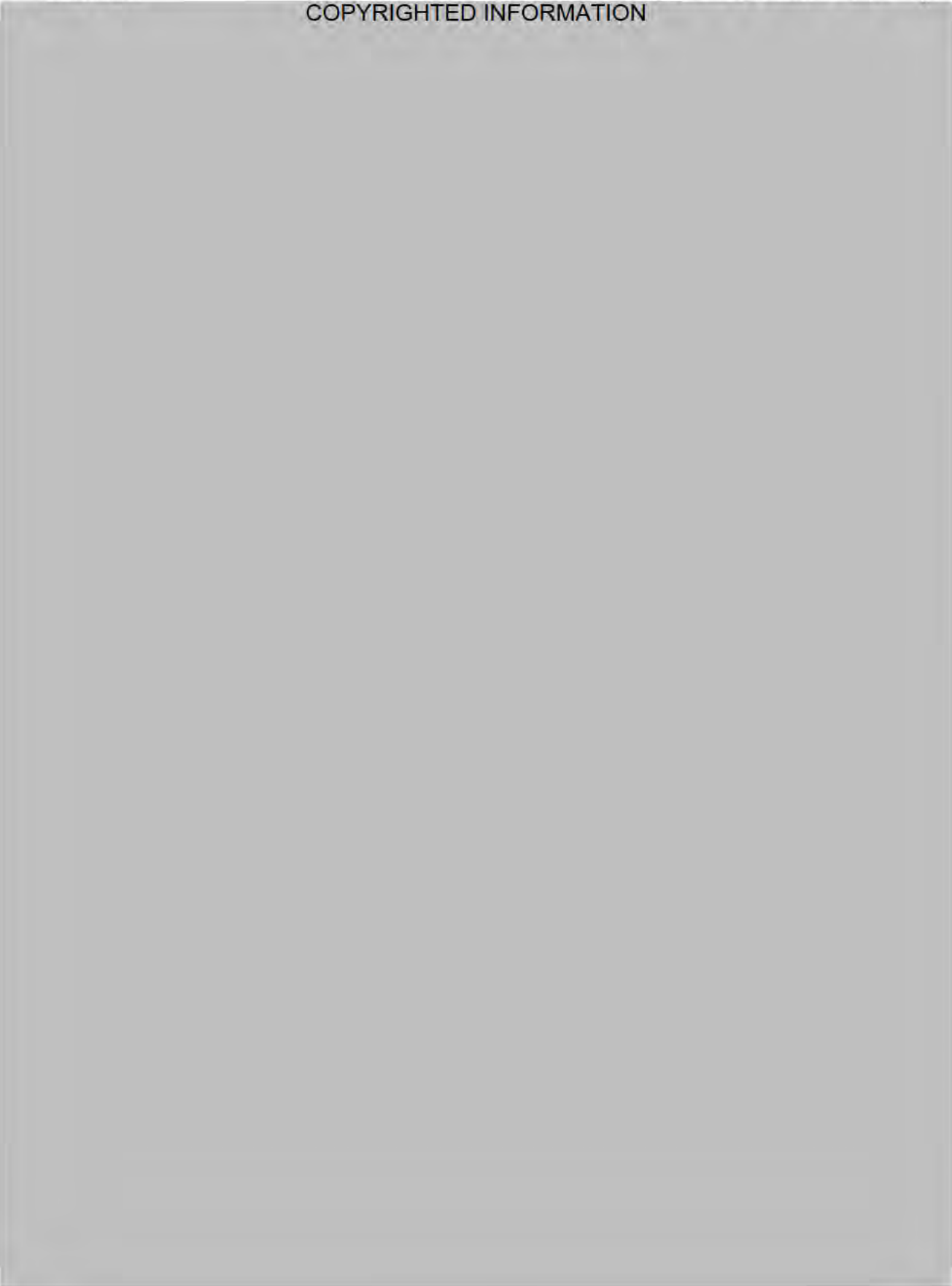
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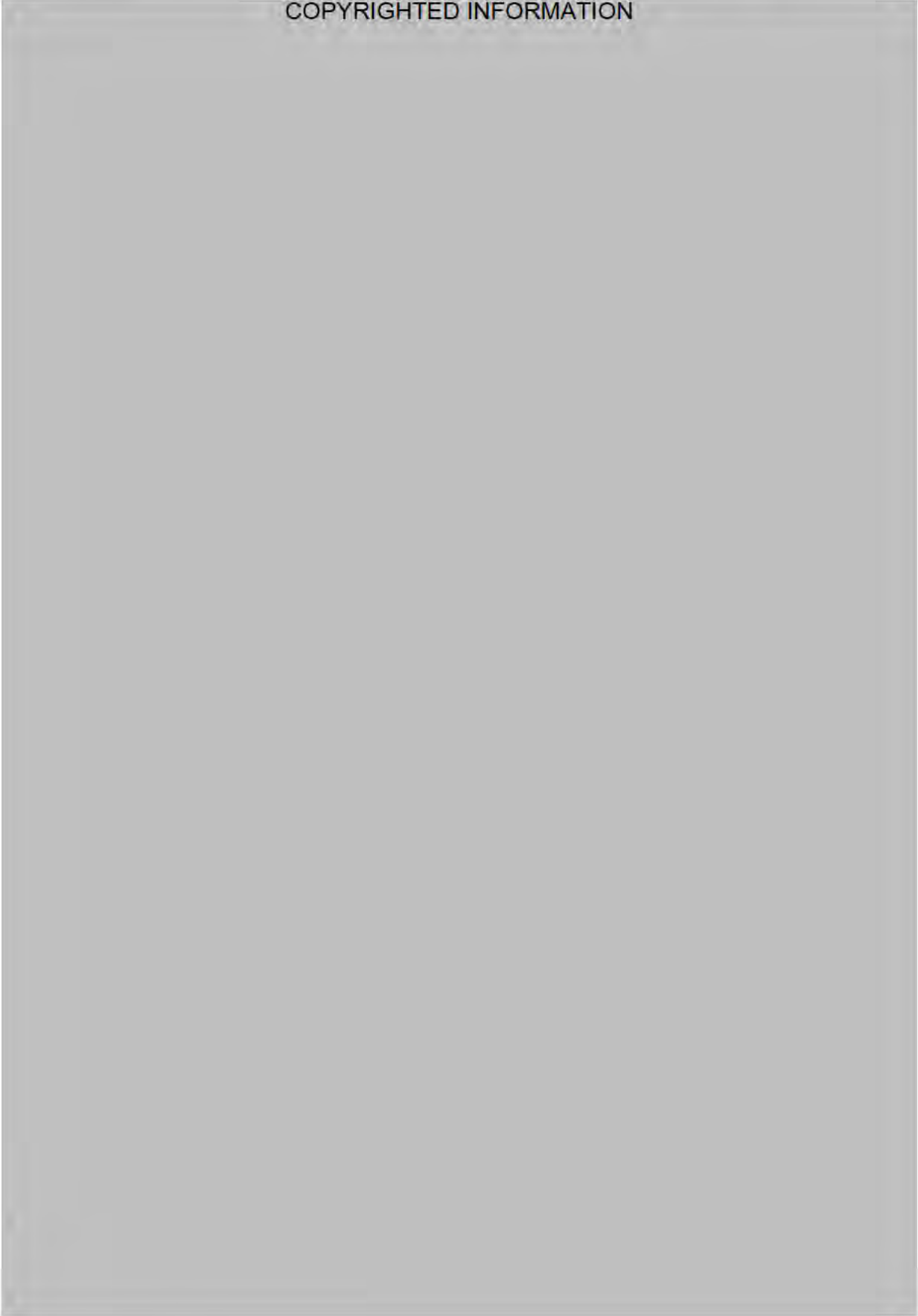
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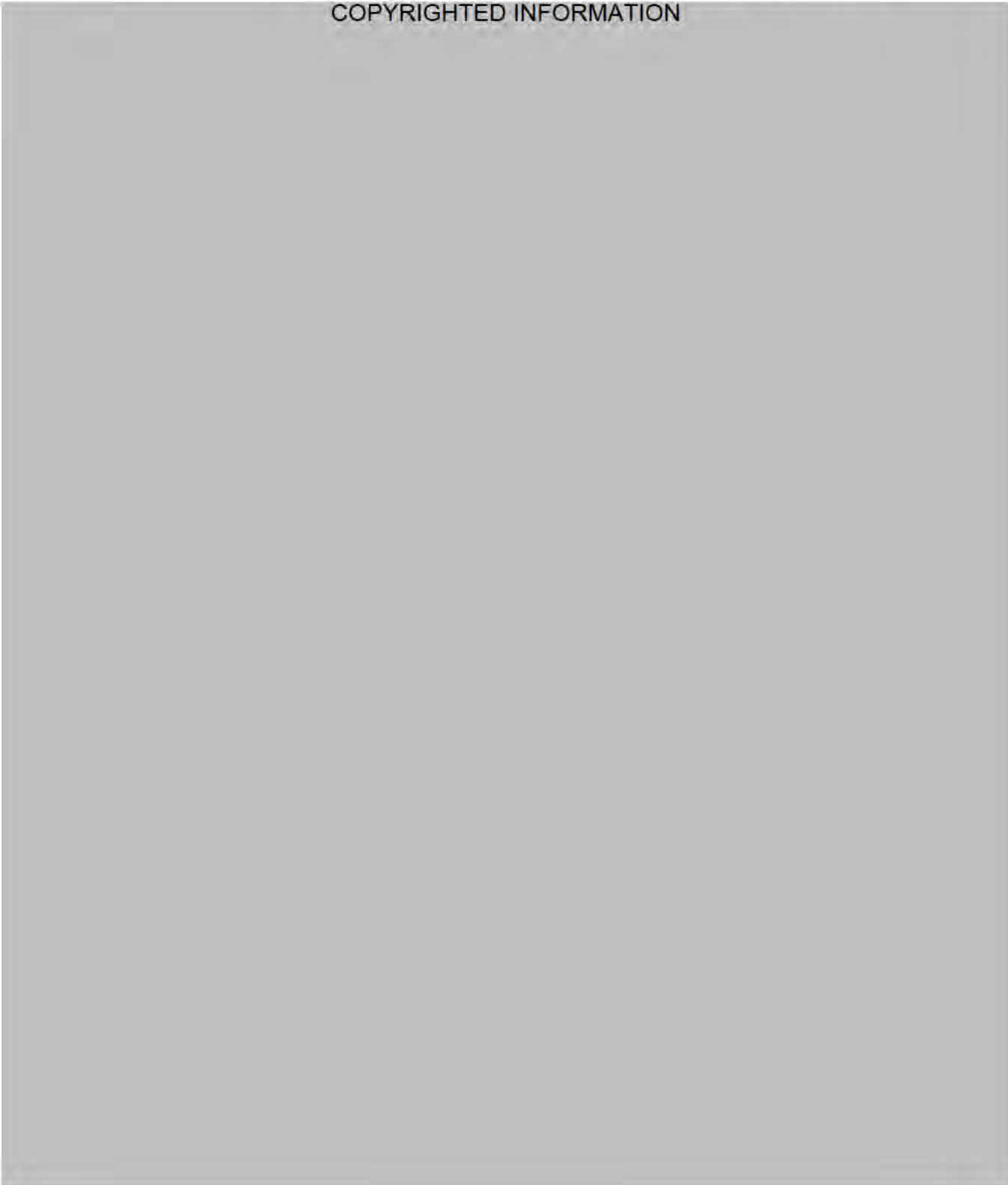
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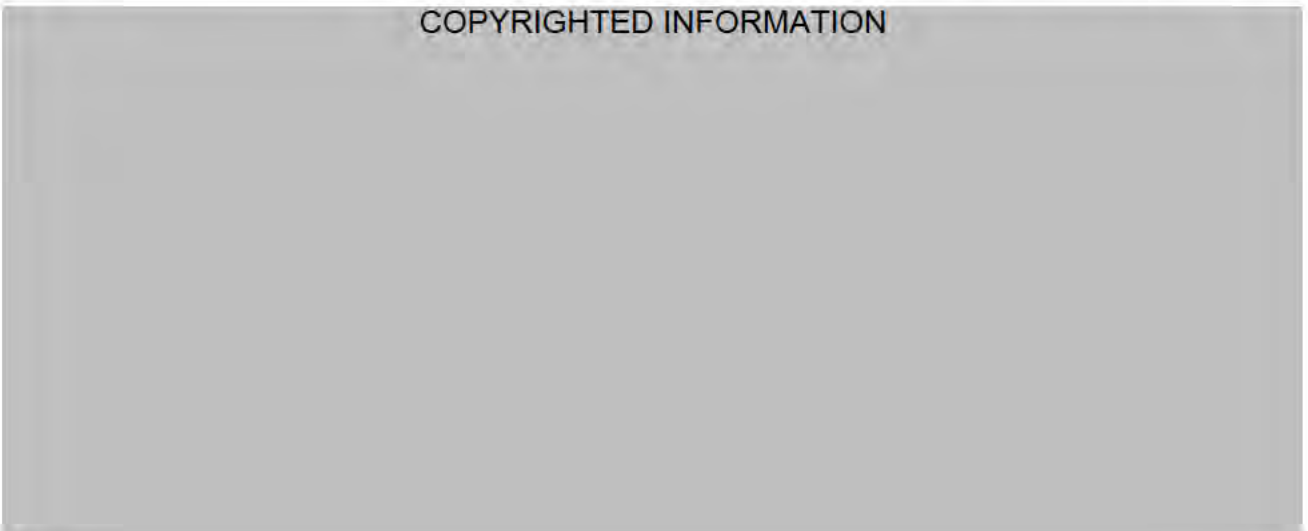
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Felicia

Temple, Robert

From: Diggs, Felicia
Sent: Tuesday, April 26, 2016 1:30 PM
To: Unger, Ellis; Temple, Robert
Cc: Blount, Aprile
Subject: Information Alert - Post PCNS AC meeting

*Can you send
the one below
to Felicia*

Good day Drs. Unger and Temple,

Tx

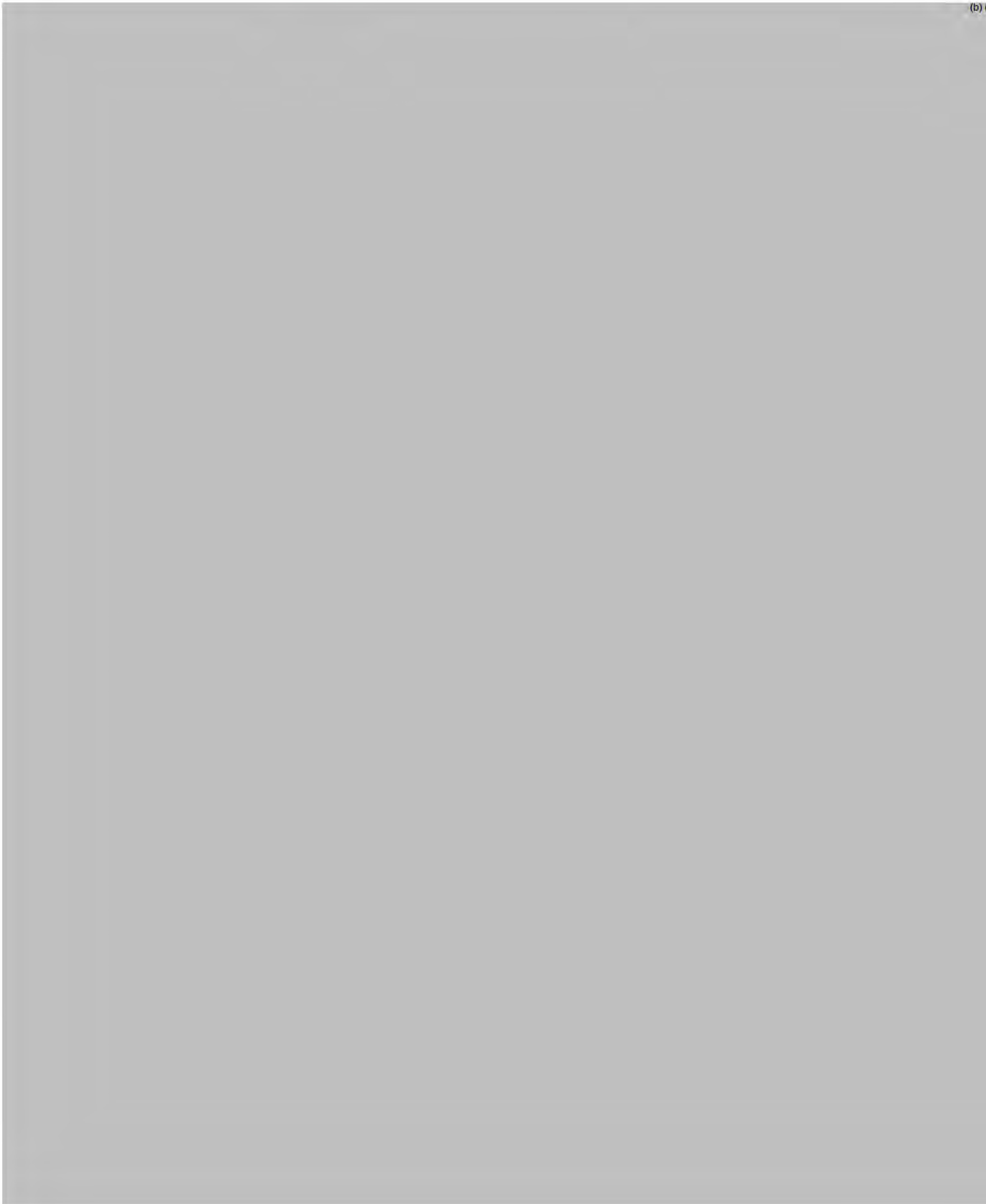
The attached document is an Information Alert on the outcome of the PCNS AC meeting yesterday for HHS. If you could review this asap and return no later than COB today it would be greatly appreciated. My plans are to send this up to HHS today. Billy made some edits and cleared the draft.



IA_PCNS_AC_Ete...

Thank you,

Felicia M. Diggs, RN, BSN, MSN
Consumer Safety Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research | Office of Executive Programs | Division of Executive Operations
240-402-4932 | Blackberry: 301-467-3742 | Fax: 301-847-8753 | Felicia.diggs@fda.hhs.gov





[Faint, illegible handwritten text, possibly bleed-through from the reverse side of the page.]

Temple, Robert

From: Diggs, Felicia
Sent: Wednesday, April 27, 2016 11:31 AM
To: Moran, Kristy
Cc: Behr, Virginia L; CDER-EOS; Drug Safety Web; Haughey, Laurie; Lolic, Milena; Lowy, Naomi; MedWatch Safety Alerts; Peddicord, Sarah; Peterson, Jayne E; Sherwood, Edward M; JW Direct Reports & Deputies
Subject: Corrected Information Alert - Peripheral & Central Nervous System Drugs Advisory Committee Post AC meeting - eteplirsen

Dear Kristy,

Please see the corrected version below and highlighted:

On April 25, the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS AC), recommended against approval of eteplirsen, Sarepta Therapeutics' experimental drug for the treatment of Duchenne muscular dystrophy. Some members of the committee noted, however, that they were impressed with the testimonials of eteplirsen's benefit from patients who received the drug. The panel voted 7 to 3 that there was not substantial evidence the drug is effective in providing clinical benefit, with 3 committee members abstaining. The panel voted 7 to 6 that eteplirsen did not increase production of a critical missing protein to a level likely to predict clinical benefit, though one committee member changed his vote from no to yes after an 8 to 5 vote was revealed. Final decision from FDA on the drug's approval is due on May 26. The meeting was largely attended by patients with DMD and their families, advocacy groups, industry, health care professionals, researchers, and those working in regulatory science. There were 52 public testimonies from many of these attendees, including a member of Congress who also had a written testimony signed by four lawmakers. The PCNS AC meeting outcome has garnered press coverage from the media that includes the Washington Post, Wall Street Journal, NBC News, Reuters, and Bloomberg News. The coverage has a range of reports with some stating that the meeting was politically charged, some noting the controversy the public has placed on the drug approval process, and others that are mixed. FDA will not issue a press release.



IA_PCNS_AC_Ete...

******PLEASE NOTE THAT THIS INFORMATION IS NOT RELEASABLE TO THE PUBLIC UNTIL THE ACTION TAKES PLACE******

Felicia M. Diggs, RN, BSN, MSN

Consumer Safety Officer

U.S. Food and Drug Administration

Center for Drug Evaluation and Research | Office of Executive Programs | Division of Executive Operations

240-402-4932 | Blackberry: 301-467-3742 | Fax: 301-847-8753 | Felicia.diggs@fda.hhs.gov

DATE: April 26, 2016

**INFORMATION ALERT
(CONFIDENTIAL)**

SUBJECT/LEAD COMPONENT: Advisory Committee Votes Against Recommending Approval for Eteplirsen to Treat Duchenne Muscular Dystrophy

WHY THIS INFORMATION IS IMPORTANT FOR THE SECRETARY: On April 25, the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS AC), recommended against approval of eteplirsen, Sarepta Therapeutics' experimental drug for the treatment of Duchenne muscular dystrophy. Some members of the committee noted, however, that they were impressed with the testimonials of eteplirsen's benefit from patients who received the drug. The panel voted 7 to 3 that there was not substantial evidence the drug is effective in providing clinical benefit, with 3 committee members abstaining. The panel voted 7 to 6 that eteplirsen did not increase production of a critical missing protein to a level likely to predict clinical benefit, though one committee member changed his vote from no to yes after an 8 to 5 vote was revealed. Final decision from FDA on the drug's approval is due on May 26. The meeting was largely attended by patients with DMD and their families, advocacy groups, industry, health care professionals, researchers, and those working in regulatory science. There were 52 public testimonies from many of these attendees, including a member of Congress who also had a written testimony signed by four lawmakers. The PCNS AC meeting outcome has garnered press coverage from the media that includes the Washington Post, Wall Street Journal, NBC News, Reuters, and Bloomberg News. The coverage has a range of reports with some stating that the meeting was politically charged, some noting the controversy the public has placed on the drug approval process, and others that are mixed. FDA will not issue a press release.

SUMMARY OF ISSUE, BACKGROUND, AND DEPARTMENT RESPONSE/ACTIONS:

- DMD is a rare genetic disease. In the United States, the prevalence of DMD at birth is about 1 in 3,500 to 1 in 6,000 males. DMD typically manifests in early childhood and progresses to loss of ambulation and death in young adulthood. DMD is caused by mutations in a gene on the X chromosome that encodes for the dystrophin protein, which imparts structural stability to membranes of muscle fiber cells. People with DMD produce little or no functional dystrophin.
- Current treatment for DMD includes corticosteroids, which may prolong function and survival by several years, and supportive care (e.g., physiotherapy, mechanical supports, orthopedic surgery, and assisted ventilation). Eteplirsen targets a specific mutation that affects approximately 13 percent of patients with DMD.
- The Committee discussed the NDA for eteplirsen, reviewed safety and efficacy data (including clinical trial results and the benefit-risk profile of the product), and commented on whether adequate data have been submitted to support approval. Support for the efficacy of

eteplirsen in DMD is based primarily on clinical data from a single open-label study of 12 patients compared to a historical control. Additional data are provided on the effect of eteplirsen on the production of dystrophin, the deficient protein that is responsible for causing DMD.

- FDA continues to work to assist sponsors in clinical development of drugs for the treatment of DMD and will take the information obtained from the PCNS AC meeting under consideration as the agency continues to review the application.

CONTACTS: Alicia Swenson-O'Brien, OS/ES, (202) 205-9953; Mary Jo Salerno, FDA/OES, (240) 402-0420; Felicia Diggs, CDER/DEO, (240) 402-4932.

Clearance history

Draft: FDiggs, DEO, 4/26/16

Edited/Cleared: BDunn, DNP, 4/26/16

Cleared: EUnger, ODE1, 4/26/16

Minor Edits: JBernstein, DEO, 4/26/16

Cleared: CBechtel, DEO, 4/26/16

Cleared: HBrown, OEP, 4/27/16

Comment: JPeterson, DACCM, 4/27/16

Edit: FDiggs, DEO, 4/27/16

Philips, Howard

From: Diggs, Felicia
Sent: Wednesday, April 27, 2016 10:55 AM
To: Moran, Kristy
Cc: Behr, Virginia L; CDER-EOS; Drug Safety Web; Haughey, Laurie; Lolic, Milena; Lowy, Naomi; MedWatch Safety Alerts; Peterson, Jayne E; Sherwood, Edward M; JW Direct Reports & Deputies
Subject: Information Alert - Peripheral & Central Nervous System Drugs Advisory Committee Post AC meeting - eteplirsen

Dear Kristy,

On April 25, the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS AC), recommended against approval of eteplirsen, Sarepta Therapeutics' experimental drug for the treatment of Duchenne muscular dystrophy. Some members of the committee noted, however, that they were impressed with the testimonials of eteplirsen's benefit from patients who received the drug. The panel voted 7 to 3 that there was not substantial evidence the drug is effective in providing clinical benefit, with 3 committee members abstaining. The panel voted 7 to 6 that eteplirsen did not increase production of a critical missing protein to a level likely to predict clinical benefit, though one committee member changed his vote from no to yes after an 8 to 5 vote was revealed. Final decision from FDA on the drug's approval is due on May 26. The meeting was largely attended by patients with DMD and their families, advocacy groups, industry, health care professionals, researchers, and those working in regulatory science. There were 52 public testimonies from many of these attendees, including a member of Congress who also had a written testimony signed by [REDACTED] (b) (5). The PCNS AC meeting outcome has garnered press coverage from the media that includes the Washington Post, Wall Street Journal, NBC News, Reuters, and Bloomberg News. The coverage has a range of reports with some stating that the meeting was politically charged, some noting the controversy the public has placed on the drug approval process, and others that are mixed. FDA will not issue a press release.



100% PCNS AC; P...

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Felicia M. Diggs, RN, BSN, MSN

Consumer Safety Officer

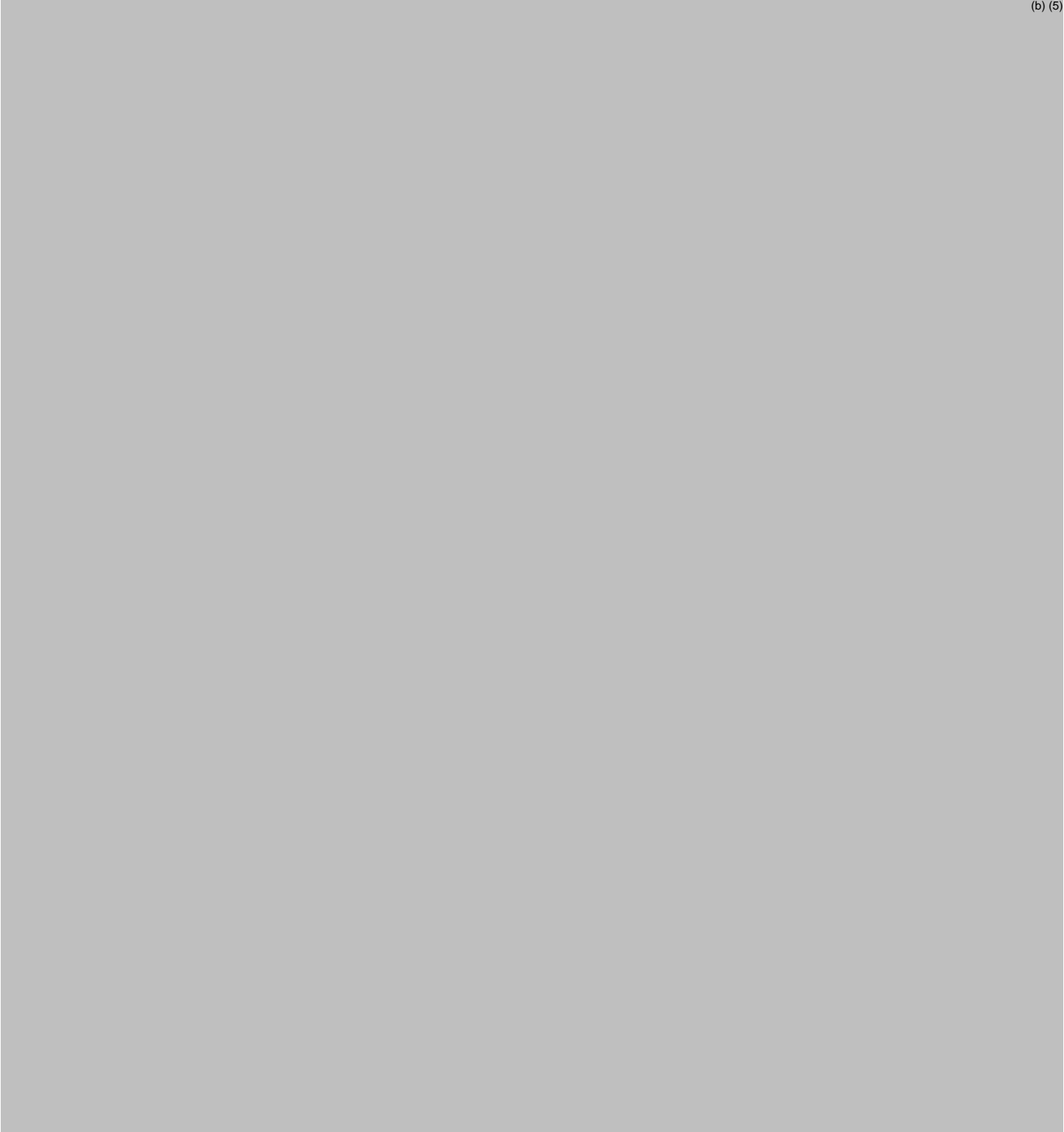
U.S. Food and Drug Administration

Center for Drug Evaluation and Research | Office of Executive Programs | Division of Executive Operations

240-402-4932 | Blackberry: 301-467-3742 | Fax: 301-847-8753 | Felicia.diggs@fda.hhs.gov

DATE: [REDACTED] (b) (5)

INFORMATION ALERT
(CONFIDENTIAL)



(b) (5)



Philips, Howard

From: Unger, Ellis
Sent: Thursday, April 28, 2016 8:51 PM
To: Lowy, Naomi; Temple, Robert; Locicero, Colleen L
Subject: FW: Complaint Received About Comments by Dr. Farkas at This Week's Advisory Committee Meeting

Any suggestions? I've never dealt with one of these.

From: Moss, Andrew **On Behalf Of** OC Ombudsman
Sent: Wednesday, April 27, 2016 12:02 PM
To: Unger, Ellis
Cc: OC Ombudsman
Subject: Complaint Received About Comments by Dr. Farkas at This Week's Advisory Committee Meeting

Hello Dr. Unger:

Please see the email below that our office received about comments made by Dr. Ronald Farkas at this week's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. We are sending to you for your information. The reason we are sending this directly to you is because both Dr. Farkas' immediate supervisor, Dr. Bastings, and his supervisor, Dr. Dunn, had formal roles at the advisory committee meeting, so we thought it was most appropriate to send the email about Dr. Farkas' comments to you.

We will let the consumer know we have sent her complaint to you for your review. If there is something more our office can do to assist in this matter please let me know.

Thank you.

Sincerely,

Andrew Moss
Deputy Ombudsman
FDA Office of the Ombudsman
Office of the Commissioner

-----Original Message-----

From: Sue Tantaró (b) (6)
Sent: Tuesday, April 26, 2016 5:33 AM
To: OC Ombudsman
Subject: My complaint os about Dr Ronald Farkas who told a room full of doctors patients and their

families that boys with Duchenne Muscular Dystrophy can't walk because they don't try not because their muscles are wasting away He is a very ignorant man and sho...

He should be dismissed from representing the FDA

Sent from my iPhone

Philips, Howard

From: Locicero, Colleen L
Sent: Friday, April 29, 2016 1:48 PM
To: Unger, Ellis; Lowy, Naomi; Temple, Robert
Subject: RE: Complaint Received About Comments by Dr. Farkas at This Week's Advisory Committee Meeting

No response is requested. Is it an option to just let it be?

From: Unger, Ellis
Sent: Thursday, April 28, 2016 8:51 PM
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Deputy Ombudsman
FDA Office of the Ombudsman
Office of the Commissioner

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To: OC Ombudsman

Subject: My complaint os about Dr Ronald Farkas who told a room full of doctors patients and their families that boys with Duchenne Muscular Dystrophy can't walk because they don't try not because their muscles are wasting away He is a very ignorant man and sho...

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Sent from my iPhone

Philips, Howard

From: Temple, Robert
Sent: Friday, April 29, 2016 10:02 AM
To: Unger, Ellis; Lowy, Naomi; Locicero, Colleen L
Subject: RE: Complaint Received About Comments by Dr. Farkas at This Week's Advisory Committee Meeting

Well, you can certainly look at his actual comments and respond to the complainant, who has not, by my memory, described his words anywhere near accurately.

From: Unger, Ellis
Sent: Thursday, April 28, 2016 8:51 PM
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Sent from my iPhone

Philips, Howard

From: Temple, Robert
Sent: Friday, April 29, 2016 4:37 PM
To: Locicero, Colleen L; Unger, Ellis; Lowy, Naomi
Subject: RE: Complaint Received About Comments by Dr. Farkas at This Week's Advisory Committee Meeting

No response seems like the right answer to me.

From: Locicero, Colleen L
Sent: Friday, April 29, 2016 1:48 PM
To: Unger, Ellis; Lowy, Naomi; Temple, Robert
Subject: RE: Complaint Received About Comments by Dr. Farkas at This Week's Advisory Committee Meeting

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He should be dismissed from representing the FDA

Sent from my iPhone

Philips, Howard

From: Temple, Robert
Sent: Monday, May 02, 2016 6:04 PM
To: Unger, Ellis; Dunn, Billy
Subject: FW: Medical Records/Advice

Suggestions. Should we get the records?

From: (b) (6)
Sent: Monday, May 02, 2016 5:49 PM
To: Temple, Robert
Subject: Medical Records/Advice

Dear Dr. Temple,

Hope you are doing well and I appreciate your time and efforts for our DMD community.

As you may or may not know, my name is (b) (6) and my son (b) (6) has been participating in the Drisapersen Clinical Trial since November of 2011. My son was part of study 044, the "failed" phase III trial in which we initially participated at (b) (6) Canada.

(b) (6) was in the trial from November of 2011 until the halt came in September of 2013 under (b) (6). (b) (6) was on the halt from Drisapersen for about 16 months and then re-dosed in the U.S. at (b) (6) in January of 2015, so about 16 months ago. He's had approximately 38 months of exposure to Drisapersen.

I wanted to ask if it's possible for me to release my son's medical records to the FDA for your review?

My son's experience on Drisapersen is more than compelling. (b) (6) turned (b) (6) years old on (b) (6). My son was diagnosed at the age of (b) (6) months on approximately (b) (6) at (b) (6). After diagnosis we sought the best doctors for our son, we found (b) (6) at (b) (6) who specializes in Duchenne Muscular Dystrophy. Our initial visit with (b) (6) was 4/08/2008. (b) (6) has been her patient now for the last 8 years. (b) (6) recommended (b) (6) starting on a regimen of steroids in Aug of 2009, he was (b) (6) years old at this time. His dose was one 6mg tab daily. (b) (6) had informed me at his (b) (6) year appointment of some upcoming clinical trials that (b) (6) would qualify for having a deletion of exons 48-50 and would need exon skipping 51.

I found out that the closest site to (b) (6) was (b) (6) Canada to participate in the Drisapersen trial. I was put in touch with (b) (6) and went through screening, more DNA testing for (b) (6) and was told that we were able to start in that trial in November of 2011. This was a double blind placebo controlled trial, we knew for this trial the child would either get 6mg/kg dosing for that first 48 weeks or placebo for that first 48 weeks, 2 muscle biopsies would be performed. We had no idea if (b) (6) was on Drisapersen or not, he was a (b) (6) year old little boy in Kindergarten at the time.

I knew about Duchenne, sadly because my cousin (b) (6) died from Duchenne in 1989. I was a teenager when he died and I saw a lot, I saw the struggles that he had. He could never come out and play in our yard, things were hard for him. My Sister and I played video games and watched movies with him. There was a lot that has always stuck with me and it was traumatic and painful to watch his demise. Long story but now we

know that my Grand Mother was a carrier of Duchenne, her 2 Daughters, my Aunt and my Mother are carriers, my cousin (b) (6) had Duchenne, my Sister and I are carriers and in fact my oldest Daughter is a carrier of Duchenne, my youngest Daughter we utilized PGD and she is not a carrier of Duchenne. It's very strong in my family.

We knew that we wanted to try our son in a trial. So we fully accepted being in a placebo controlled trial because we felt at the end of the 48 weeks we knew we'd then get the medication for sure. So I wanted to add that because I saw the other drug company state that the community doesn't want to do placebo controlled trials, but we agreed to do that and many of us did from here in the U.S. and other countries. I've seen Duchenne and if there is a possibility to halt the progress or improve, we absolutely will accept whatever to hopefully have a better outcome, which (b) (6) experience has been very profound.

If allowed I'd like for all of you doctors to take a look at his records. You will see that at (b) (6) years old just before starting in the Drisapersen trial 4/07/2011, (b) (6) NSAA was 29/34 and our last visit 4/04/2016 (b) (6) is now at 34/34 on the NSAA at (b) (6) years old. (b) (6) rises under 2 seconds without a gower maneuver in which you'll note previous to the trial he always had a gower or a partial gower and now he doesn't at all. I visit (b) (6) usually annually, but I have the visit when (b) (6) was (b) (6) years old and then today at (b) (6) The visit when (b) (6) was (b) (6) this visit the halt of Drisapersen was happening and he had been off medication for about 9 months. His NSAA on 6/4/2014 was 32/34, but on 4/07/2016 it's at 34/34, same PT, same physicians. (b) (6) runs up the 4 stair climb in under a second.

Honestly, this is incredible and the doctors that see him are blown away. This year (b) (6) also had an MRI done on (b) (6) pelvis and legs done. He has a lot of healthy muscle, minimal inflammation; (b) (6) says this is amazing and not typical of a (b) (6) year old Duchenne boy. Also something that I'd like noted is (b) (6) decrease in his CK levels. Our records are from when (b) (6) was (b) (6) onward with (b) (6). He had levels in the past like 38,000 and his last one was 6,800 and one would think that's the progression, however (b) (6) is so functional, he walks through all the airports, he has an absolute normal gait, he runs normal. When he was really young under (b) (6) he twisted his whole body to run, he had that lordosis, his stomach protruded. (b) (6) doesn't twist he has a flat stomach no lordosis, it's a different kid.

This would be a travesty with a medication that is working so well in many boys such as (b) (6) I've seen other boys on Drisapersen 16 and 17 with incredible function, similar to (b) (6)

I have videos of (b) (6) very young all the way through, which I'm sure most parents have of their children, I submitted one video that shows clear improvement. I have others that show his twisting as he ran and stomach protruding, back before the initial trial.

There are so many measures that I think it would really help show you and paint a picture of what has happened over the years with (b) (6) I would like the opportunity to share with you or whoever would be the best to share our experience. I wanted initially to bring my son in to have the doctors on the FDA panel back in November to look at my son's arms and body to see that we don't have site reactions. I had sent an email, but was told at adcomm it would have had to be pre-arranged. (b) (6) only has some hardening on the back of his arm, it's not bothersome to him and it's not noticeable. (b) (6) has zero fat on his body so he likes injections in his arms where he has a little, so we go back and forth and front to back on them and he is fine with that.

If you saw (b) (6) in person at the Drisapersen adcomm, you will see that even though he takes steroids he doesn't have the cushion face, he walks normal, he's not heavy, he runs, he looks like any other (b) (6) year old boy, except he is small because of being on steroids for almost 7 years. He plays competitively on a soccer team. It's true that (b) (6) couldn't even hold up a bike before the trial and after being on Drisapersen for a

year and 10 months he was riding and still is a 2 wheel bike, running, playing on a soccer team, running upstairs.

(b) (6) said “ (b) (6) I’ve never seen an over (b) (6) year old Duchenne boy run the 10 meter in under 3 seconds. That’s huge because that’s pretty much all she sees is Duchenne patients.

I would really like for one of you or any of you to let me know your thoughts on this. It would be such an utter tragedy to not look further into this when it’s so life altering. Honestly, my son’s experience wasn’t expected. Seeing a family member die and it’s not pretty what happens in Duchenne, I am speechless how amazing Drisapersen has worked for (b) (6) (b) (6) documents all rise times, Gower scores, hoping or no hoping etc, every measure that would be important factors are in the records. I can sign a release of his records, I receive hard copies and have all (b) (6) records available as well the online mychart.

Is this possible to either send them to one of you directly or even if I need to come to a meeting. I watched the Eteplirsen adcomm and I saw the BD and when I see all or nearly all of those boys no longer being able to rise from the floor? They clearing show declines in all functional measures, have lordosis and heavy. They are barely older than (b) (6) and my son is rising no gower easily, (b) (6) has a NSAA of 34/34, he rides bikes, runs, etc. It’s extremely concerning to me because I can see how my son is so active, he walks normal and runs normal. He throws footballs daily with all the boys at school and in our neighborhood, riding bikes to his school with friends. He’s living a normal life and I’m very concerned that if Drisapersen goes away so does his normal life. This could help so many children and young men, what my cousin would have given to have had this experience.

I truly want and need some advice because (b) (6) was in a failed trial and look at him. He’s amazing and he wouldn’t be the way he is without Drisapersen.

What advice can you give me? Can you please look at my son’s medical records?

If you look at my son’s medical history you can also look at this protein levels in his urine. There has been so much talk on this, however many Duchenne kids have higher levels already because of all the high levels of supplements they take. (b) (6) is only on vitamin D3 supplement, but all physicians will tell you to make sure and drink plenty of fluids as not to get protein in their urine. I feel especially with fatal, rare disease, we must look deeper into medical history, steroid regimen etc. to see the full picture. Most in this community have records that show what’s happening in the big scheme of things and may be helpful for drug approvals. That’s just my opinion.

Sincerely,

(b) (6)

DMD



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 206488

Drug Name: EXONDYS 51™ (eteplirsen)

Indication(s): Duchenne muscular dystrophy (DMD)

Applicant: Sarepta

Date(s): Submission date: 6/26/2015
PDUFA Date: 2/26/2016

Review Priority: Priority Review

Biometrics Division: Division I, Office of Biometrics (HFD -710)

Statistical Reviewer: Xiang Ling, Ph.D.

Concurring Reviewers: Kun Jin, Ph.D., Team Leader
Jim Hung, Ph.D., Director

Medical Division: Division of Neuropharm (HFD -120)

Clinical Team: Christopher Breder, M.D., Ph.D.
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Project Manager: Fannie Choy

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DRAFT

1 EXECUTIVE SUMMARY

The data, overall, did not provide statistical evidence to support the efficacy of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

The only randomized controlled study submitted by the applicant, Study 201, can only be considered as exploratory because of study design and statistical analysis issues. In Study 201, patients were randomized to receive 50 or 30 mg/kg eteplirsen, or placebo. The study endpoints were assessed through Week 24. The statistical analysis plan of Study 201 did not include a method for statistical adjustment for testing multiple doses and/or multiple endpoints. The primary endpoint in Study 201 was the percent of dystrophin positive fibers in muscle biopsy tissue. The interpretation of the immunohistochemistry raw data is discussed in the clinical review. There was no nominally significant difference between eteplirsen 50 mg/kg, eteplirsen 30mg/kg and placebo for the 6MWT, which was the key clinical endpoint in Study 201.

The comparison of eteplirsen with historical controls, as proposed by the applicant in the open-label extension of Study 201 (called Study 202 by the applicant), is statistically uninterpretable, as this open-label extension did not have a prespecified statistical analysis plan, and had an inadequate control for bias. Among the potential sources of bias in the open-label extension of Study 201 are possible differences in various factors between eteplirsen-treated patients and the selected historical control cohort unaddressed by the applicant's attempt to match patients, the potential selection bias due to the *post-hoc* identification of the control cohort by the applicant, and other known sources of bias with the use of a historical control.

2 INTRODUCTION

2.1 Overview

Study 201 is the only randomized, double-blind, placebo-controlled study in this application. It was conducted at a single site in US in 12 subjects with genotypically confirmed DMD. Efficacy was assessed through the first 24 weeks of this study, while safety was assessed through Week 28. Upon completion of Study 201, all 12 patients were enrolled into an open-label extension study (Study 202) to continue receiving once-weekly treatment with eteplirsen. Study 202 was still ongoing at the time of NDA submission and interim study results were submitted for a cumulative 168 weeks of treatment, from Week 1 in Study 201 through the interim data cut at Week 140 in Study 202.

A historical control cohort was identified from 2 DMD patient registries for comparison to eteplirsen-treated patients in Study 201/202.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directories: [\\CDSESUB1\evsprod\NDA206488\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\dmd-51](#) and [\\CDSESUB1\evsprod\NDA206488\0006\m5\datasets](#).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The key clinical efficacy endpoint results were reproduced by this reviewer from the raw data. Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The first patient was enrolled in Study 201 on July 18, 2011 and the study was completed on February 29, 2012. Protocol 201 was amended 7 times, 3 of them were implemented after the study was initiated and the last version was dated January 07, 2012. In Amendment 6 (dated November 04, 2011), the protocol changed the endpoint of 6-Minute Walk Test (6MWT) from exploratory endpoint to a secondary endpoint. In Amendment 7 (dated January 07, 2012), the duration of the study was extended from 24 to 28 weeks. The efficacy analyses were only specified in the statistical analysis plan (SAP), dated February 20, 2012.

Study 201 was not designed as a clinical efficacy study and not powered for efficacy analysis. The primary endpoint was the percent of dystrophin positive fibers as measured in muscle biopsy tissue, i.e., a biomarker. The key clinical secondary endpoint, 6MWT, was specified midway through the trial and the analyses were not specified until the trial was close to completion.

Study Design

This is a randomized, single-center, double-blind, placebo-controlled, multiple-dose study to assess the efficacy, safety, tolerability, and PK of once-weekly i.v. infusions of eteplirsen in subjects with genotypically confirmed DMD with an appropriate genetic lesion. Eligible subjects were randomized to receive 50 or 30 mg/kg eteplirsen or placebo, then placebo subjects were further randomized to 1 of 2 groups to create 4 treatment groups as shown in Table 1. Groups 1 and 2 received 50 or 30 mg/kg eteplirsen once a week for 28 weeks. Group 3a received placebo once a week for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks, and Group 3b received

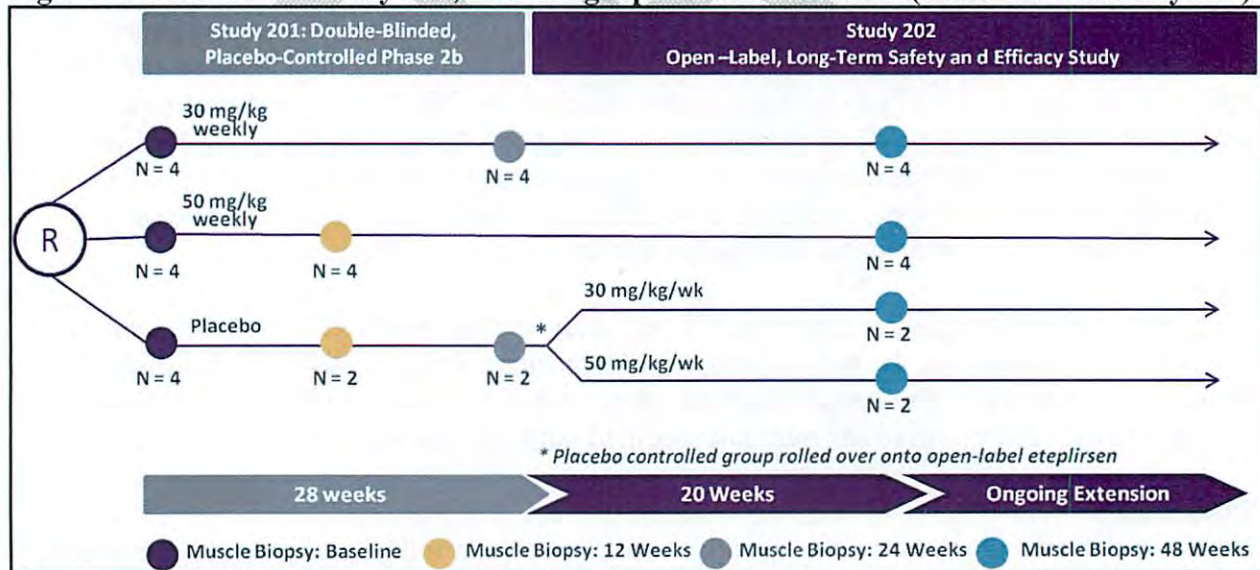
placebo once a week for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks. Beginning Week 25, all parties were aware that all subjects were receiving either 50 or 30 mg/kg eteplirsen.

Table 1: Treatment Groups

Group	N	Treatment
1	4	50 mg/kg eteplirsen IV once weekly for 28 weeks
2	4	30 mg/kg eteplirsen IV once weekly for 28 weeks
3a	2	Placebo IV for 24 weeks then 50 mg/kg eteplirsen for 4 weeks
3b	2	Placebo IV for 24 weeks then 30 mg/kg eteplirsen for 4 weeks

All patients underwent muscle biopsies at baseline for analysis of exon skipping and dystrophin expression. Repeat biopsies were performed at Week 12 for patients in Group 1 and Group 3a and at Week 24 for patients in Group 2 and Group 3b. Efficacy was assessed through the first 24 placebo-controlled weeks of this study, while safety was assessed through Week 28. Upon completion of this study, all 12 patients were rolled into an open-label extension (called Study 202 by the applicant) to continue receiving once-weekly treatment with eteplirsen for additional 212 weeks. In the open-label extension, all patients underwent a third muscle biopsy from the deltoid muscle at Week 20 and optionally a fourth muscle biopsy at approximately Week 140.

Figure 1. Overview of Study 201, Including Open-label Extension (Described as Study 202)



Efficacy Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint is the change from baseline in percent of dystrophin positive fibers as measured in the muscle biopsy tissue using immunohistochemistry (IHC) at Week 12 for groups 1 and 3a and at Week 24 for groups 2 and 3b.

Key Efficacy Endpoints:

1. Changes from Baseline in CD3, CD4, and CD8 lymphocyte counts in muscle biopsy tissue at Week 12 for groups 1 and 3a and at Week 24 for groups 2 and 3b.
2. Changes from Baseline to Week 24 in 6-Minute Walk Test (6MWT).

The following clinical assessments were described as exploratory endpoints in the protocol (Amendment 7, dated 07 January 2012), but are included as key secondary endpoints together with 6MWT in the SAP (dated February 20, 2012):

- Timed 4 Step Test.
- Maximum voluntary isometric contraction test (MVICT) to measure elbow flexion and extension, knee flexion and extension, and grip strength.
- Timed 10-meter run from the North Star Ambulatory Assessment (NSAA).
- NSAA total score.

There is no clear description of hierarchal ordering among all those secondary endpoints. In the open-label extension (described as Study 202) only 6MWT is included as primary clinical endpoint.

3.2.2 Statistical Methodologies

Testing and summary statistics of all efficacy endpoints will combine placebo subjects into a single group. Some efficacy assessments including 6MWT were performed on Days 1 and 2 of the Week 1 (baseline), Week 12, and Week 24 visits and once at the Week 4, 8, 16, and 20 visits. On those visits where 2 tests were performed, the maximum/best observed value is used for the primary analysis. If data for any one visit day are missing, then the non-missing value from the same visit is used.

Efficacy Analysis Population

The efficacy analysis set is the Full Analysis Set (FAS), consisting of all subjects randomized into the study who received any amount of study drug.

Statistical Analysis Method

For this exploratory study, all statistical analyses are conducted at two-sided alpha level of 0.05. No multiplicity adjustment was specified for testing multiple doses and/or multiple endpoints, so all p-values are exploratory only.

The primary efficacy endpoint, the change from baseline in percent of dystrophin positive fibers, was analyzed by comparing the 50 mg/kg eteplirsen treatment group at Week 12 to the combined placebo treatment group, and the 30 mg/kg eteplirsen treatment group at Week 24 to the combined placebo treatment group, using the ANCOVA for ranked data with Baseline values and duration of DMD as covariates.

The analysis of changes from baseline to Week 24 in the clinical assessment parameters (6MWT, Timed 4 Step Test, MVICT, Timed 10-meter run, and NSAA total score) was based on a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) with treatment (placebo, 30 mg/kg, 50 mg/kg), time, and treatment-by-time interaction terms as fixed effects, subject nested within treatment as random effects, with the Baseline value and time since DMD diagnosis as covariates. A first-order autoregressive (AR1) covariance structured matrix is used. The treatment comparison is made between each of the active treatments and placebo. The same MMRM analysis described above would be repeated to compare the combined eteplirsen groups to placebo.

If there was strong evidence suggesting that data for any endpoint deviated from normal distribution, then ANCOVA for ranked data was to be utilized.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patients were recruited for this study nationwide across the US. A total of 12 patients were randomized and all patients received scheduled infusions of study medication and completed the study as planned. All patients were 7 to 10-year old male and, except for one patient of Asian descent, all were white. The time since DMD diagnosis ranged from 18 to 112 months, with a median duration of 57 months. Numerically, there appears to be some imbalance in baseline 6MWT among the treatment groups (Table 2).

Table 2: Demographic and Baseline Disease Characteristics

Parameter		Placebo to Eteplirsena N = 4	Eteplirsen			All Patients N = 12
			30 mg/kg N = 4	50 mg/kg N = 4	All Eteplirsen N = 8	
Age	Mean	8.5	9.3	8.5	8.9	8.8
	Median	8.5	9	8.5	9	9
	Min, Max	7, 10	9, 10	7, 10	7, 10	7, 10
Mutation, n (%)	45-50	0	2 (50.0)	1 (25.0)	3 (37.5)	3 (25.0)
	48-50	0	1 (25.0)	0	1 (12.5)	1 (8.3)
	49-50	3 (75.0)	0	2 (50.0)	2 (25.0)	5 (41.7)
	50	1 (25.0)	0	0	0	1 (8.3)
	52	0	1 (25.0)	1 (25.0)	2 (25.0)	2 (16.7)
6MWT, meters	Mean	394.5	355.3	396	375.6	381.9
	Median	379	359	395	380.5	380
	SD	42.25	74.78	26.61	56.34	50.92
	Min, Max	364, 456	261, 442	365, 429	261, 442	261, 456
Time since DMD diagnosis, months	Mean	50.3	52.5	66.5	59.5	56.4
	Median	51	57	68	57	57
	SD	13.74	14.06	44.29	31.33	26.4
	Min, Max	36, 63	32, 64	18, 112	18, 112	18, 112

^a Includes both 30 mg/kg and 50 mg/kg

Source: Table 10-2 and 10-3 of the CSR.

3.2.4 Results and Conclusions

3.2.4.1 Analyses of the Primary Endpoint

The following analyses were based the fiber data derived by the applicant. The validity of the immunohistochemistry (IHC) raw data is beyond the scope of this review, and is addressed in the clinical review, to which the reader is referred for interpretation of the IHC results.

There was no statistically significant difference between the 50 mg/kg eteplirsen group and placebo at Week 12 ($p=0.958$; Table 3). At Week 24, the mean percentage of dystrophin-positive muscle fibers was higher in the eteplirsen 30 mg/kg group than the placebo. Patients treated with 30 mg/kg eteplirsen demonstrated 23% increase in the mean percentage of dystrophin positive fibers from baseline to Week 24. There appeared to be no increases from baseline in placebo patients. The nominal p value (0.002) for the comparison between eteplirsen 30 mg/kg group and the placebo group can only be considered exploratory, as there was no plan to control the type 1 error due to multiple comparisons, and the other comparison between 50mg/kg and placebo in Study 201 was negative.

Table 3: Dystrophin-Positive Fibers Detected by IHC with MANDYS106

Time point		Placebo	30 mg/kg Eteplirsen N = 4	50 mg/kg Eteplirsen N = 4
Baseline	Mean	15.64	18.19	11.00
	Median	15.58	17.80	11.51
	SD (SE)	10.742 (5.371)	5.501 (2.751)	4.668 (2.334)
	Min, Max	3.2, 28.2	11.9, 25.3	5.4, 15.6
On-Treatment	Mean	11.59	41.14	11.79
	Median	9.44	38.77	11.81
	SD (SE)	7.130 (3.565)	10.097 (5.049)	4.456 (2.228)
	Min, Max	5.7, 21.7	32.7, 54.3	6.4, 17.2
Change from Baseline	Mean	-4.05	22.95	0.79
	Median	-6.13	23.46	2.52
	SD (SE)	5.834 (2.917)	5.792 (2.896)	7.099 (3.549)
	Min, Max	-8.5, 4.5	15.9, 29.0	-9.3, 7.4
	p-value ^a		0.002	0.958

Source: CSR Table 11-1 and Table 14.2.1.1.2, confirmed by FDA reviewer.

^aBased on ANCOVA model for ranked data with treatment (placebo, 30 mg/kg, 50 mg/kg) as a fixed effect and baseline value and time since DMD diagnosis as covariates.

3.2.4.2 Analyses of 6MWT

As shown in Table 4, placebo-treated patients experienced a mean decline of 17.3 meters in 6MWT from baseline to Week 24, while patients in the 30 and 50 mg/kg eteplirsen groups showed mean declines of 134.8 and 2.3 meters, respectively. ANCOVA for ranked data showed no nominally significant differences between the treatment groups. The result of the MMRM analysis showed a nominally statistically significant difference between the placebo and 30 mg/kg eteplirsen groups, in favor of placebo (p=0.026; Table 4).

Table 4: Analysis Results of Change from Baseline in 6MWT

	Placebo	30mg/kg Eteplirsen N = 4	30mg/kg Eteplirsen mITT N = 2	50mg/kg Eteplirsen N = 4
Baseline				
Mean	394.5	355.3	407	396
Median	379	359	407	395
SD(SE)	42.25(21.12)	74.78(37.39)	49.50(35.00)	26.61(13.30)
Min, Max	364, 456	261, 442	372, 442	365, 429
Week 24				
Mean	377.3	220.5	394.5	393.8
Median	377.5	204	394.5	403.5
SD (SE)	19.00 (9.50)	203.14 (101.57)	51.62 (36.50)	53.67 (26.84)
Min, Max	354, 400	43, 431	358, 431	325, 443
Change at Week 24				
Mean	-17.3	-134.8	-12.5	-2.3
Median	-12	-116	-12.5	1.5
SD (SE)	28.06 (14.03)	144.71 (72.36)	2.12 (1.50)	29.89 (14.95)
Min, Max	-56, 11	-296, -11	-14, -11	-40, 28
treatment effect*		-102.4		25.6
95% CI *		(-192.2, -12.5)		(-62.7, 113.8)
P-value *		0.026		0.563

*Based on mixed model repeated measures (MMRM).

Source: Table 14.2.5.2.1 and Table 14.2.5.2.2 of Study 201 CSR,

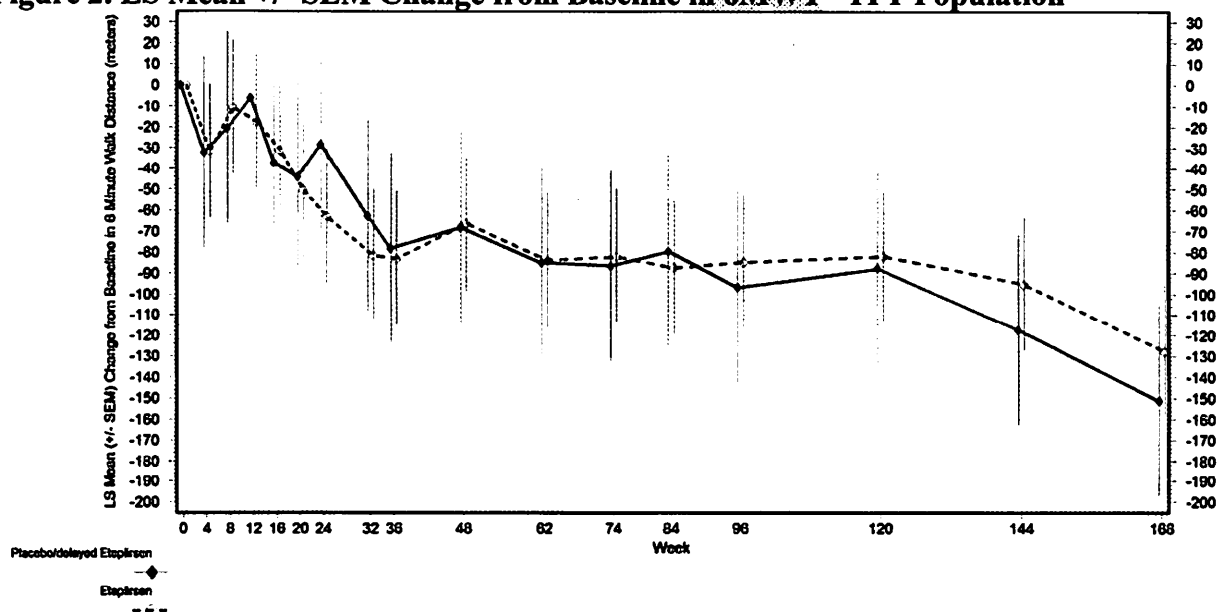
The applicant stated that the large decline in the 30 mg/kg eteplirsen group was attributable to Patients 009 and 010, who showed signs of rapid disease progression within weeks after enrollment. Therefore, the applicant conducted *post-hoc* analyses using Modified Intent-to-Treat (mITT) Population which excluded those 2 patients. For the mITT population, the mean change from baseline to Week 24 in MWT was a decline of 12.5 meters for the 30 mg/kg eteplirsen group. Both ANCOVA on ranked data and the MMRM analysis showed no nominally significant differences between the treatment groups in mITT.

The mITT population was not pre-specified in the SAP. Moreover, the mITT was defined based on the outcome data (instead of enrollment criteria or baseline character). Therefore, analysis on the mITT population could be misleading.

3.2.4.3 Analyses of the open-label extension study (described by the applicant as Study 202)

The 6MWT at Week 168 was compared between the combined eteplirsen group and placebo/delayed eteplirsen group. Analyses on ITT population did not achieve nominal statistical significance ($p=0.68$ by MMRM). The changes from baseline in 6MWT by assessment week for the combined eteplirsen group and placebo/delayed eteplirsen group are shown in Figure 2.

Figure 2. LS Mean +/- SEM Change from Baseline in 6MWT - ITT Population



Source: Figure 14.2.5.2.2.1 of Study 202 CSR.

3.2.4.4 Comparison against Historical Controls

Historical Control Cohort

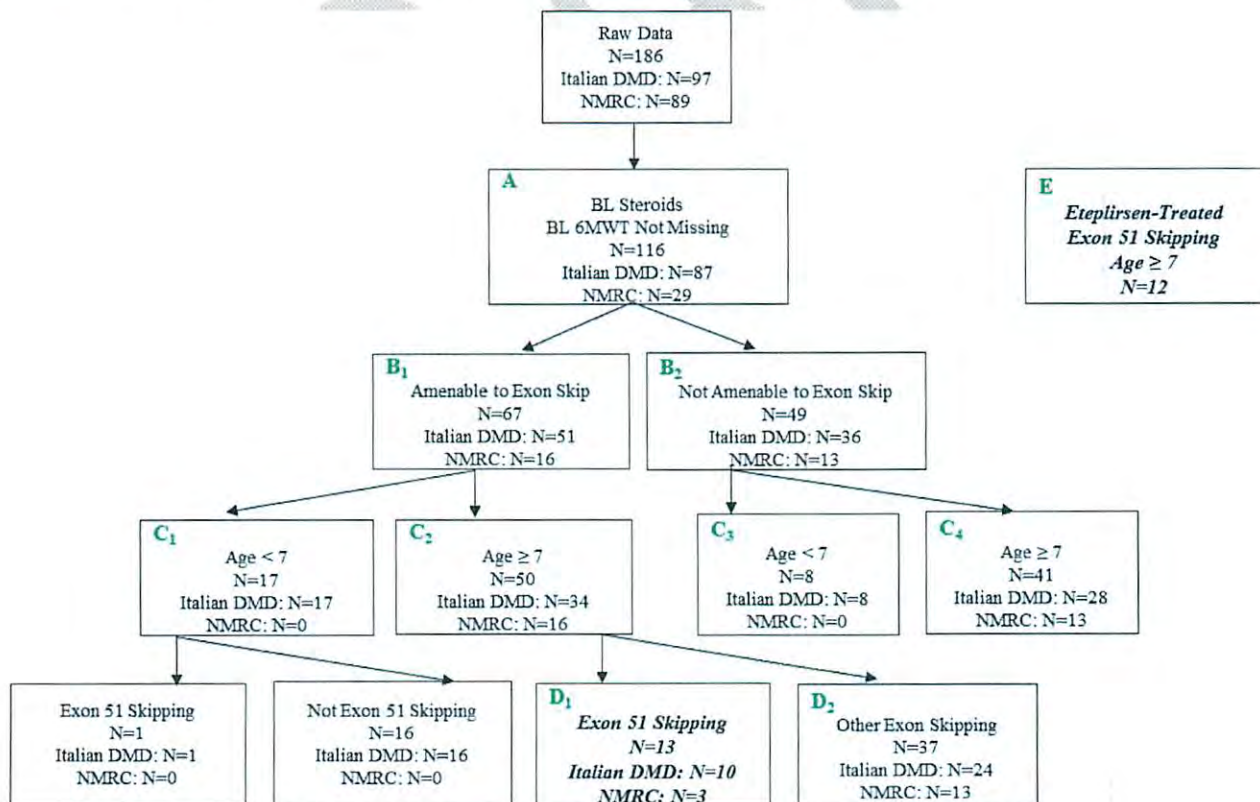
The comparison of eteplirsen with historical controls was not part of an adequate and well-controlled study. The applicant obtained historical data after observations were made for the eteplirsen patients. Historical data were obtained from 2 DMD patient registries (Italian DMD Registry and the Leuven Neuromuscular Reference Center – NMRC) for comparison to eteplirsen-treated patients. The following filters were applied to try to match patients in the historical control cohort:

1. Corticosteroid use at Baseline (use/non-use)
2. Sufficient longitudinal data for 6MWT available
3. Age ≥ 7 years
4. Genotype amenable to any exon skipping therapy
5. Genotype amenable to exon 51 skipping therapy

The Italian DMD registry is a longitudinal multicenter observational cohort study involving 11 tertiary neuromuscular centers in Italy. Patients were recruited between January 2008 and June 2010 and were to be followed for at least three years. The Italian DMD cohort contained the 6MWT results at Baseline (Month 0) and at Months 12, 24, and 36, with age and steroid use entered for each visit and with genotype information for 97 patients. Of these patients, 10 valid cases were identified based on applying the 5 filters.

The NMRC registry was an observational, single center, cohort study of DMD up to 17.5 years of age attending the NMRC between January 2007 and September 2012. The NMRC dataset contained 6MWT results at various time points, the patient's age and steroid use at the same time points, and genotype information for 89 patients. However, discrete visit designations (i.e., Baseline, Month 12, etc.) were not identified in the dataset. The first time points with non-zero meters on the 6MWT assessment for patients who were ≥ 7 years of age and on a steroid, were designated as the Baseline visit. Only 3 cases were identified based on applying filters (Figure 3).

Figure 3: Historical Controls and Eteplirsen-Treated Cohort



Source: Figure 1 of Study SR-15-031 CS.

Applicant’s Comparison of Eteplirsen with Historical Control

The results for 6MWT in eteplirsen-treated patients compared with historical controls matched on all 5 criteria mentioned above are shown in Table 5. The difference in LS mean change from baseline on 6MWT at 36 months was 141 meters. The nominal p-value reported by the applicant is not meaningful because the open label extension with historical control comparison was not an adequate and well-controlled study, for the reasons described below.

Table 5: Applicant’s Result of 6MWT in Eteplirsen Compared to Historical Controls

Patients Included	Groups Compared		Age	6MWT Baseline	6MWT Month 36**
HC + eteplirsen-treated, Steroid-Treated, Amenable to Exon 51 Skipping, ≥7 years old	HC	N	13	13	11
		Mean / LS Mean ^a (SE)	9.45 (0.403)	357.6 (18.51)	115.1 (33.54)
		Min, Max	7.3, 11.8	200, 458	
	eteplirsen-treated	N	12	12	12
		Mean / LS Mean ^a (SE)	9.41 (0.342)	363.2 (12.18)	256.4 (33.11)
		Min, Max	7.3, 11.0	256, 416	

* LS Mean for 6MWT Month 36 only

** LS Mean difference =141 and p=0.009 at month 36.

Source: Applicant’s analyses with output table modified by the reviewer.

Reviewer’s Discussion and Conclusion of the Historical Control Study

According to the ICH E10 guidance on Control Group and Related Issues in Clinical Trials, the major and well-recognized limitation of externally controlled (including historical control) trials is inability to control bias. The test group and control group can be dissimilar with respect to a wide range of observable and unobservable factors that could affect outcome. It may be possible to match the historical control group to the test group in observed factors but there is no assurance for any unobserved factors. “The lack of randomization and blinding, and the resultant problems with lack of assurance of comparability of test group and control group, make the possibility of substantial bias inherent in this design and impossible to quantitate.”

Because of the serious concern about the inability to control bias, the use of the external control design is restricted only to unusual circumstances.

1. ICH E10 states that “an externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable...” However, such prior belief does not exist for eteplirsen.
2. ICH E10 states that “use of external controls should be limited to cases in which the endpoints are objective...” However, performance on the 6-minute walk test can be

influenced by motivation. Patients may not achieve maximal 6MWT due to concerns of falling or injury, or patients could try harder with encouragement and with the expectation that the drug might be effective.

3. Pocock's criteria¹ for acceptability of a historical control group require that "the methods of treatment evaluation must be the same," and "the previous study must have been performed in the same organization with largely the same clinical investigators." This is especially important when assessing endpoints such as 6MWT, in contrast to hard endpoints such as mortality. For this NDA, these requirements are not met.

Moreover, the historical control group was identified *post-hoc* in this NDA, leading to potential selection bias that cannot be quantitated. If a historical control is to be utilized, selection of the control group and matching on selection criteria should be prospectively planned without knowing the outcome of the drug group and control group.

Based on ICH E10, "a consequence of the recognized inability to control bias is that the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials." The success criteria for this historical control study were not discussed or pre-specified in the protocol.

Given all these concerns, including issues of comparability of eteplirsen-treated patients and historical control cohort patients, the fact that 6MWT is not a "hard" efficacy endpoint, the potential of selection bias due to the *post-hoc* identification of the control cohort by the applicant, and all the known pitfalls with the use of historical controls, the comparison of the eteplirsen with the historical control is not statistically interpretable.

3.3 Evaluation of Safety

Please see the clinical review.

¹ Pocock SJ. The combination of randomized and historical controls in clinical trials. *Journal of Chronic Diseases*. 1976; 29:175-188.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses are not applicable as the study 201 was conducted at a single site in the US and all 12 patients were 7 to 10-year old male and, except for one patient of Asian descent, all were white.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study 201 was designed as an exploratory study. No multiplicity adjustment was specified for testing multiple doses and/or multiple endpoints.

The sample sizes of both Study 201 and the historical control study are very small. The robustness of the study result is a concern since a single patient can change the results substantially. The interpretation of results is also difficult because the sample may not represent the DMD patient population at large. Small studies can be useful for hypothesis generating but usually do not have the ability to provide definitive evidence for a drug's effect.

5.2 Collective Evidence

In Study 201, there was no statistically significant difference between the 50 mg/kg eteplirsen group and placebo at Week 12 ($p=0.958$). Treatment with 30 mg/kg eteplirsen for 24 weeks increased the mean percentage of dystrophin-positive muscle fibers in DMD patients compared to placebo; however, the nominal p value (0.002) can only be considered exploratory due to the lack of multiplicity control.

The MMRM analysis of 6MWT at Week 24 in Study 201 showed a statistically significant difference between the placebo and 30 mg/kg eteplirsen groups, in favor of placebo ($p=0.026$). There was no statistically significant difference between the 50 mg/kg eteplirsen group and the placebo ($p=0.563$). These results must be considered as exploratory only.

The open-label extension with historical control is not statistically interpretable.

5.3 Conclusions and Recommendations

The data overall did not provide statistical evidence to support the efficacy in subjects who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

Philips, Howard

From: Temple, Robert
Sent: Tuesday, May 03, 2016 3:51 PM
To: Unger, Ellis
Subject: RE: Eteplirsen review: ONE SCIENTIFIC POINT. [Slight correction to previous email]

I did not respond to him.

From: Unger, Ellis
Sent: Monday, May 02, 2016 9:31 PM
To: Temple, Robert
Subject: RE: Eteplirsen review: ONE SCIENTIFIC POINT. [Slight correction to previous email]

Did you answer this guy and ask for additional information? Apparently someone from FDA did...

From: Temple, Robert
Sent: Wednesday, April 27, 2016 3:30 PM
To: Unger, Ellis; Bastings, Eric; Dunn, Billy; Farkas, Ronald
Subject: FW: Eteplirsen review: ONE SCIENTIFIC POINT. [Slight correction to previous email]

From: Himanshu Gupta (b) (6)
Sent: Wednesday, April 27, 2016 11:15 AM
To: Woodcock, Janet; Temple, Robert
Subject: Eteplirsen review: ONE SCIENTIFIC POINT. [Slight correction to previous email]

Please ignore the previous email — this completes a partial sentence in the previous email.

Dear Dr. Woodcock and Dr. Temple,

I am sorry to bother you both with this email, but due to its paramount importance I am compelled to write. I just want to convey one issue regarding Eteplirsen's review — in particular, regarding FDA's comparison of patients based on age and baseline, at points other than "baseline".

MY POINT: Consider two example patients X and Y who are both say 11 years old and have the same 6MWD of say 350. Patient X is untreated (control group), while Y has already been on Eteplirsen for 2 years (i.e., since he was 9 years old). If Eteplirsen is efficacious (important assumption), then Y's disease severity is likely to be worse than that of X, and thus X and Y are not comparable.

REASON: Note Y's 6mwd is 350 only because of 2-year treatment with Eteplirsen, which presumably preserved his 6 MWD but perhaps didn't alter his inherent disease condition. Thus, Y's 6 MWD at 11 years may not be an accurate representation of his overall disease severity. In other words, their baseline characteristics could be very different. My argument may be speculative — but I believe its rational enough to seriously question the comparison between X and Y. **This calls into question the analysis presented by FDA review team in Figures 3, 6, 7, 8, (of the memorandum by Dr. Dunn) and Figures 8, 9, 10, 11, 13, 16, 19, 20, 22 (of the memorandum by Dr. Farkas).**

The above point has been made by Sarepta too (e.g., in their addendum), but I thought I'll offer an independent and different perspective to you.

ABOUT ME: I'm an Associate Professor of Computer Science at Stony Brook University. I have a PhD in Computer Science from Stanford University. I am [REDACTED] ^{(b) (6)}, but by now am very emotionally involved with the whole cause. I have intimate knowledge of almost everything public pertaining the drug.

I would greatly appreciate an acknowledgement that you have READ the email. I have a few more points to convey, and if you are receptive to them, I would be happy to email them to you (in brief).

Thanks very much.
Himanshu

=====

Himanshu Gupta, PhD (Stanford)
Associate Professor of Computer Science
Stony Brook University, Stony Brook NY
<http://www.cs.stonybrook.edu/~hgupta>

Temple, Robert

From: Jenkins, John K
Sent: Thursday, May 05, 2016 8:38 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Temple, Robert; Dunn, Billy; Unger, Ellis; Jenkins, John K
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen
Attachments: response-to-05may16-clinical-ir-re-promovi-accrual.pdf

Janet

Attached is Sarepta's response to the question of how many boys have had a baseline and a second biopsy in the ongoing trial. There are 62 boys with baseline biopsies and 10 each with biopsies at week 24 and 48. Sarepta anticipates that we might ask them to do an interim analysis and states:

"Importantly, the protocol does not provide for an interim analysis for clinical or laboratory endpoints, and therefore any analysis prior to the end of study would require an amendment to protocol 4658-301. The estimated timeline for a protocol amendment—including document generation, submission to 37 clinical trial sites, and approval by IRBs—is 3 to 6 months."

Given that these data are significantly more than currently available for assessment of pre/post assay for dystrophin to support AA, the review team believes it would be very important to obtain these data before making a decision on approval. The 62 baseline samples would provide a very solid estimate of untreated patients and the data out to one year exceeds by 24 weeks the time point that Sarepta argues is required for dystrophin production to be observed. We cannot comment on the accuracy of Sarepta's statement about the need for IRB review and approval to perform an interim analysis and the timeline that would be required to obtain such approval.

What are your thoughts?

John

From: Bastings, Eric
Sent: Thursday, May 05, 2016 5:16 PM
To: Jenkins, John K; Unger, Ellis; Temple, Robert
Cc: Dunn, Billy; Farkas, Ronald
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

We have twenty patients with biopsies both at baseline and at a later timepoint (half at 24 weeks and half at 18 weeks).

Sarepta argues that it would take 3-6 months to make protocol changes and get IRB approval to do the analysis. I am not clear they would need IRB approval for that analysis.

Eric

From: Choy, Fannie (Yuet)
Sent: Thursday, May 05, 2016 5:10 PM
To: Bastings, Eric; Farkas, Ronald
Cc: Dunn, Billy; Choy, Fannie (Yuet)
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

Sarepta's response re: # of pts with 2nd biopsy. Thanks

Fannie

From: Matthew Rael [<mailto:MRael@Sarepta.com>]
Sent: Thursday, May 05, 2016 4:59 PM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Hi Fannie,

Please find attached our response to the information request from this morning.

Regards,

Matt

Matthew Rael, MS
Senior Manager, Regulatory Affairs
p 617.274.4029 c (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, 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 PROMOV1 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

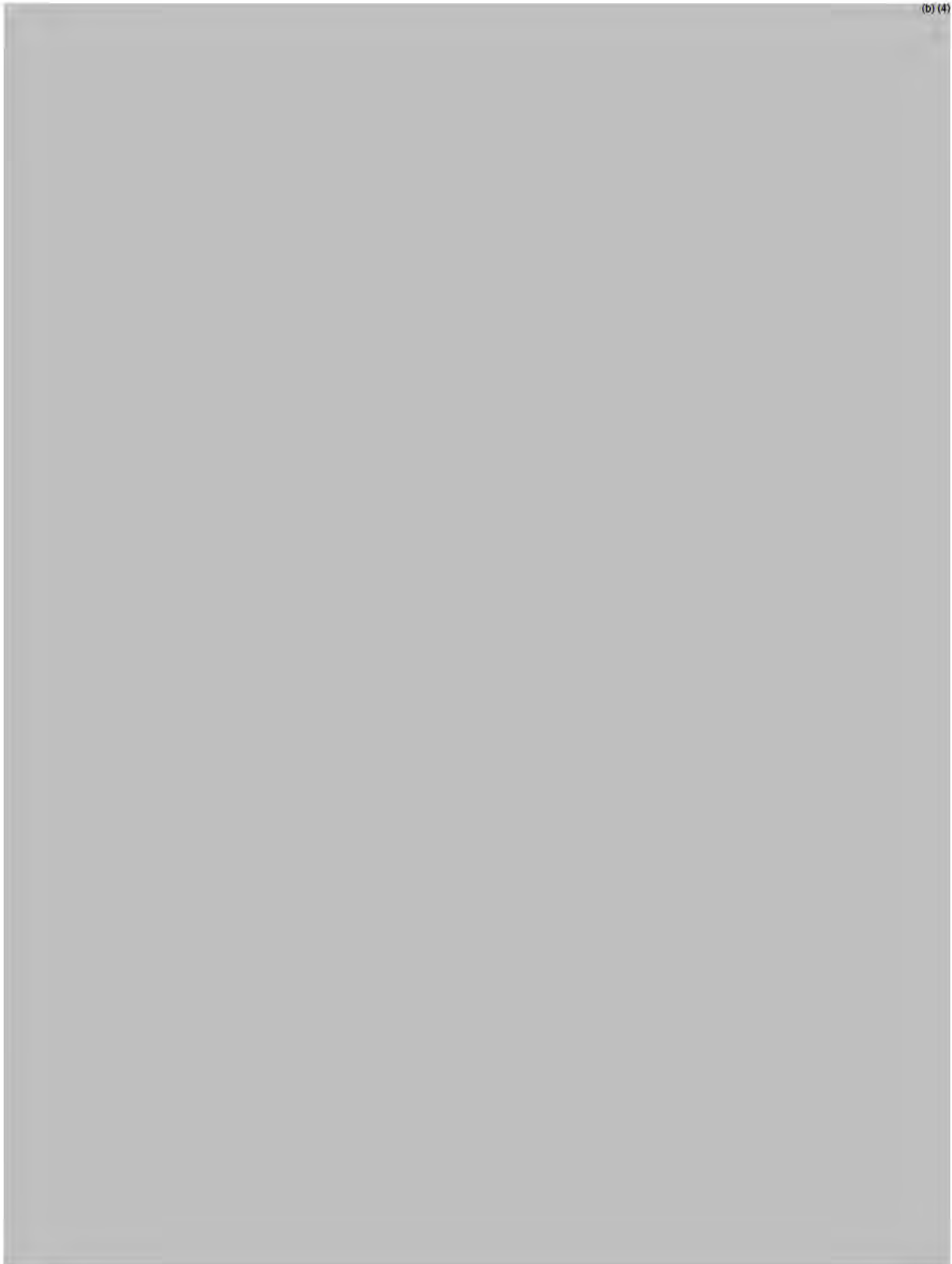
Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov

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Philips, Howard

From: Temple, Robert
Sent: Thursday, May 05, 2016 5:20 PM
To: Bastings, Eric; Jenkins, John K; Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Agree. Not clear why they need IRB approval. Study isn't blinded, so what would early data do to protocol. And even if they did, it's hard to see why it could not be done by phone. Perhaps it would help to be explicit on EXACTLY what we want them to do.

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Sent: Thursday, May 05, 2016 5:16 PM
To: Jenkins, John K; Unger, Ellis; Temple, Robert
Cc: Dunn, Billy; Farkas, Ronald
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

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Eric

From: Choy, Fannie (Yuet)
Sent: Thursday, May 05, 2016 5:10 PM
To: Bastings, Eric; Farkas, Ronald
Cc: Dunn, Billy; Choy, Fannie (Yuet)
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

Sarepta's response re: # of pts with 2nd biopsy. Thanks

Fannie

From: Matthew Rael [<mailto:MRael@Sarepta.com>]
Sent: Thursday, May 05, 2016 4:59 PM
To: Choy, Fannie (Yuet)
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Regards,

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p 617.274.4029 c (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

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Sent: Thursday, May 05, 2016 9:47 AM

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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.

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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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Philips, Howard

From: Bastings, Eric
Sent: Thursday, May 05, 2016 5:21 PM
To: Temple, Robert; Jenkins, John K; Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

We have not told them yet what to do. We only asked for the number of patients who had biopsies so far.

But they are obviously reading our intentions...

Eric

From: Temple, Robert
Sent: Thursday, May 05, 2016 5:20 PM
To: Bastings, Eric; Jenkins, John K; Unger, Ellis
Cc: Dunn, Billy; Farkas, Ronald
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Agree. Not clear why they need IRB approval. Study isn't blinded, so what would early data do to protocol. And even if they did, it's hard to see why it could not be done by phone. Perhaps it would help to be explicit on EXACTLY what we want them to do.

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Senior Manager, Regulatory Affairs

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215 First Street, Cambridge, MA 02142 USA

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

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Dear Shamim:

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Regards,
Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

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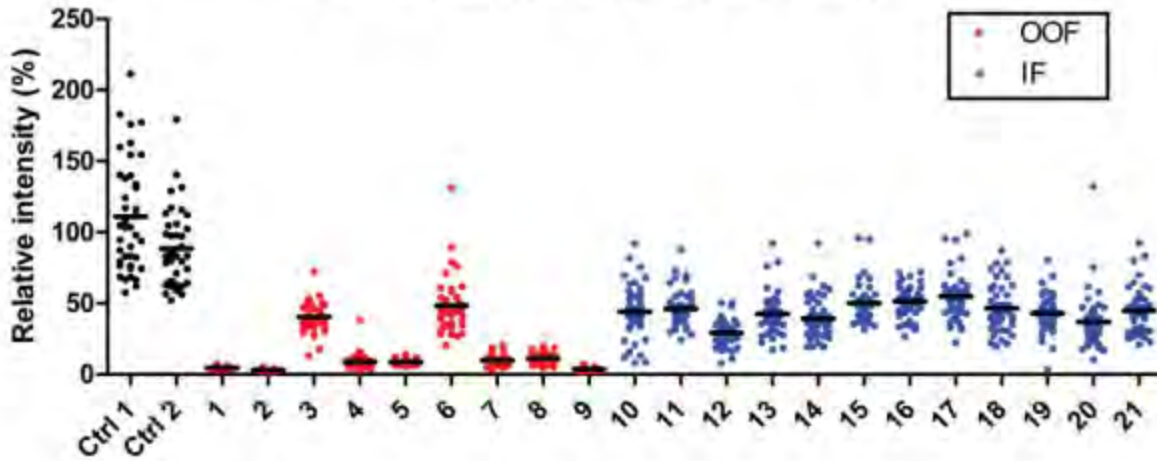
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Philips, Howard

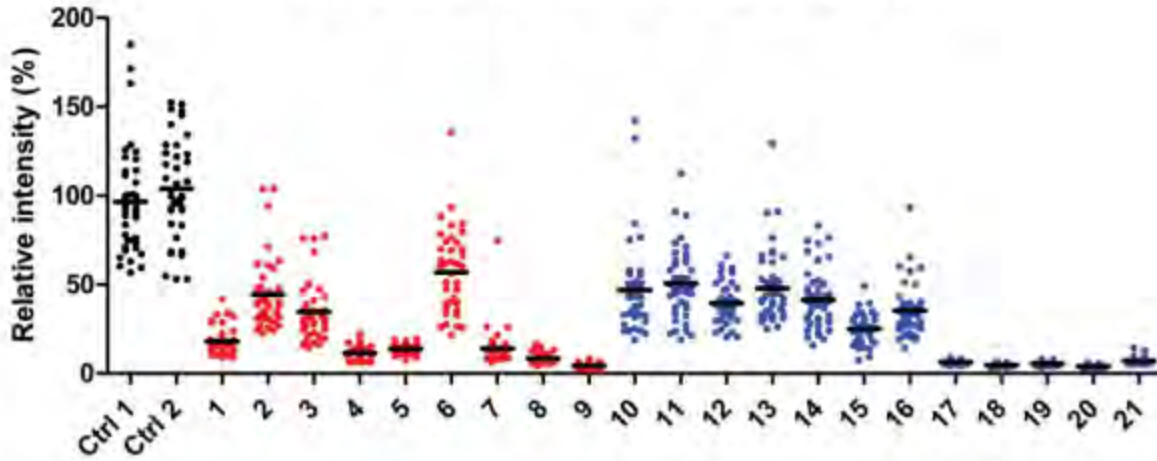
From: Farkas, Ronald
Sent: Thursday, May 05, 2016 12:58 PM
To: Bastings, Eric; Dunn, Billy; Rao, Ashutosh; Breder, Christopher D; Unger, Ellis; Temple, Robert
Subject: some additional explanation of dystrophin levels in exon 44 patients

There was additional discussion in the FDA presentation to the PCNS AC of data suggesting that dystrophin levels in exon 44 skippable patients with less severe phenotypes may be substantially higher than 1%. The figure below, from the supplemental material for Anthony et al (2014)²³ shows a comparative immunohistochemical analysis of dystrophin expression in patients with in-frame (IF) (blue) or out-of-frame (OOF) (red) deletions around exons 44 and 45. Patients 1 through 5 are exon 44 skippable, and patients 6 through 9 are exon 45 skippable.

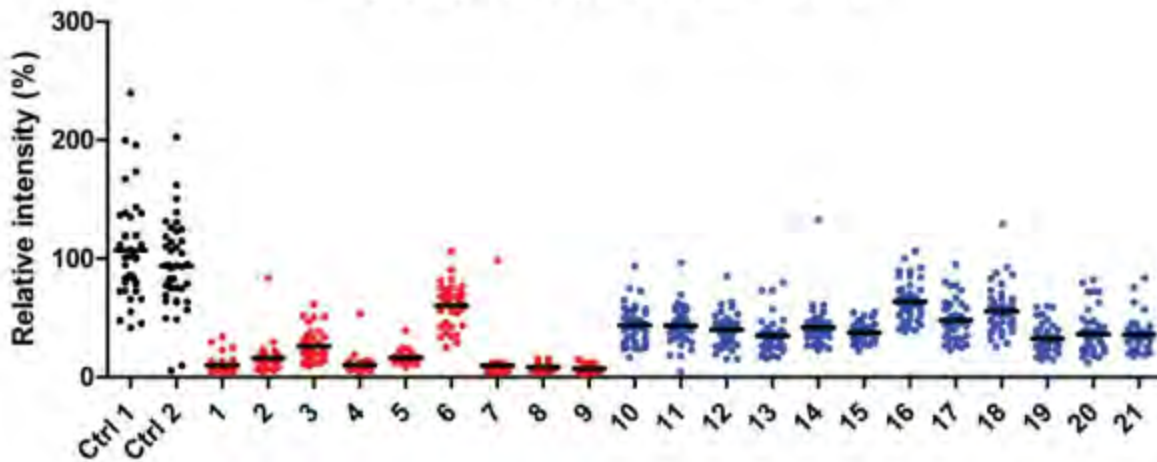
Dystrophin (Mandys 106, exon 43)



Dystrophin (MANEX50, exons 49-50)

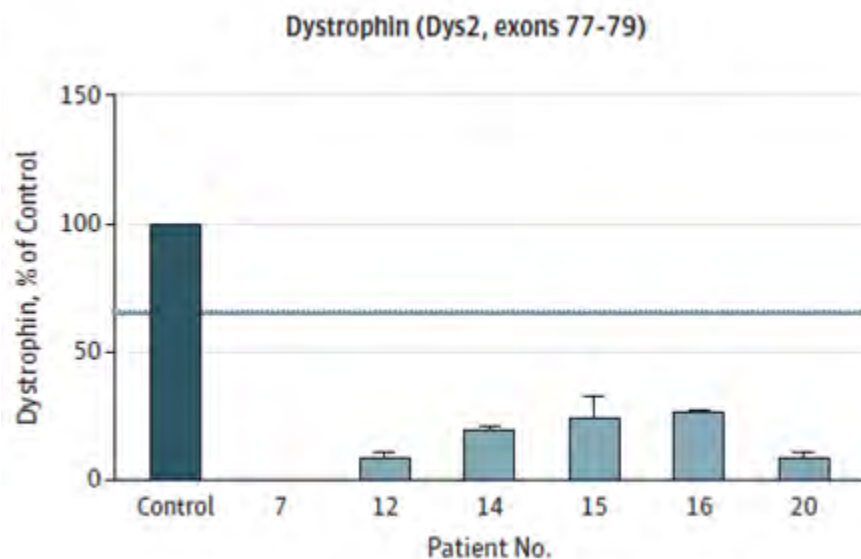


Dystrophin (Dys2, exons 77-79)



The following are key observations about this data:

- Among both exon 44 and 45 skippable patients, there is a wide range of relative dystrophin intensities. A number of other antibodies were used with results that were generally directionally consistent.
- Patients 3 and 6 had the highest dystrophin expression and the mildest course of disease progression, with Patient 3 reported as ambulant at age 17 years, not running, with difficulty climbing stairs, and Patient 6 reported as ambulant at age 37 years.
- The 4 other patients had dystrophin intensities that appeared to be lower, although results were not entirely consistent across the different antibodies. Patients 1 and 2 were walking indoors at age 15 years and 14 years, respectively, whereas Patient 4 lost ambulation at age 11, and Patient 5 lost ambulation at age 12.
- Dystrophin levels in patients 3 and 6 (and perhaps patient 2) appear to be similar to dystrophin levels in the in-frame BMD patients. Western blot data for Patients 7, 12, 14, 15, 16, and 20 are available [although not of ideal quality], and shown below (note that the blue horizontal line is the average dystrophin expression in exon 51 model BMD patients).



Importantly, because Patients 3, 6, and perhaps 2 have immunofluorescence levels similar to the in-frame BMD patients as measured within the same study, it may be reasonable to conclude that dystrophin levels by Western blot might also have been, if measured, roughly similar, somewhere between about 10% and 25% of normal. Even considering the potentially large degree of error in such a “cross-method comparison” dystrophin levels were likely substantially higher than 1% of normal in these exon 44 patients with milder clinical course.

Philips, Howard

From: Breder, Christopher D
Sent: Friday, May 06, 2016 3:02 PM
To: Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Dunn, Billy; Rao, Ashutosh; Bhattaram, Atul; Ligon, Sharnell (CDER); Kozauer, Nicholas; Hung, Hsien Ming J; Ling, Xiang; LaVange, Lisa; Jin, Kun; Nevius, S Edward; Rosenberg, Amy
Cc: Rawlings, Kimberly; Bolek, Michelle; Shreeve, Chris
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

Here is the paper using adaptive randomization I had described at the end of our meeting.



Regards,

Chris

Christopher D. Breder, MD PhD

WO22 4218
(301) 796-1365

-----Original Appointment-----

From: Diggs, Felicia

Sent: Monday, February 29, 2016 9:46 AM

To: Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Choy, Fannie (Yuet); Dunn, Billy; Breder, Christopher D; Rao, Ashutosh; Ware, Jacqueline H; Bhattaram, Atul; Ligon, Sharnell (CDER); Blount, Aprile; CDER 120 Calendar; Kozauer, Nicholas; Hung, Hsien Ming J; Ling, Xiang; LaVange, Lisa; Jin, Kun; Nevius, S Edward; Rosenberg, Amy

Cc: Rawlings, Kimberly; Bolek, Michelle; Shreeve, Chris

Subject: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

When: Wednesday, May 04, 2016 3:00 PM-4:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: WO BLDG 51, Rm 6139

Date: Wednesday, May 4, 2016 3:00 p.m. – 4:00 p.m.

WO BLDG, 51, Rm. 6139

Please note, there will not be handouts or presentation materials for this meeting.

Topic: Discuss application eteplirsen, NME (NDA 206488) Post Peripheral and Central Nervous System Advisory Committee Meeting

CDER Staff Contacts: Fannie Choy, RPMS

CDER Executive Operations Staff Contact: Felicia Diggs, DEO liaison

Invited Attendees: Janet Woodcock, Richard Moscicki, Robert Guidos, John Jenkins, Doug Throckmorton, Robert Temple, Felicia Diggs, Sharnell Ligon, Fannie Choy, Ellis Unger, Billy Dunn, Eric Bastings, Ronald Farkas, Veneeta Tandon, Christopher D Breder, Ashutosh Rao, Evelyn Mentari, Sally Jo Yasuda, Alice Hughes, Jackie Ware, Amy Rosenberg

Reason for Briefing: The purpose of this meeting is to discuss the outcome and plan of actions for application eteplirsen, NME (NDA 206488) post advisory committee meeting held on April 25, 2016. Eteplirsen proposed indication is for the treatment of patients with Duchene muscular dystrophy due to a deletion in the dystrophin gene that is amenable to exon 51 skipping.

Felicia Diggs invites you to an online meeting using WebEx.

Meeting ID: 743 273 026

Meeting Password: (b) (4)

To join this meeting

-
1. Go to <https://fda.webex.com/fda/j.php?MTID=ma7561b02ff9f34ee95154670c616a94>
 2. If requested, enter your name and email address.
 3. If a password is required, enter the meeting password: (b) (4)
 4. Click "Join".
 5. Follow the instructions that appear on your screen.

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-
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ORIGINAL ARTICLE

Calcitonin Gene–Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine

Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Husstedt, M.D., Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, Ph.D., Stephane Pollentier, M.D., and Lyrna M. Lesko, M.D., for the BIBN 4096 BS Clinical Proof of Concept Study Group

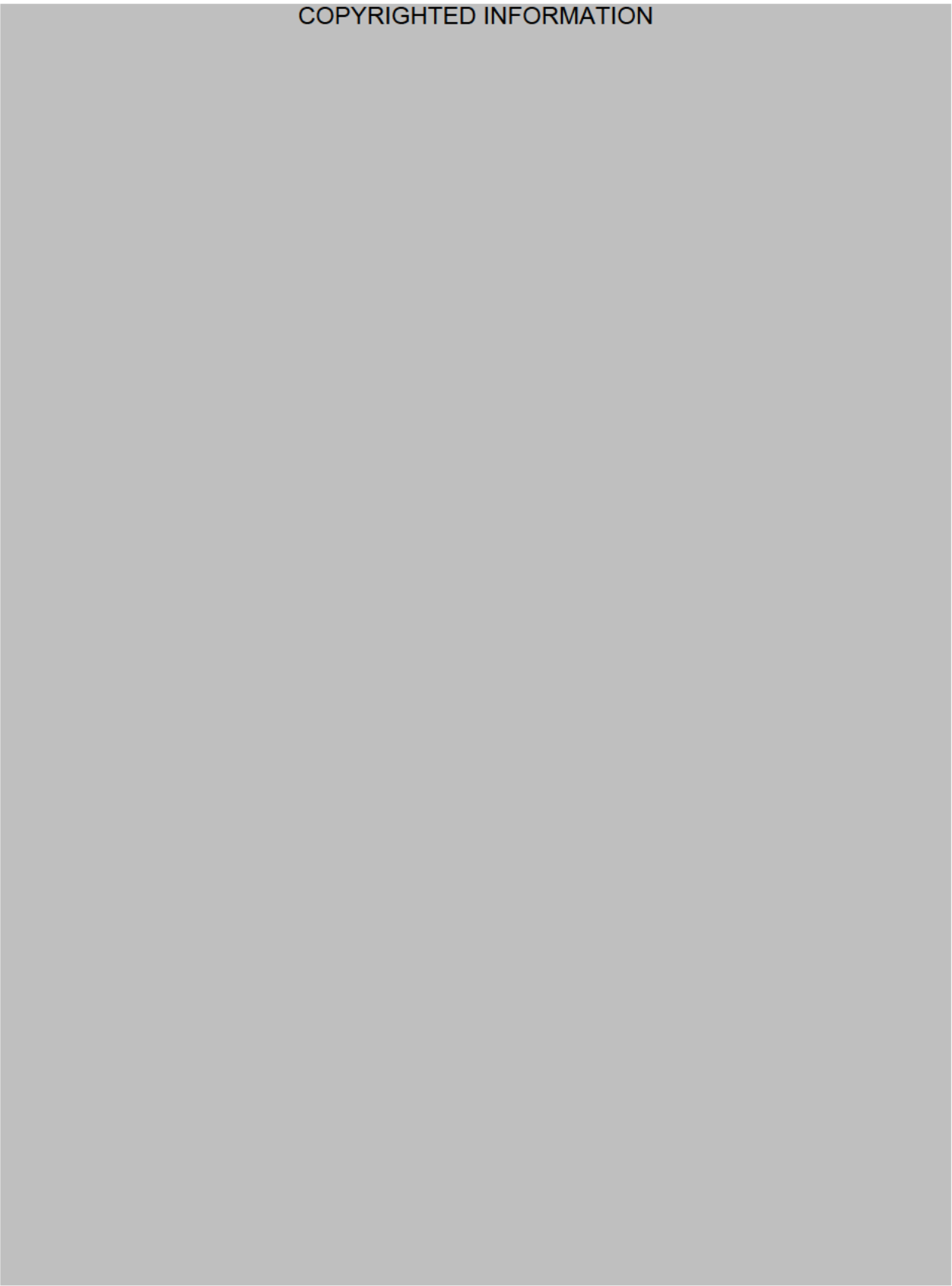
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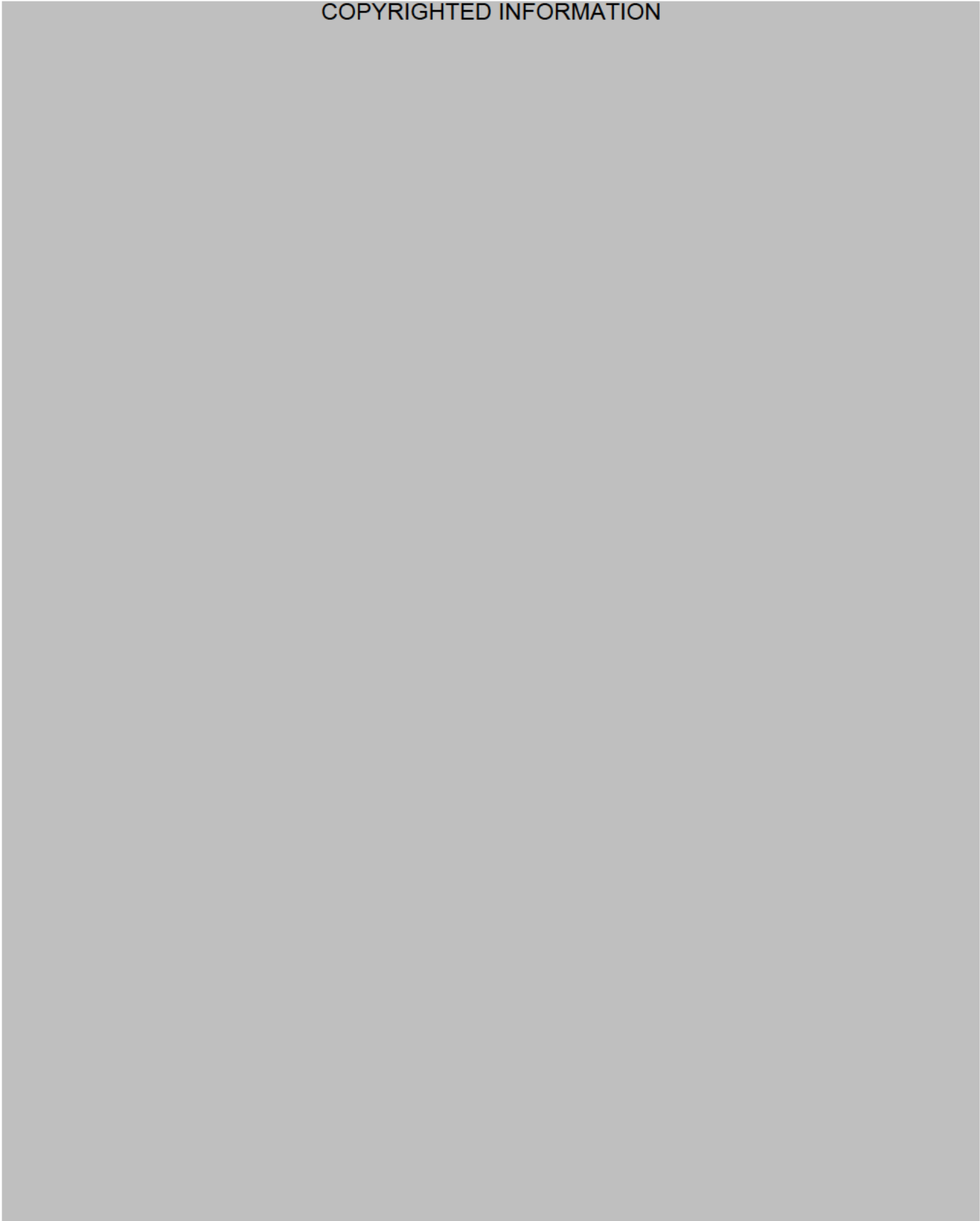
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Temple, Robert

From: Woodcock, Janet
Sent: Sunday, May 08, 2016 10:08 AM
To: Jenkins, John K
Cc: Temple, Robert; Dunn, Billy; Jenkins, John K; Unger, Ellis; Moscicki, Richard
Subject: Re: FDA Information Request: re: NDA 206488 / eteplirsen

Glad to hear they are getting these biopsies and sorry they will take some time to read out. Although these would have provided much more certainty one way or another re dystrophin production the fact that they can't be gotten soon means the situation is unchanged from my point of view so I would like to proceed as discussed. Thanks. Jw

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: May 5, 2016 at 8:37:41 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Cc: Unger, Ellis <Ellis.Unger@fda.hhs.gov>, Moscicki, Richard <Richard.Moscicki@fda.hhs.gov>, Dunn, Billy <Billy.Dunn@fda.hhs.gov>, Jenkins, John K <John.Jenkins@fda.hhs.gov>, Temple, Robert <Robert.Temple@fda.hhs.gov>
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

Janet

Attached is Sarepta's response to the question of how many boys have had a baseline and a second biopsy in the ongoing trial. There are 62 boys with baseline biopsies and 10 each with biopsies at week 24 and 48. Sarepta anticipates that we might ask them to do an interim analysis and states:

"Importantly, the protocol does not provide for an interim analysis for clinical or laboratory endpoints, and therefore any analysis prior to the end of study would require an amendment to protocol 4658-301. The estimated timeline for a protocol amendment—including document generation, submission to 37 clinical trial sites, and approval by IRBs—is 3 to 6 months."

Given that these data are significantly more than currently available for assessment of pre/post assay for dystrophin to support AA, the review team believes it would be very important to obtain these data before making a decision on approval. The 62 baseline samples would provide a very solid estimate of untreated patients and the data out to one year exceeds by 24 weeks the time point that Sarepta argues is required for dystrophin production to be observed. We cannot comment on the accuracy of Sarepta's statement about the need for IRB review and approval to perform an interim analysis and the timeline that would be required to obtain such approval.

What are your thoughts?

John

From: Bastings, Eric
Sent: Thursday, May 05, 2016 5:16 PM

To: Jenkins, John K; Unger, Ellis; Temple, Robert
Cc: Dunn, Billy; Farkas, Ronald
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

We have twenty patients with biopsies both at baseline and at a later timepoint (half at 24 weeks and half at 18 weeks).

Sarepta argues that it would take 3-6 months to make protocol changes and get IRB approval to do the analysis. I am not clear they would need IRB approval for that analysis.

Eric

From: Choy, Fannie (Yuet)
Sent: Thursday, May 05, 2016 5:10 PM
To: Bastings, Eric; Farkas, Ronald
Cc: Dunn, Billy; Choy, Fannie (Yuet)
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

Sarepta's response re: # of pts with 2nd biopsy. Thanks

Fannie

From: Matthew Rael [<mailto:MRael@Sarepta.com>]
Sent: Thursday, May 05, 2016 4:59 PM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Hi Fannie,

Please find attached our response to the information request from this morning.

Regards,

Matt

Matthew Rael, MS
Senior Manager, Regulatory Affairs
p 617.274.4029 c (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, 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
301-796-9842 fax
fannie.choy@fda.hhs.gov

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Philips, Howard

From: LaVange, Lisa
Sent: Monday, May 09, 2016 9:43 AM
To: Breder, Christopher D; Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Dunn, Billy; Rao, Ashutosh; Bhattaram, Atul; Ligon, Sharnell (CDER); Kozauer, Nicholas; Hung, Hsien Ming J; Ling, Xiang; Jin, Kun; Nevius, S Edward; Rosenberg, Amy
Cc: Rawlings, Kimberly; Bolek, Michelle; Shreeve, Chris; LaVange, Lisa
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

I was not able to attend the briefing last week but noticed the circulation of this article illustrating adaptive randomization in a clinical trial. There have been several publications recently in the statistical literature on the pros and cons of outcome-adaptive randomization, and a general consensus is evolving that these designs are not beneficial in two-arm trials but may be with multiple randomization arms. The article by Hey and Kimmelman (Clinical Trials, 2015) touches on the ethical aspects of adaptive randomization, and no fewer than six commentaries were published with this article, plus a rejoinder from the original authors! The commentary by Don Berry may be of interest, and also that of Korn and Freidlin. See attached.



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Lisa

From: Breder, Christopher D
Sent: Friday, May 06, 2016 3:02 PM
To: Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Dunn, Billy; Rao, Ashutosh; Bhattaram, Atul; Ligon, Sharnell (CDER); Kozauer, Nicholas; Hung, Hsien Ming J; Ling, Xiang; LaVange, Lisa; Jin, Kun; Nevius, S Edward; Rosenberg, Amy
Cc: Rawlings, Kimberly; Bolek, Michelle; Shreeve, Chris
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

Here is the paper using adaptive randomization I had described at the end of our meeting.

<< File: NEJM Adaptive Randomization Paper.pdf >>
Regards,

Chris

Christopher D. Breder, MD PhD

WO22 4218
(301) 796-1365

-----Original Appointment-----
From: Diggs, Felicia

Sent: Monday, February 29, 2016 9:46 AM

To: Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Choy, Fannie (Yuet); Dunn, Billy; Breder, Christopher D; Rao, Ashutosh; Ware, Jacqueline H; Bhattaram, Atul; Ligon, Sharnell (CDER); Blount, Aprile; CDER 120 Calendar; Kozauer, Nicholas; Hung, Hsien Ming J; Ling, Xiang; LaVange, Lisa; Jin, Kun; Nevius, S Edward; Rosenberg, Amy

Cc: Rawlings, Kimberly; Bolek, Michelle; Shreeve, Chris

Subject: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

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Date: Wednesday, May 4, 2016 3:00 p.m. – 4:00 p.m.

WO BLDG, 51, Rm. 6139

Please note, there will not be handouts or presentation materials for this meeting.

Topic: Discuss application eteplirsen, NME (NDA 206488) Post Peripheral and Central Nervous System Advisory Committee Meeting

CDER Staff Contacts: Fannie Choy, RPMS

CDER Executive Operations Staff Contact: Felicia Diggs, DEO liaison

Invited Attendees: Janet Woodcock, Richard Moscicki, Robert Guidos, John Jenkins, Doug Throckmorton, Robert Temple, Felicia Diggs, Sharnell Ligon, Fannie Choy, Ellis Unger, Billy Dunn, Eric Bastings, Ronald Farkas, Veneeta Tandon, Christopher D Breder, Ashutosh Rao, Evelyn Mentari, Sally Jo Yasuda, Alice Hughes, Jackie Ware, Amy Rosenberg

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Meeting ID: 743 273 026

Meeting Password: (b) (4)

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Commentary on Hey and Kimmelman

Edward L Korn and Boris Freidlin

Clinical Trials

13

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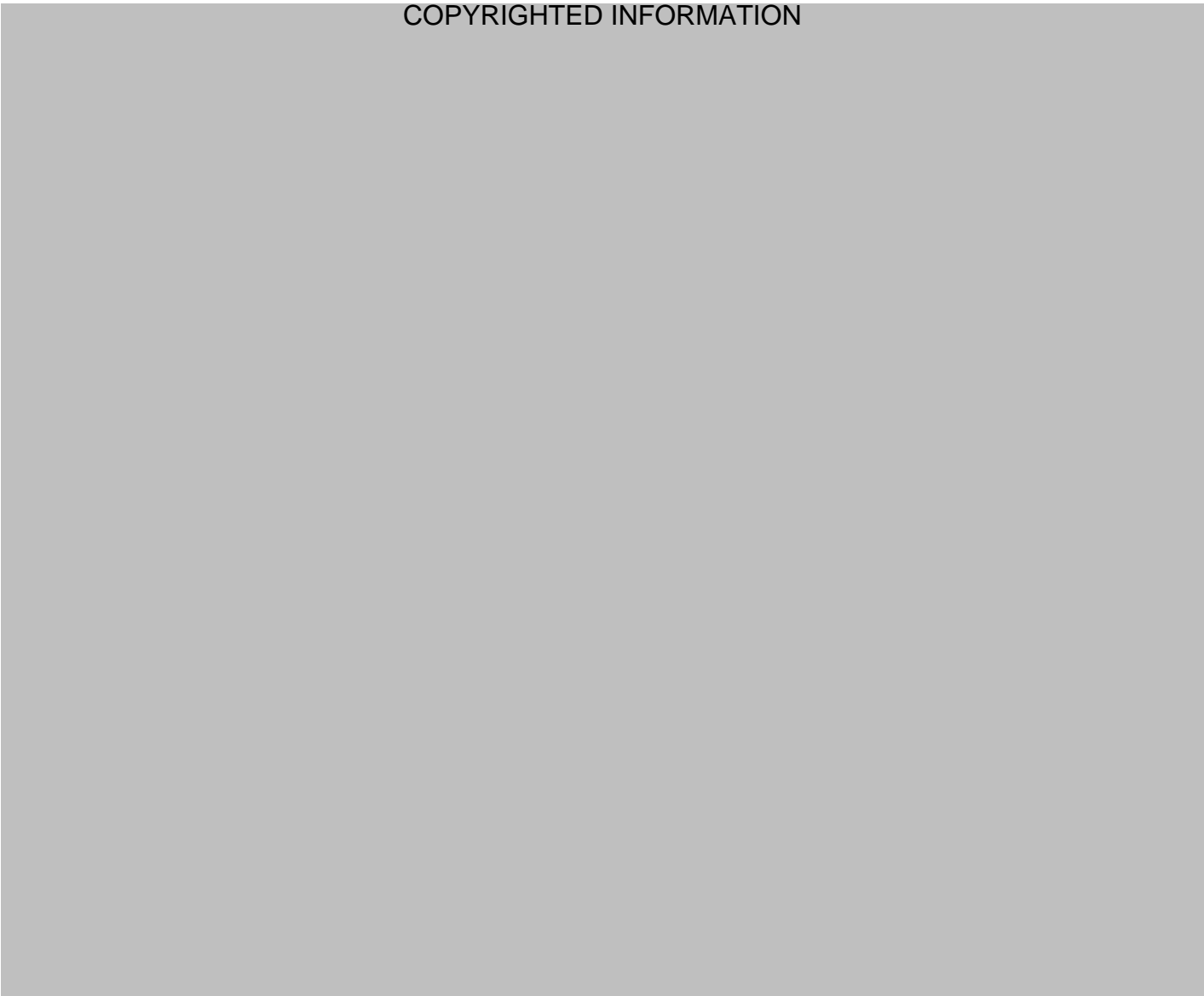


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Commentary on Hey and Kimmelman

Donald A Berry

Clinical Trials

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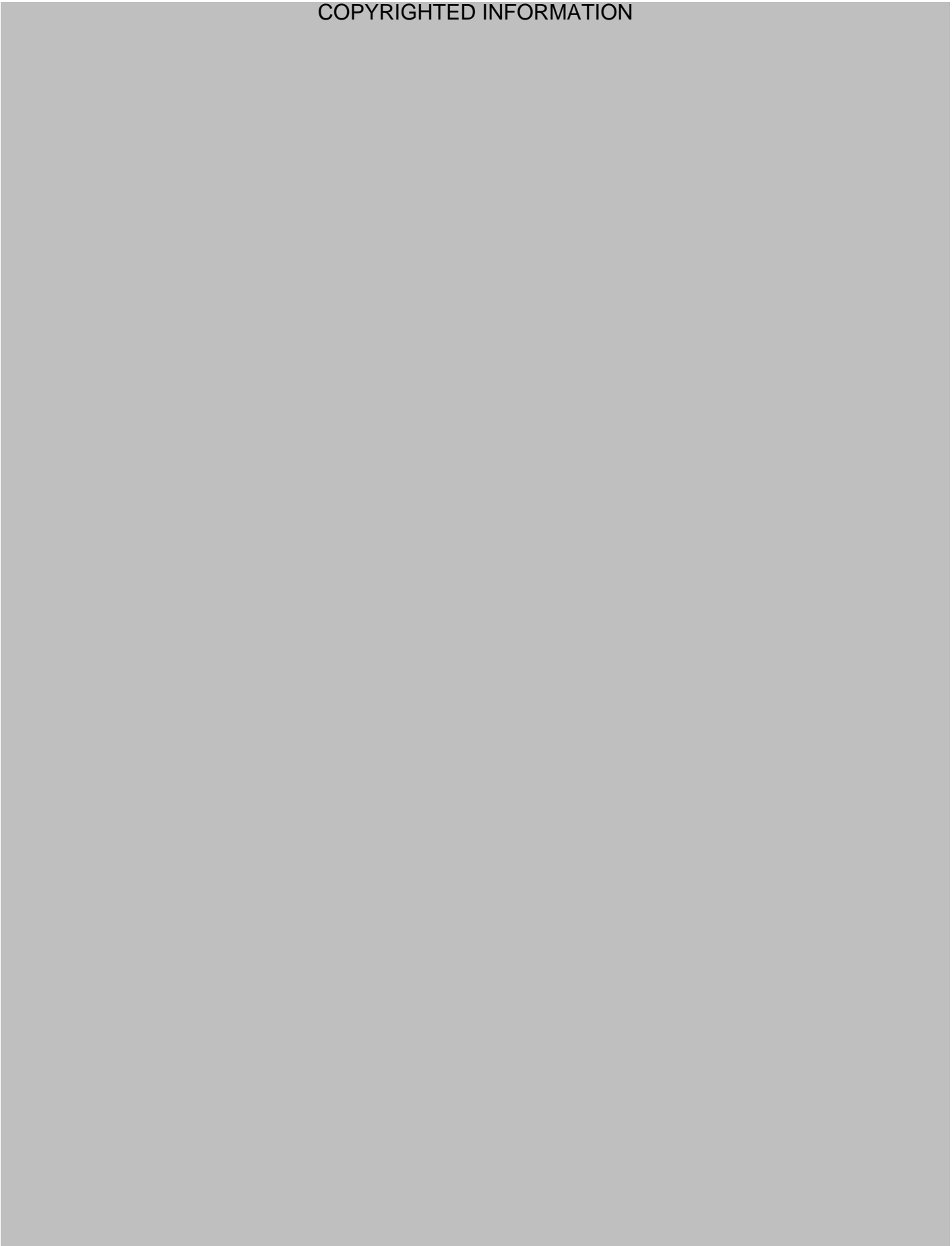
DOI: 10.1177/1740774515569011

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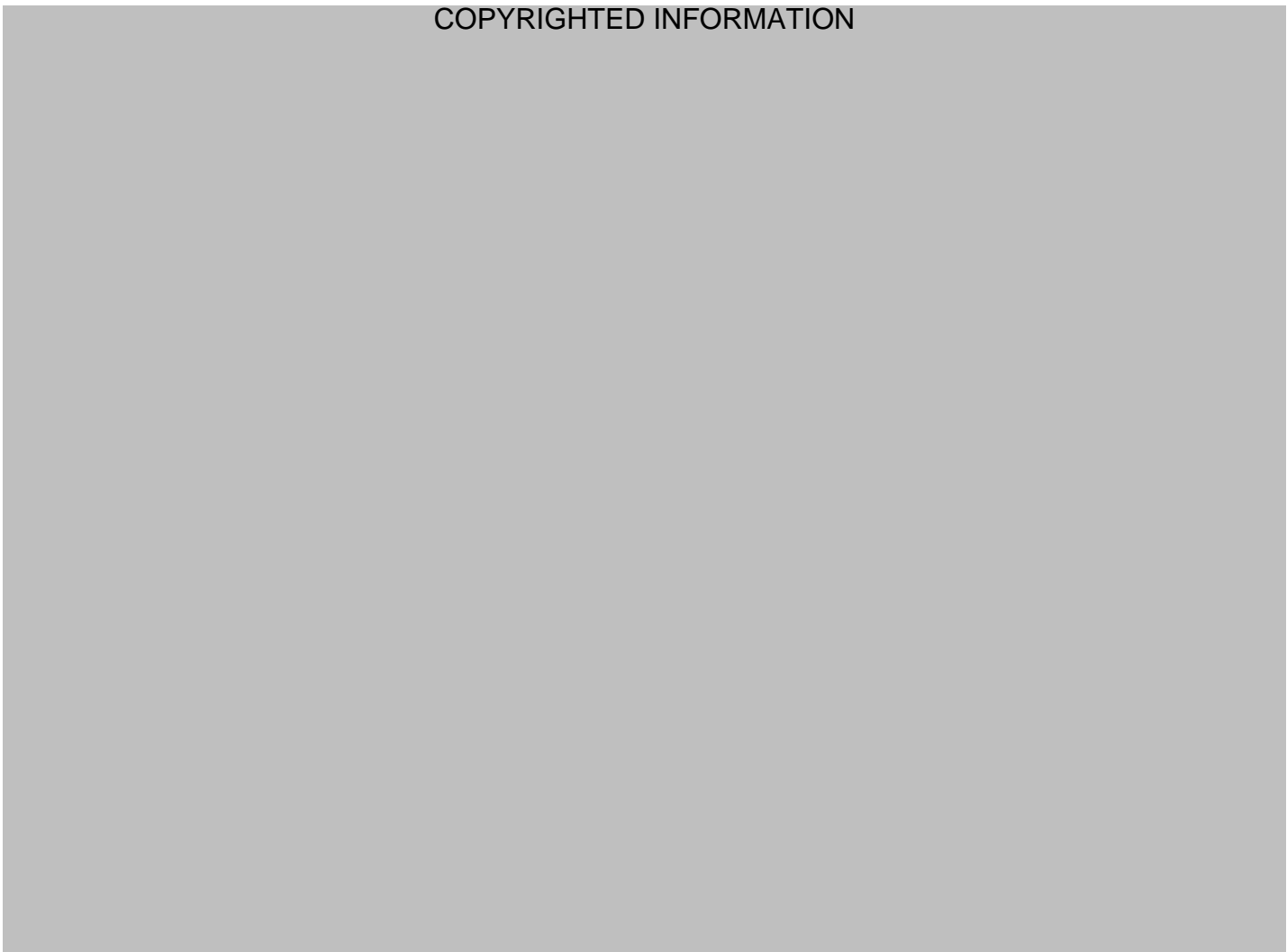


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Are outcome-adaptive allocation trials ethical?

Spencer Phillips Hey and Jonathan Kimmelman

Clinical Trials

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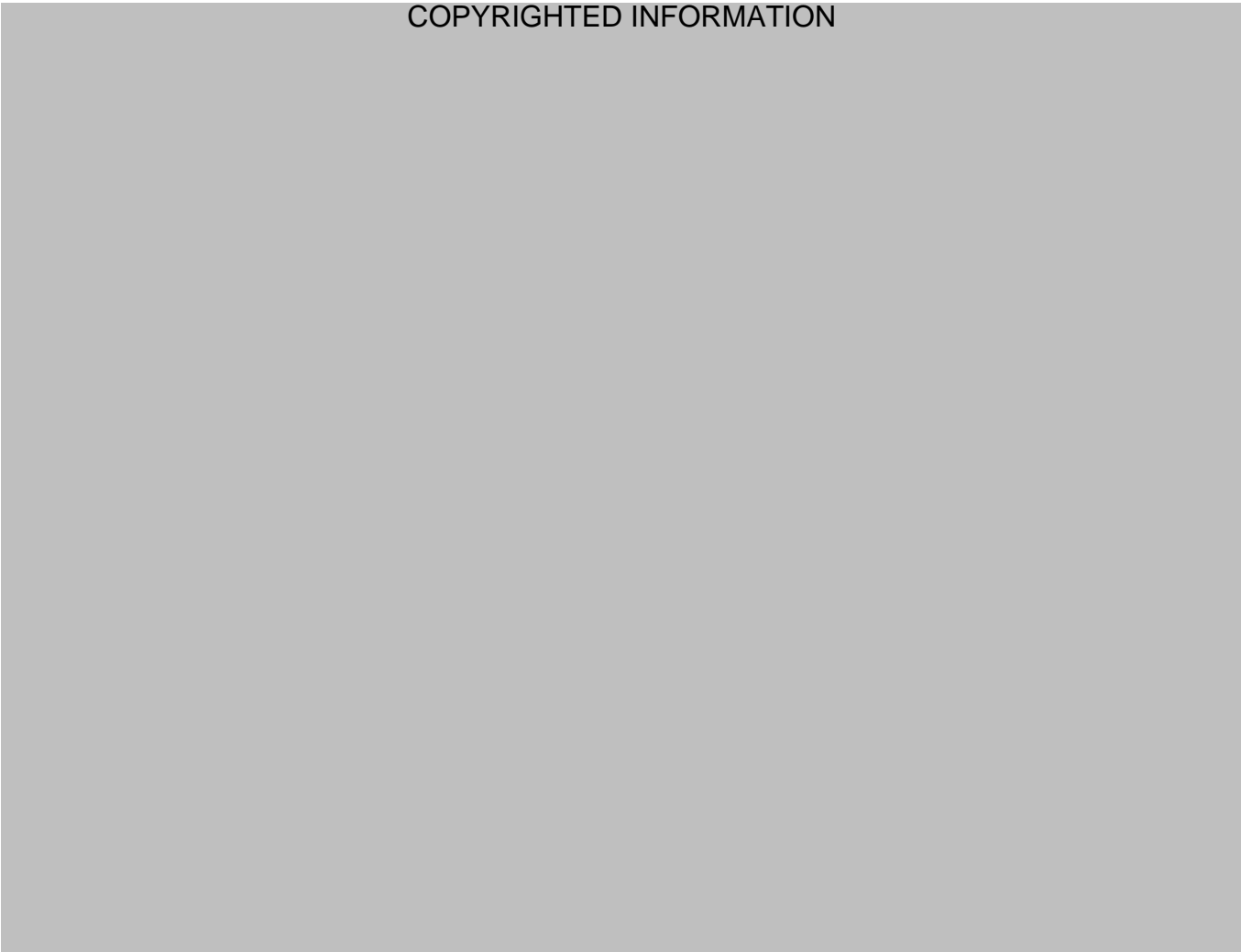


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Philips, Howard

From: Lowy, Naomi
Sent: Tuesday, May 10, 2016 7:53 AM
To: Unger, Ellis; Temple, Robert
Subject: WSJ and eteplirsen



WSJ & Legal Testi
for the FDCA.D...

A Legal Test for the FDA

Black letter law dictates approval for a muscular dystrophy drug.

May 9, 2016 7:20 p.m. ET

[27 COMMENTS](#)

The Food and Drug Administration will decide this month whether to approve an innovative drug for a fatal form of muscular dystrophy, and one question is whether the agency's management will rebuke the dubious science propagated by its staff reviewers. Here's another: Will FDA defy a law that directs the agency to pick up the pace on treatments for rare diseases?

Eteplirsen by [Sarepta Therapeutics](#) **SRPT-0.40%** produces dystrophin, the protein missing in boys with Duchenne muscular dystrophy, a condition that destroys every muscle in a decline from walking to wheelchair to death. Eteplirsen shows zero safety risks and four years of striking results in a clinical trial of 12 boys. FDA reviewers assert that the study is too small and maybe the drug doesn't work, though Duchenne experts world-wide say otherwise.

As it happens, Congress in 2012 passed a law that should settle the issue. The Food and Drug Administration Safety and Innovation Act grants FDA considerable flexibility to accelerate approval for life-threatening disease drugs dealing with an unmet medical need. FDA can sign off on a drug that "has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit." For those without decoder glasses, that means: The drug delivers on some promised action, and in a way that likely helps the patient.

The trial turned up evidence that eteplirsen makes good on pumping out dystrophin, a feat no treatment has managed. It's reasonable, even obvious, to predict that dystrophin would benefit a kid whose body can't produce it. Definitive proof is not required, and the law stipulates that FDA can yank a drug from the market if later trials fail. Sarepta will have results from more trials in two years or so. If that sounds soon enough to delay approval, consider the hundreds of boys who by then won't walk.

Congress tells FDA to weigh the condition's severity, rarity and other available treatments. Duchenne snatches a boy's ability to move around, feed himself and turn over in bed, and a lost capability never returns. That's severe. At one in 3,500 male births, the condition is rare, which is one reason Sarepta couldn't conduct large trials that shoot up half of patients with a placebo, as FDA prefers. The list of alternative treatments is short: none.

The law further requires—not suggests—that FDA engage with patients. The nonprofit Jett Foundation interviewed eight of the 12 boys in the trial. Boys who were collapsing from failed muscles stopped falling almost entirely; the four who suffered fractures returned to walking, which is highly unusual. The foundation's Christine McSherry told an FDA panel last month that patients would support the agency pulling eteplirsen if the drug eventually proves ineffective. That isn't the tenor of someone reaching for a pitchfork, though some in the press insist this case pits science against hysterical parents.

FDA's reviewers say the law can't rescue "inconclusive" scientific data, but the best way to shore up the evidence is to approve the drug. Janet Woodcock, who runs FDA's drug evaluation division and will render the agency's final decision, acknowledged at an FDA committee meeting about eteplirsen last month that some uncertainty is legally acceptable for novel drugs treating such severe diseases. She is right, and in this case following the law and approving the drug also leads to the correct medical and moral outcome.

It's hard to imagine a drug with a stronger legal case for accelerated approval, given eteplirsen's safety profile, promising clinical results and patients who know it works. If FDA still says no, Congress should be prepared to pass more invasive reform that forces the agency to serve the people it allegedly represents.

eteplersin

Temple, Robert

From: Diggs, Felicia
Sent: Thursday, May 12, 2016 10:01 AM
To: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis
Subject: FYI; eteplersin

Just an FYI: I'm attending the American Course on Drug Development and Regulatory Sciences and the presenter (Ramsey Baghdadi) for the topic on Drug Pricing used the AC meeting on eteplersin for the first segment of his slide presentation with quotes from you all. The presentation was unbiased and very positive. The speaker indicated FDA is doing a great job in handled the review of the application and the AC meeting.



day3-0900am-B...

Felicia M. Diggs, RN, BSN, MSN

Consumer Safety Officer

U.S. Food and Drug Administration

Center for Drug Evaluation and Research | Office of Executive Programs | Division of Executive Operations

240-402-4932 | Blackberry: 301-467-3742 | Fax: 301-847-8753 | Felicia.diggs@fda.hhs.gov

Drug Pricing and Innovation



Vs.



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Exploring The Limits Of Flexibility



What Are The Limits Of Regulatory Flexibility On Innovation?

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Sarepta: A Real-Time, Real-World Case



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Eteplirsen for DMD: Perfect Policy Storm

Key Elements

Approval Standards
Accelerated Approval
Surrogate Endpoints
Substantial Evidence
Patient Input
Expanded Access
Biomarker Validation
Pricing
Outside Pressure



Sarepta Case

Failed Single Phase III
Predicts Clinical Benefit?
Dystrophin production
"No evidence"
"Unprecedented"
Can't make enough
Dystrophin Unvalidated
Multiple \$100Ks, More?
Patients, Politicians, Docs

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Eteplirsen for DMD: The Data



Eteplirsen Application

Developed to treat DMD patients who have confirmed mutation of the dystrophin gene amenable to exon 51 skipping. Eteplirsen may increase production of truncated form of dystrophin. DMD is caused by genetic mutations in the dystrophin gene that result in near absence of the dystrophin protein from muscle. Dystrophin is thought to maintain the structural integrity of the muscle cell membrane. 9K-12K US DMD patients; 13% (1,300-1,900) of DMD patients may respond to exon-skipping.

Randomized placebo-controlled trial of 12 boys. Three Arms: 30mg/50mg/placebo over 24 weeks

Primary Endpoint: Change in % of Dystrophin Positive Fibers in skeletal muscle as measured through biopsies. Secondary Outcome Endpoint: Improvement from baseline in 6-minute walk test

Failed Primary Endpoint (17% of biopsies with detectable dystrophin)

Failed 6MWT Endpoint

No Correlation Between Dystrophin Levels and 6MWT Performance

No Difference In Dystrophin Between High Dose and Low Dose

Sarepta Conducted Post Hoc Analysis Comparing 12 Boys To Historical Control = Δ 162 Meters

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Pre-Panel: Outside Pressure On All Sides



In-Person Meetings With Politicians



UCLA Letter, 36 DMD experts



109 House Members Sign Letter To CDER Director

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Pricing as a Contextual Backdrop



In 2013, Ex-CEO Chris Garabedian on Eteplirsen If Approved: "Most expensive drug in history."



At the same time...

"We're writing a prescription for a drug for the whole country." – FDA's Pulmonary, Allergy, & Rheumatology Division Director Badrul Chowdhury on agency philosophy.

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An Army of Patients Advance on FDA



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FDA Reviewers: "No Evidence of Efficacy"



Clinical team leader Ron Farkas:
"There does not appear to be **any**
evidence of efficacy for eteplirsen."



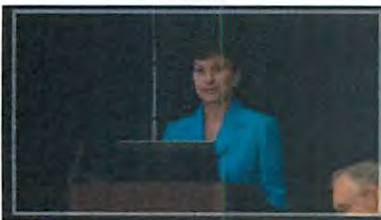
Neurology Products Division
Director Billy Dunn cited "grave
concerns" with the data



Deputy Eric Bastings: "Was it
possible to conduct an adequate and
well controlled study?"

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Janet Woodcock To The Rescue?



Woodcock Speech

"Much of the effort in evaluating a drug development program goes into avoiding a specific mistake: that is erroneously approving a drug that is not that effective."

"There often is little consideration of another error, which is failing to approve a drug that actually works. In devastating diseases, the consequences of this mistake can be extreme, but most of these consequences are born by patients who traditionally have little say in how the standards are implemented."

On Accelerated Approval: "An inherent presumption in this program of accelerated approval, which is written in the preamble to our regulation about it, is that more uncertainty is going to be tolerated, initially, and that in fact, sometimes, we will collectively get it wrong. Otherwise, accelerated approval would really have no different standards than regular approval."

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Two Senior FDA Views On Evidence



Unger At Sarepta Adcomm

"**Unprecedented** to have all the patients in the room."

Message to the panel: You have to reconcile what you heard today from the patients with the data you have in front of you.



Temple On Substantial Evidence

"The main message I have is that we're really quite flexible in the quantity of data that we accept

"**What we have never said we would do except for accepting one study sometimes is accept evidence that falls short of the mark.** So whether it's evidence for a surrogate or evidence of the real effect or whatever it is, we want it to be convincing at an acceptable level and we haven't modified that

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The AdComm Votes Eteplirsen Down

Vote On Accelerated Approval (Dystrophin Production) = 7-6 No

Vote On Full Approval = 7-3-3 No



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What Should FDA Do On May 26?



1. **Reject:** A Placebo Controlled Trial?
2. **Reject:** More Data On Dystrophin As Surrogate?
3. **Approve:** Accelerated Approval?
4. **Approve:** Full Approval?
5. **Something Else?**

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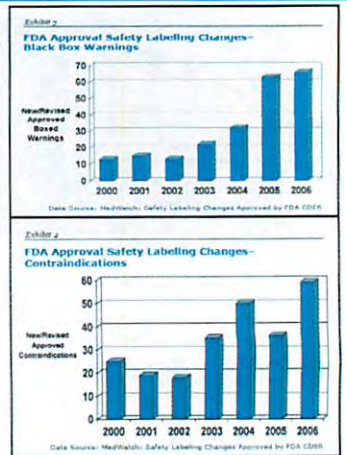
How Did We Get Here?



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The Regulatory Impact of Vioxx

- A skyrocketing in precautions at FDA after 2004 *Vioxx* recall.
- A doubling in “black box” warnings in 2006 to almost 70.



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“Breakthrough” In FDASIA 2012

FDASIA Sec. 902

Breakthrough Therapies: Excerpt From Section 902 of FDASIA

(1) IN GENERAL. The Secretary shall, at the request of the sponsor of a drug, expedite the development and review of such drug if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. (In this section, such a drug is referred to as a “breakthrough therapy.”)

(2) REQUEST FOR DESIGNATION. The sponsor of a drug may request the Secretary to designate the drug as a breakthrough therapy. A request for the designation may be made concurrently with, or at any time after, the submission of an application for the investigation of the drug under section 355(i) or section 351(a)(2) of the Public Health Service Act.

(3) DESIGNATION.

(A) IN GENERAL. Not later than 60 calendar days after the receipt of a request under paragraph (2), the Secretary shall determine whether the drug that is the subject of the request meets the criteria described in paragraph (1). If the Secretary finds that the drug meets the criteria, the Secretary shall designate the drug as a breakthrough therapy and shall take such actions as are appropriate to expedite the development and review of the application for approval of such drug.

(B) ACTIONS. The actions to expedite the development and review of an application under subparagraph (A) may include, as appropriate—

- (i) holding meetings with the sponsor and the review team throughout the development of the drug;
- (ii) providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable;
- (iii) involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review;
- (iv) assigning a cross-disciplinary subject lead for the Food and Drug Administration review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and
- (v) taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment.

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“Breakthrough”

“All Hands on Deck”



How Many Hands Are There?

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New Drug Approvals

Real Innovation is Rewarded

- Now 16 (!) special designations at FDA
- 50th Breakthrough approval coming this year
 - 46 indications approved with six pending at FDA*
 - Initially thought would have 2-3 designations per year
 - 400 requests for Breakthrough; 130 designations granted
 - Breakthrough approvals accelerating: 22 approvals in 2015, more than the previous two years combined (15 in 2014; three 2013).
- Oncology innovation is “on fire”
 - Clear understanding of mechanism; friendly regulators in OHOP
 - Few cases of approvals based on Phase I data
 - Reviews complete months before user fee deadline
 - 50% of Breakthrough approvals in oncology/hematology



*as of May 3, 2016

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FDA’s Cancer Head: A Decade Matters

2005

When asked what is the number-one thing oncology drug developers can improve upon to secure approval, Pazdur is unhesitant in his answer: “randomized clinical trials.”



“We’re not making any progress in cancer simply by lowering the standards by which we approve drugs.”

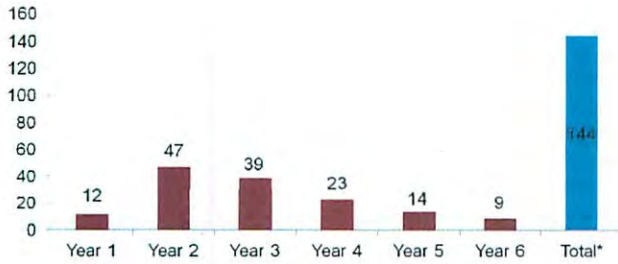
Present

“With these new drugs, we’re redefining diseases and we’re seeing unprecedented levels of efficacy.”

“In the 1960’s we didn’t do randomized trials because there was nothing to compare the drugs to. Now the drugs are so efficacious it’s almost going to be unethical sometimes to compare the drugs.”

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REMS: A Regulatory Fad



**Shared REMS affecting multiple sponsors are counted as a single REMS

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Califf: Leader With Knowledge + Respect



- Confirmed (!)
- Leading Clinical Trialist
- Scientists, Politicians, FDAers Like Him
- Public Citizen: We Opposed Him, But We Respect him

Priorities Include:

1. Staff Recruitment
2. Evidence Generation (Real World Evidence)
3. Many Other Things: Precision Medicine, Cancer Moonshot, Abuse-Deterrant Opioids, Patient-Focused Drug Development, Tobacco

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FDA In Peak Form



"Float like a butterfly, sting like a bee. The hands can't hit what the eyes can't see."



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FDA Climate: Extremely Good Overall...



- Innovator Oriented
- Confident and Decisive*
- Risk Tolerant*
- Operating At High Efficiency*

*(Relatively Speaking)

But: We Are Past The Peak



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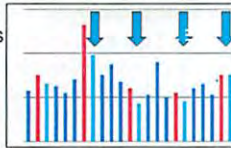
The User Fee Cycle: Resources...

- 2007 FDA Amendments Act is FDA's Biggest "Raise" Since PDUFA (1992)
- Recruitment of New Reviewers Takes Time; So Does Training



...And Requests

- PDUFA Reauthorization Process Encourages Innovation Focus At FDA



The Pre-PDUFA Bump

"21st Century Cures"

- Patient-focused drug development
- Formalize and fund FDA's biomarker qualification initiative
- Six-month exclusivity extension for new orphan indications
- Antibiotics incentives, including limited-use approval pathway
- Process for FDA to sign off on accelerated approval development plan
- Streamlined FDA review of sNDAs
- Encourage FDA to accept "clinical experience" (observational/claims data) for sNDAs

Senate Medical Innovation Bill

- Establish "Intercenter Institutes"
- Fix annual pay rates for hires
- Precision Medicine Initiative
- Establish a limited population antibacterial approval pathway
- Advancing Targeted Therapies for Rare Diseases Act
- Permanently extend rare pediatric disease priority review vouchers
- Add Zika virus to voucher program
- Establish specific procedures for FDA review of combination products
- **Topics for floor debate: laboratory-developed test regulations and orphan drug exclusivity extension

- (1) Patient-Focused Drug Development
- (2) Breakthrough Therapy program capacity
- (3) Exploration and knowledge development related to use of Real World Evidence
- (4) Post-market safety surveillance



Pricing Backlash Started...With Innovation



"The extraordinarily high cost of your drug raises additional concerns because of the role of the federal government in speeding its approval. Gilead filed for and received a Priority Review and Breakthrough Therapy designation, which reduces the FDA goal date from 10 to 6 months."

Gilead asked to explain "the value to the company of the expedited review...and how any savings provided by the expedited review factored into pricing decisions for the drug."



Rep. Henry Waxman
Ranking Democrat
Energy & Commerce Committee



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Sovaldi The Wrong Guy To Pick On?



- Underpriced! (relatively speaking)
- Curative
- ~\$11 bil. to develop via M&A
- Rapid uptake
- Short lifecycle
- Large vulnerable population
- Medicare/USPSTF screening stamp of approval



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Harvoni Combo Priced ≤ Competition



12-weeks *Harvoni* (*Sovaldi* + *ledipasvir*) cost of ~ \$96,000

=

12-weeks *Sovaldi* + ribavirin + PEG Interferon

Or

12-weeks JnJ's *Olysio* (simeprevir) + ribavirin + PEG Interferon



Gilead CEO John Milligan

- 33% Discount for patients who can take 8-week regimen ~ \$66,000
- 50% of Hep C patients eligible for 8-week regimen

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Gilead: Price Controversy A "Distraction"



"We took the previous difficult available therapy that was a much higher cost, didn't charge a premium for our drug that had a higher efficacy and lower side effects...I mean, you were seeing people go through [liver] transplantations or die before transplantation. For these patients with the disease, it's all a distraction and disappointment. It is a cure. It's only 12 weeks long, now once a day. It's highly effective in more than 95% of patients, and the long-term costs of caring for those people with advanced liver disease will be offset by the costs initially. Yes, I think it is a distraction, it's disappointing, and it raises larger issues."



John McHutchison
EVP Clinical Research
December 2014
FDA/CMS Summit

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An Age Old Complaint



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A Short History Of Pricing Flaps...

- *Lopid (c. 1990)*
- *Centoxin (1992)*
- *Zofran (1995)*
- *Nexium (2000)*
- *Zevalin (2001)*
- *Avastin (2005)*
- *Lucentis (2007)*
- *Makena (2011)*
- *Sovaldi*
- *Daraprim*
- *Jublia/Nitropress/Isuprel*
- *Xtandi*

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The “High Cost of Drugs”



•Overall Spending Growth

- Rx Market Share
- Patent Cliff Helps
- Focus on Specialty Trend

•Pricing Fairness

- Annual Price Increases
- Price Discrimination
- Cheaper Alternatives

•Sticker Shock

- Just the Price
- Can Personalized Medicine Work?

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ACA's “Godfather” Deal



Gave
Medicaid Rebates
Donut hole discounts
Market share tax

Got
New customers
Biologic IP
protections
No Part D Rebates

CONTINUED CONTROL OVER LAUNCH PRICE

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ACA Adds \$13.4B/Year In Rx Spending

Rx Spending (\$bil.)	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
With ACA Impacts	255.7	263.0	260.8	262.3	275.9	294.9	311.6	330.7	350.6	372.7	397.9	425.5	455.0
Without ACA Impacts	257.4	262.3	259.9	261.5	267.4	281.1	297.8	316.5	337.0	359.7	384.4	411.0	439.7
Difference	-1.7	0.7	0.9	0.8	8.5	13.8	13.8	14.2	13.6	13.0	13.5	14.5	15.3

Concerns over access due to formulary placement and major shift toward generics

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Pharma Losing The Public Debate



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How Did Congress Respond To Rx Pricing?



Stern Talking To?



Punish?



Reward?



Threaten.

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Taking On The Real Villains...



Turing



Valeant

“Hedge Funds Masquerading As Pharmaceutical Companies.” - Merck CEO Ken Frazier

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NIH "March-In" Rights On Drug Patents?



NIH Director Francis Collins

"March-in does not appear to have really been designed to be utilized in a fashion where the price is the obstacle. It seems more to be a circumstance where the product was simply not available because it was not being commercialized and then NIH had the authority to step in and take over."

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Letters and a Drug Pricing Forum

A Balanced Response?



HHS Drug Pricing Forum



"If we don't deal with this now, it will be a top three issue for my successor, and the top issue for their successor."
Andy Slavitt, CMS



CMS Letters To Hep C Companies

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Pricing: Tune Out The Noise



1. Generic Drug Medicaid Rebate
2. Proposed Medicare Part B Demo

THAT'S IT!

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Generic Medicaid Rebate: Ironic Solution



Previously: Generic drugs were subject to a flat 13% rebate under Medicaid.

Now: Generic drugs require an additional rebate (on top of flat 13%) equal to the amount by which a drug's Medicaid price has increased above inflation.

SAME AS BRAND DRUGS

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National Demonstration Model

“A model must either reduce spending without reducing the quality of care, or improve the quality of care without increasing spending, and must not deny or limit the coverage or provision of any benefits.”

Current Formula: Medicare pays ASP + 6%

Part B Demo: ASP + 2.5% + \$16.80

CMS Administrator: A Series of “Experiments”

- **Reduce Incentive To Choose Pricier Drug Based On Spread**
- **Really Changing The Formula, But Still Has A %**
- **Specialists/Oncologists Hurt Most; Better for Primary Care?**

• **Discounting or eliminating patient cost-sharing.** Patients are often required to pay for a portion of their care through cost-sharing. This proposed test would decrease or eliminate cost sharing to improve beneficiaries’ access and appropriate use of effective drugs.

• **Feedback on prescribing patterns and online decision support tools.** This proposed test would create evidence-based clinical decision support tools as a resource for providers and suppliers focused on safe and appropriate use for selected drugs and indications. Examples could include best practices in prescribing or information on a clinician’s prescribing patterns relative to geographic and national trends.

• **Indications-based pricing.** This proposed test would vary the payment for a drug based on its clinical effectiveness for different indications. For example, a medication might be used to treat one condition with high levels of success but an unrelated condition with less effectiveness, or for a longer duration of time. The goal is to pay for what works for patients.

• **Reference pricing.** This proposed model would test the practice of setting a standard payment rate—a benchmark—for a group of therapeutically similar drug products.

• **Risk-sharing agreements based on outcomes.** This proposed test would allow CMS to enter into voluntary agreements with drug manufacturers to link patient outcomes with price adjustments.



Hundreds of Democrats write letter to CMS asking the agency to stop moving forward with the pilot.



- The “geographic scope” and whether “it should be smaller.”
- Impact on “some specialties,” particularly “oncology and rheumatology.”
- Impact on smaller and/or rural practices.
- Whether to proceed in two (or more) steps as proposed

House Hearing Scheduled For May 17

“We are listening and willing to adjust as needed.”

-Patrick Conway, CMS Deputy Administrator on May 4

Benefits of a Fragmented System



Part D: Contracting sponsor-plans, 2 drugs/class, protected classes
Part B: ASP + 6% (for now), national coverage decisions
Medicaid: 23.1% mandatory rebate, supplemental, states
VA: Medicaid rebate, separate contracting for vets
ACA Exchanges: 1 drug/class, P&T Committees
Private Insurance/PBMs: Formulary tools, exclusion (defections too)

NO SINGLE POWER TO EXCLUDE

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Et tu, Obama? Post-ACA "Pharma Deal"



White House HHS Budget Proposals Since 2010:

- Direct price negotiation in Part D
- Reduce biologic market exclusivity
- Drug Importation

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Look Who's Talking About Drug Prices?



"Price gouging like this in the specialty drug market is outrageous. Tomorrow I'll lay out a plan to take it on." - Hillary Tweet on Sep. 21, 2015



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The Politics of Drug Pricing



Presidential Promises

I have a plan!



- ✓ \$250/month co-pay cap
- ✓ Rx reimports
- ✓ "Research or rebate"
- ✓ Part D rebates and price negotiation
- ✓ No DTC tax credits
- ✓ End "pay for delay"
- ✓ Reduce biologics exclusivity to 7 years

That was my plan!



- ✓ Medicaid inflation rebate on generics
- ✓ Rx reimports
- ✓ No patents if fraud
- ✓ Part D rebates and price negotiation
- ✓ End "pay for delay"
- ✓ Pricing transparency
- ✓ Close Part D "donut hole" 3 years early

Great plan!



- ✓ Pricing transparency
- ✓ Rx imports
- ✓ Part D negotiation

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“I caution against solutions that seek to lower the safety and efficacy standards for medical products on which Americans rely.”

Do drug developers want a playing field with low barriers to entry?

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Regulatory & Innovation

- Innovation climate continues but...
- Approvals and review times probably tick downward
- Rare diseases and cancer continue as focus areas
- Relative stability at FDA

Pricing

- Medicare will try more “experiments”
- More idea activity from outside parties: ICER, IoM, PEW
- Pressure shift to payors for limiting access?

Potential De-Stabilizing Events?

- Regulatory: **Eteplirsen gets approved, question FDA standards**
- Pricing: **The Million Dollar Drug (Spark Therapeutics)**
- Everything: **Trump Presidency... We just don't know.**

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Questions?

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