

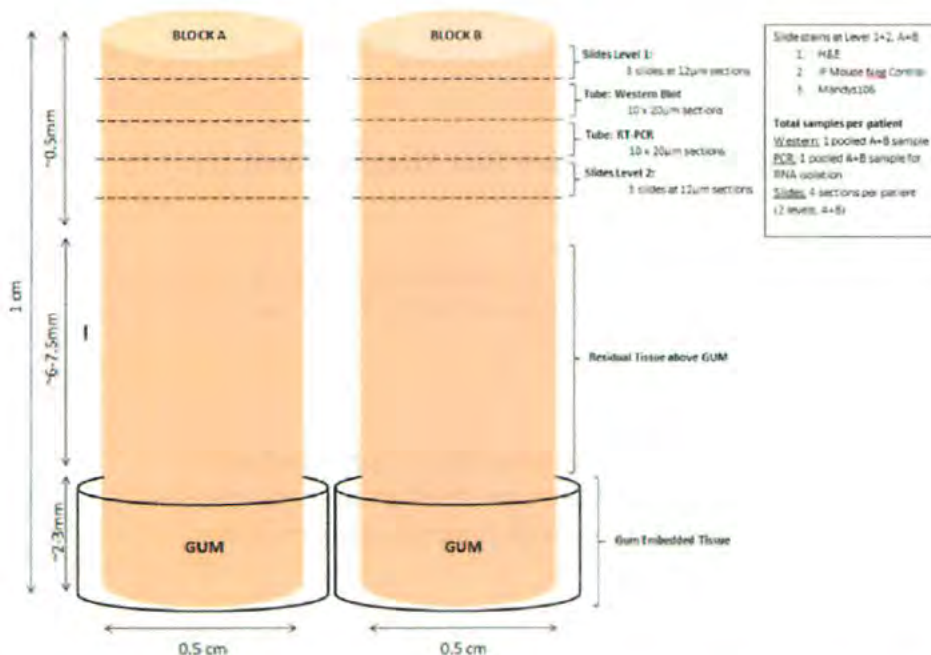
From: Rao, Ashutosh
Sent: Thursday, May 12, 2016 9:19 AM
To: Farkas, Ronald; Unger, Ellis; Bhattaram, Atul
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Subject: RE: WB question
Attachments: __cdsesub1_evspod_nda206488_0004_m5_53-clin-stud-rep_535-rep-effic-safety-stud_dmd-51_5352-stud-rep-uncontr_4658-us-202_4658-us-202-sr-cr-15-003.pdf

Hi Ellis,

My understanding of their WB tissue allocation and replicates is summarized below. We can discuss further if that helps; although, we may need to ask the sponsor if the points below from the attached report don't address our concerns.

Two blocks (A and B) are prepared for each patient sample. Each block was sectioned for a western blot sample. See illustration below from SR-CR-15-003 (tissue allocation protocol, attached). The 20 micron sections from both blocks are pooled during homogenization to provide sufficient tissue for lysate preparation and run in duplicate for western blot.

Figure 2: Patient Sample Tissue Allocation Plan



Biopsy blocks were sectioned as indicated in Figure 1. Gum Tagacanth is used to attach the biopsy block to the cryostat chuck. Block A and B represent two blocks obtained from each patient participating in the Week 180 biopsy. Tissue sections from Block A and B were pooled for Western blot and RT-PCR analysis.

The assay precision for their validated WB was (b) (4)%, which is not unheard of for a primary human tissue-based WB. An RSD > (b) (4)% was considered a "fail" so the numbers in the table you have were all within (b) (4)% RSD. An RSD close to or less than (b) (4)% is better, especially if this was a clonally expanded cell line or homogenous primary tissue sample, but in this disease condition where there is known heterogeneity and ongoing degeneration of the tissue I don't know if it's possible to get a very high precision – so heterogeneity and a (b) (4)% RSD here might be reflective of the biology of the

sample and not the assay itself. For instance, you can see the % RSD recommended for tissue in this paper (20-50% - http://www.nature.com/gt/journal/v12/n1s/fig_tab/3302627t3.html#figure-title). One could even argue that WB isn't a fully quantitative method to expect high precision, compared to say HPLC or mass spec method, which is why we had tried to get them to do the quantitative mass spec method that Hoffman had developed.

Keep in mind that the "failed" gels from their validation report were related to the calibration curve's linearity and not necessarily due to the inter-sample precision. The assay was validated such that the gel was considered a "fail" if the healthy standard curve's linearity was < ^(b)₍₄₎%.

From: Farkas, Ronald
Sent: Thursday, May 12, 2016 8:22 AM
To: Unger, Ellis; Bhattaram, Atul; Rao, Ashutosh
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Subject: RE: WB question

It isn't clear to me whether a single homogenate was divided in 2, or if 2 separate sets of cryosections were separately homogenized –

Ash, do you know?

Below is some text from the protocol:



From: Unger, Ellis
Sent: Thursday, May 12, 2016 12:17 AM
To: Bhattaram, Atul; Rao, Ashutosh
Cc: Farkas, Ronald; Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Subject: WB question

Dear All,

The agreement between gels 1 and 2 seems poor, at least for many patients (see table).

If gel 1 and gel 2 are run from different cuts of a single muscle sample, then the difference could be from heterogeneity within the sample, i.e., some differences would be expected.

BUT -- if they prepare a lysate from a single muscle sample, divide it, and run two gels on the same lysate, then these differences suggest that the assay has poor precision.

I've never run a Western blot and have very little knowledge, so if my question is naïve, I won't be offended!

Thoughts...

Treatment at Week 180	Subject	4 th Biopsy Gel #1	4 th Biopsy Gel #2	Average for 4 th Biopsy; BLOQ set to 0	Average for 4 th Biopsy Actual Values
30 mg/kg	002	BLOQ	0.28	0.14	0.15
	006	2.83	2.11	2.47	2.47
	007	BLOQ	BLOQ	0	0.16
	008	0.93	1.02	0.98	0.98
	009	0.58	0.46	0.52	0.52
	010	1.45	1.78	1.62	1.62
50 mg/kg	003	BLOQ	BLOQ	0	0.18
	004	1.22	0.66	0.96	0.96
	005 ⁹	NA	NA	0	0
	012	0.75	BLOQ	0.38	0.5
	013	NA	1.15	1.15	1.15
	015	2.43	1.67	2.05	2.05

Source: nda206488_0024_m1_us_111-info-amend_clinpharm-20151204.pdf

Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Thursday, May 12, 2016 9:58 AM
To: Bastings, Eric; Unger, Ellis
Cc: Farkas, Ronald; Dunn, Billy; Breder, Christopher D; Rao, Ashutosh; Temple, Robert; Choy, Fannie (Yuet)
Subject: Quick Minutes for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee
Attachments: DNP_QuickMins_PCNS 4.25.16_RT-EU-AR-EB.doc

Attached please find the edited Quick Minutes. Please let me know if this is final and I can return to the AC staff.

Thanks
Fannie

From: Farkas, Ronald
Sent: Wednesday, May 11, 2016 8:23 PM
To: Choy, Fannie (Yuet)
Subject: RE: (DUE today: 5/10) Quick Minutes for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee

No, nothing from me
Thanks
Ron

From: Dunn, Billy
Sent: Wednesday, May 11, 2016 5:54 PM
To: Bastings, Eric; Choy, Fannie (Yuet)
Cc: Farkas, Ronald
Subject: RE: (DUE today: 5/10) Quick Minutes for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee

Nothing additional from me.

From: Bastings, Eric
Sent: Wednesday, May 11, 2016 5:38 PM
To: Choy, Fannie (Yuet)
Cc: Dunn, Billy; Farkas, Ronald
Subject: RE: (DUE today: 5/10) Quick Minutes for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee

I finished my edits. Thanks.

Eric

From: Choy, Fannie (Yuet)
Sent: Tuesday, May 10, 2016 3:55 PM
To: Dunn, Billy; Bastings, Eric; Farkas, Ronald

Cc: Choy, Fannie (Yuet)

Subject: (DUE today: 5/10) Quick Minutes for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee

Following up whether you have a chance to review the Quick Minutes and have additional edits. The document is due back to AC staff today.

Thanks
Fannie

From: Rao, Ashutosh

Sent: Monday, May 09, 2016 2:07 PM

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

Cc: Choy, Fannie (Yuet)

Subject: RE: CONFIDENTIAL: Quick Minutes for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee

I made a few editorial changes to the discussion sections for Q2 and Q7. Overall, the document looked okay to me.

Thanks
Ash

From: Unger, Ellis

Sent: Friday, May 06, 2016 5:12 PM

To: Breder, Christopher D; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh; Temple, Robert

Cc: Choy, Fannie (Yuet)

Subject: RE: CONFIDENTIAL: Quick Minutes for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee

All,

Bob made some edits on the quick minutes, and in making mine, I wanted to be sure that I was remembering correctly.

More importantly, given that AA is going to hinge on the dystrophin issue, I wanted to know exactly what each committee member said.

So I went back and basically transcribed the discussion around questions 1 and 2. I've also made edits in sharepoint, but below is what I transcribed.

For Q1, the bold text next to each name was my summation. For first question here, the red and green highlighting is used to summarize the answers to 2 questions: FIRST - their answer as to whether dystrophin was produced. SECOND - whether delta is clinically meaningful.

There is highlighting in yellow to help me count up the various members who voiced particular positions.

Link:

<http://fda.yorkcast.com/webcast/Play/a6b3b94c459a4dcbb617a954382d678a1d>

Starts at 8:17 on tape.

1. Dr. Mark Green: YES- but don't know whether clinically significant NO

"I think there is moderate evidence for dystrophin production – but more difficult than that – we don't have a clue how much is clinically significant – or about the function of the dystrophin. I think it's a difficult biomarker"

2. Onyike – No. Never says if dystrophin was produced, thinks threshold is unknown, but could be low, or low in a subset of patients. +/- YES

"As I recall from Farkas, it would appear that there are some people who have very very low levels of dystrophin, and much better clinical function than you'd anticipate. So therefore, it seems to me that there might not even exist a threshold of effect, but rather it's possible that dystrophin couples in some way that is indirect to function. Two people suggested that it might take very low levels to achieve a significant clinical effect. It's not clear if this would apply to all patients or some, or whether there's a marker that could predict how dystrophin links to clinical effect. I suspect there may not be a threshold per se, or that it may vary by individual or by subgroup. We have no idea what the range is, but it may very well dip very low. The threshold is ambiguous – may not be one, or it may vary widely. We don't know what range is, but it may dip very low." (He never says if he thinks that dystrophin was produced)

3. Kesselheim – No. can't draw a conclusion because controls were invalid, and comparative evidence was weak ???

"To me the answer depends on the methods used for assay. I wasn't convinced, or I am still questioning whether the biopsies were the correct ones. Why were 2 muscle groups compared? I was dismayed by *the inconsistencies in comparative evidence*. So I can't draw a firm conclusion about 0.8."

4. Hoffman – Yes, ???

"I think there is plenty of evidence that the MOA of eteplirsen is to skip exon 51 and produce dystrophin, through PCR, Western blot, and IF. Chair- we're not questioning the MOA, the question is whether there is a large amount, whether the biopsy were correct, and

I think there is plenty of evidence is that the MOA is to skip exon 51 and produce dystrophin – both from animal studies and clinical. "

5. Ovbiagele: NO – you would need matched pre- post- controls to reach a conclusion. ???

"Issue is not enough pre- and post-treatment data. For me, there isn't the evidence there. No matched baselines. So the evidence isn't there. The comparisons were with other controls – not the pre- and post."

6. Gunvalson - YES YES

"I agree with Richard that. The issue was to produce dystrophin. And the drug did. And I believe we're seeing clear benefit. I believe the amount produced is sufficient to product benefit."

JW – information from studies might influence the clinical meaningfulness.

7. Criseo – leans towards NO, but doesn't say no explicitly. Concerned about lack of dose-response. ???

"Where's the dose effect? I don't see a dose effect.

Someone responds: maybe there isn't enough of a difference in doses. Long discussion about that.

8. Alexander – it's surprising that there isn't more scientific consensus.

9. Romitti – Yes, there is some dystrophin produced. No comment on clinical meaningfulness. ???

“Lab methods are constantly evolving. We may not know what we wish we knew, after 3 blinded reviewers, I felt more comfortable. I think even though the amount may have been less, or less striking, I think there is still evidence here that there is a difference. The evidence may not be high, but lab methods are challenging. Given state of the science, and with the re-reads, I think we do see some dystrophin here.” Applause.

Dunn – you mentioned a difference – that obviously implies a difference between A and B. What do you mean.

Rom – I’m referring to the table – it was 17%.

Dunn – what change are you referring to? What comparison.

Rom – the comp is around 0.8

Chair – can we see table – FDA slide 37

Dr. Romitti – 2 different methods here. I’m lumping both methods. Sponsor’s original endpoint was positive fibers. I’m more comfortable with re-analysis. But also commenting on FDA’s suggestion to use Western blot. Western blot – unknown threshold. I think both provide evidence that there has been some change.

Onyike – asked Q to audience. Not addressed 2° time constraints.

10. Ovbiagele – No. Doesn’t comment on whether any is produced, but believes whatever was produced was not clinically meaningful. No correlation between Western blot and 6MWD. No.

“No correlation between 6mw and Western blot – of the 4 patients with best 6MWD, 2 had high dystrophin, 2 had low. The clinical meaning is not clear based on that.”

Chair:” There is moderate evidence of dystrophin production, though we don’t know how much is clinically significant. We don’t know if what is produced is as clinically active as native dystrophin. There might not be a threshold effect, or the threshold may vary wildly among individuals, but it may dip very low. No idea what the range is but may dip very low. Not convinced that biopsies were correct. Dismayed at quality of comparative evidence. Not enough pre- and post- data on same patients. Where is dose effect? Maybe not enough of a range. Production is patchy. Surprised that there is no consensus on the amount needed. “

Question 2:

Hoffman YES – by all testing methods, I believe there is proof that dystrophin was produced and that eteplirsen was responsible for it. [Dystrophin produced]

Green – YES I believe that dystrophin was made by the drug. I am very troubled by not understanding a clinically significant amount. And I’ve been extraordinarily influenced and impressed by the people who spoke about this drug earlier, and their observations. [Dystrophin produced]

Benjamin Dupree YES It appears to me that there is (as was described by Paul Ramidid) there might be a – there’s a change, and I think given that the results described, that it’s reasonably likely to predict clinical benefit. [Dystrophin produced]

Shari Gun YES – dystrophin was produced, and it’s demonstrated in the clinical abilities of these boys. That...You don’t regain lost milestones in DMD. Never. I believe that the qualitative data was good. And I hope FDA would require qualitative data in new studies. Number of falls has tremendous information. [Dystrophin produced]

Krisio – NO **Studies not well-controlled.** Wrong tissue samples. **No correlation between clinical and dystrophin produced.** It's a measurement issue, and that's why I voted no.

Ramiti NO→ YES We do see some difference. Would I have liked a better controlled study? Yes. But we do see some difference, that was uhm - - some evidence of improvement in endpoints, and given the overall size of the study. **[Dystrophin produced]**

Glen Nuckles NO I think that Western blot comparison is the most important for determining dystrophin level. Different patients and different muscles, and **I don't find that this fits the definition of an AWC.**

Foley YES I believe that Western blot in combination with IF are very important. RtPCR proved that drug worked by intended mechanism. There's likely Patchy dystrophin expression but I think the clinical efficacy seen is likely 2° to the dystrophin increase, no matter what degree of increase was seen. **[Dystrophin produced]**

Kesselheim NO

Clearly does induce production. **Studies provided were not AWC** because of the problems noted earlier: sampling, comparisons that were made, lack of adequate comparators before and after, and the staining issues. Question of reasonably likely to predict – I was moved by the **lack of assn between findings from the results and some of the clinical findings.** Still an open Q, it is possible that the drug still works, but that the methods being used weren't specific enough to identify that. **[Dystrophin produced]**

Alexander NO Concerns about the techniques of measurement. The relatively modest absolute amounts of dystrophin produced, as well as the **absence of more scientifically rigorous selection and management of controls** to allow for comparisons that would lead me to be more confident. **[Dystrophin produced]**

Onyike NO Granted - I am willing to accept (for the purpose of this question) that eteplirsen led to dystrophin production, but it's very small – and it's still within the range of what people with the disease have. **And so with that in mind it's very important to have some coupling between dystrophin production and a clinical effect. We don't have that.** And so I can't get from dystrophin production, even if I accept that, to any kind of clin effect, without some understanding of the threshold of mechanisms. If it were large amount, we'd have a different conversation. But it's a very small amount, too small to just go from dystrophin production to clinical effect. Now as to whether there was Clinical efficacy, that is a separate issue in terms of clinical measures. It is possible for example for a medicine to have a clinical effect without you knowing why. We don't know how Tylenol or heparin work. So I'm not entirely sure that one should lock the clinical effect to dystrophin production.

Gonzales NO While I believe it is more likely than not that the drug does produce dystrophin, the clinical data, as presented, with the use of historical control, was very problematic for me, and doesn't convince me that whatever dystrophin is being produced is demonstrating a clear benefit clinically. **[Dystrophin produced]**

Bruce Og NO for many of the same reasons mentioned. I had problems with the techniques, but even if I give a pass to the techniques, and there was some dystrophin production, **I don't think the study was well-controlled** and, most importantly to the question that was asked, whether the level was likely to produce a clinical benefit, there was **a lack of correlation between the dystrophin level and the outcomes.**

From: Choy, Fannie (Yuet)

Sent: Tuesday, May 03, 2016 12:50 PM

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

Cc: Choy, Fannie (Yuet)

Subject: RE: CONFIDENTIAL: Quick Minutes for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee

Dear all,

I placed the document in SharePoint for version controls.

Link to Quick Minutes: [Eteplirsen AC Quick Minutes](#)

Thank you,
Fannie

From: Choi, Moon Hee
Sent: Tuesday, May 03, 2016 9:56 AM
To: Choy, Fannie (Yuet)
Cc: Ngo, Diem-Kieu (CDR,USPHS); Woodcock, Janet; Jenkins, John K; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh
Subject: CONFIDENTIAL: Quick Minutes for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee
Importance: High

*****Information contained in this email is confidential and has not been released to the public.*****

Good morning Fannie,

Attached you will find the quick minutes for the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee on eteplirsen. Please coordinate the divisions' review, track any changes and email the revised revision to me by **Tuesday, May 10, 2016**.

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

*****Information contained in this email is confidential and has not been released to the public.*****

Temple, Robert

From: Unger, Ellis
Sent: Friday, May 13, 2016 10:23 AM
To: Rao, Ashutosh
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert; Farkas, Ronald; Bhattaram, Atul
Subject: RE: WB question

Thanks, Ash.

What do you think of this text??

Two blocks were prepared from each patient sample. Sections from both blocks were pooled during homogenization for lysate preparation, and Western blots were run in duplicate.

The individual (anonymized) values for the Western blot analysis are shown in Table 3. As reported by the review team, the analysis showed a mean dystrophin value of $0.93\% \pm 0.84\%$ of normal (mean $\pm$ standard deviation) after 3 to 3.5 years of eteplirsen treatment (3 years in patients initially randomized to placebo; 3.5 years in the other patients). Mean values were virtually the same for the lower (30 mg/kg/week) and higher (50 mg/kg/week) dose groups.

Of note, the Western blot values are (b) (5), both between patients and between duplicate runs *within* patients (i.e., repeatability; intra-assay precision), Table 3.

Mean (b) (5) values range from a maximum of 2.47% in Patient J, to near-zero in Patient H, to zero in 2 patients (E and G). For some patients, there were considerable discrepancies between duplicate runs (the intra-assay difference was $>0.5\%$ in Patients B, C, D, and J). Aside from patients with zero or near-zero dystrophin, only 3 patients showed reasonable intra-assay agreement: Patients F, L, and K.

(b) (5)

Table 3: Week 180 Western Blot Analysis – Study 201/202

(b) (5)

From: Rao, Ashutosh
Sent: Friday, May 13, 2016 9:37 AM
To: Unger, Ellis; Farkas, Ronald; Bhattaram, Atul
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Subject: RE: WB question

Hi Ellis,

For values that were below LOQ and reported as 0 for those two patients, I am not sure those numbers are interpretable for statistical tests. In my opinion, we really need more data to do a meaningful precision/intermediate precision analyses from treated samples but I am not a statistician so it might be best to check with one.

I apologize for the over-simplification; by 'this table' I meant all the data that led to this table including the loading controls, standard curve samples, precision and *intermediate* precision samples. Here is further clarification on the precision and intermediate precision calculations. The items below are either from IR responses to specific questions we asked the sponsor about the %RSD and acceptance criterion on October 2015, the validation report, or the WB protocol. From the WB protocol pasted below, the Sponsor included the actinin loading control values for the %RSD calculations. Here is what they say –



This table shows a template data sheet, if it would be useful, we could ask for the raw data sheets for patients 002 and 012 to see how they reported it.

Here are the average %RSD values for precision that they got during validation –

Table 8: Precision and Repeatability

Replicate Number	Band Intensity		
	4% Normal	2% Normal	0.5% Normal
1	309394	154357	11619
2	113067	140813	10801
3	243552	62242	15740
4	342239	75818	9359
Mean	252063	108315	11881
SD	101342	46032	2737
%RSD	40.21	42.50	23.03
Acceptance Criteria	Less than (b) (4) % RSD	Less than (b) (4) % RSD	Less than (b) (4) % RSD
Pass/Fail	Pass	Pass	Pass

The acceptance criteria for intermediate precision (between two analysts) was an RSD of (b) (4)%. Here is what they showed during method validation.

Table 9: Intermediate Precision

Day	Analyst	Band Intensity		
		4% Normal	2% Normal	0.5% Normal
1	1	309394	154357	11619
1	2	103067	140843	10807
1	1	234552	62242	9359
1	2	342239	75818	15740
2	1	409173	123085	35574
2	2	308968	197527	18599
2	1	162301	52595	7705
2	2	378141	126949	31447
Mean		283304	116677	17600
SD		103408	49895	10469
%RSD		36.5	42.8	59.5
Acceptance Criteria		Less than (b) (4) % RSD	Less than (b) (4) % RSD	Less than (b) (4) % RSD
Pass/Fail		Pass	Pass	Pass

Using a (b) (4) % RSD criteria for the two replicates for patients 002 and 012 and using the actual values (instead of 0), we get %RSDs of 72.8 (0.75 and 0.24) and 122.5% (0.02 and 0.28). Again, I am not sure one could use a BLOQ value for RSD calculation and we really need more data points (I think) but there may be others with more statistics background who might disagree.

From: Unger, Ellis
Sent: Thursday, May 12, 2016 6:33 PM
To: Rao, Ashutosh; Farkas, Ronald; Bhattaram, Atul
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Subject: RE: WB question

Thanks Ash. I'm having some trouble. You say "An RSD (b) (4) was considered a "fail" so the numbers in the table you have were all within (b) (4) RSD."

But there are 2 patients with both a zero value and a non-zero value;

Patient 1002 – values are 0 and 0.28
Patient 1012 – values are 0.75 and 0

For these 2 patients, the ratio of the SD/mean = 1.414214. The other patients have an RSD (b) (4), as you say.

How can those two patients be included, given that their RSD = 1.414, which is (b) (4)

Thanks,
Ellis

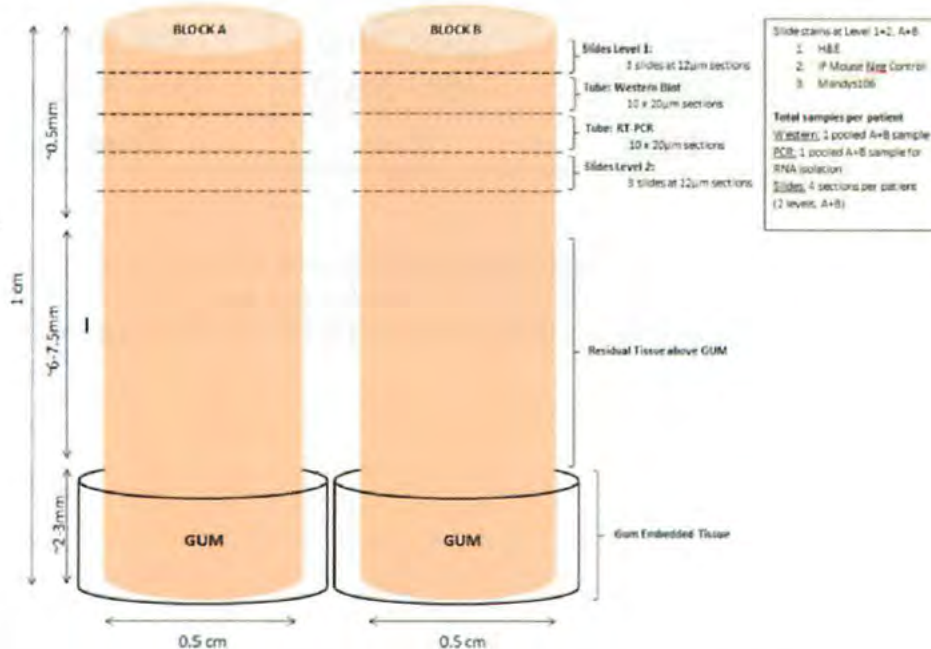
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Subject: RE: WB question

Hi Ellis,

My understanding of their WB tissue allocation and replicates is summarized below. We can discuss further if that helps; although, we may need to ask the sponsor if the points below from the attached report don't address our concerns.

Two blocks (A and B) are prepared for each patient sample. Each block was sectioned for a western blot sample. See illustration below from SR-CR-15-003 (tissue allocation protocol, attached). The 20 micron sections from both blocks are pooled during homogenization to provide sufficient tissue for lysate preparation and run in duplicate for western blot.

Figure 2: Patient Sample Tissue Allocation Plan



Biopsy blocks were sectioned as indicated in Figure 1. Gum Tagacanth is used to attach the biopsy block to the cryostat chuck. Block A and B represent two blocks obtained from each patient participating in the Week 180 biopsy. Tissue sections from Block A and B were pooled for Western blot and RT-PCR analysis.

The assay precision for their validated WB was (b) (4)%, which is not unheard of for a primary human tissue-based WB. An RSD > (b) (4), was considered a "fail" so the numbers in the table you have were all within (b) (4)% RSD. An RSD close to or less than (b) (4)% is better, especially if this was a clonally expanded cell line or homogenous primary tissue sample, but in this disease condition where there is known heterogeneity and ongoing degeneration of the tissue I don't know if it's possible to get a very high precision – so heterogeneity and a (b) (4)% RSD here might be reflective of the biology of the sample and not the assay itself. For instance, you can see the % RSD recommended for tissue in this paper (20-50% - http://www.nature.com/gt/journal/v12/n1s/fig_tab/3302627t3.html#figure-title). One could even argue that WB isn't a fully quantitative method to expect high precision, compared to say HPLC or mass spec method, which is why we had tried to get them to do the quantitative mass spec method that Hoffman had developed.

Keep in mind that the "failed" gels from their validation report were related to the calibration curve's linearity and not necessarily due to the inter-sample precision. The assay was validated such that the gel was considered a "fail" if the healthy standard curve's linearity was < (b) (4)%.

From: Farkas, Ronald

Sent: Thursday, May 12, 2016 8:22 AM

To: Unger, Ellis; Bhattaram, Atul; Rao, Ashutosh

Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert

Subject: RE: WB question

It isn't clear to me whether a single homogenate was divided in 2, or if 2 separate sets of cryosections were separately homogenized –

Ash, do you know?

Below is some text from the protocol:

(b) (4)

From: Unger, Ellis

Sent: Thursday, May 12, 2016 12:17 AM

To: Bhattaram, Atul; Rao, Ashutosh

Cc: Farkas, Ronald; Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert

Subject: WB question

Temple, Robert

esep *Tues*

To: Woodcock, Janet (Janet.Woodcock@fda.hhs.gov)
Subject: FW: eteplirsen IHC data

I asked Ellis about the immunofluorescence data and specifically the table in our A.C. presentation. You can see what he said. The baseline values in the right half of the table, which seem very close to the on-therapy values, including the 180 week values, are indeed the re-read values, not the original values, although it is noted that both sets of baseline values are pretty close. The results seem on their face fairly discouraging, even though we all agree that the immunofluorescence measures are not good quantitative measure of dystrophin and these figures are not quantitative.

From: Unger, Ellis
Sent: Friday, May 13, 2016 4:58 PM
To: Temple, Robert
Subject: eteplirsen IHC data

Bob,

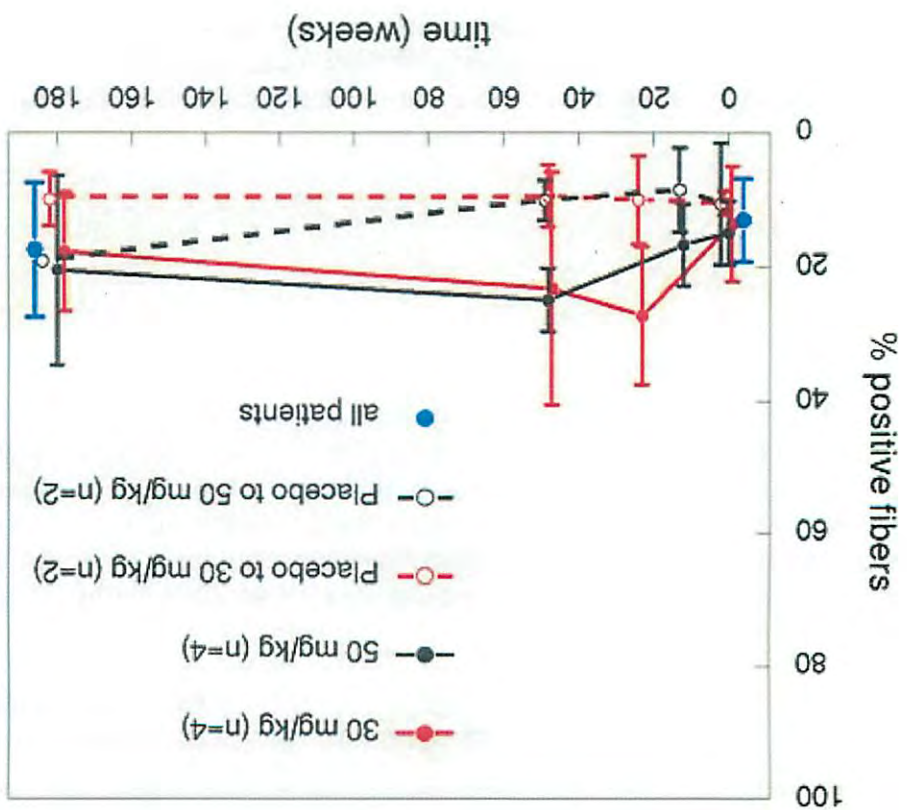
The data on the left side of the table are from the original analysis by the technician at Nationwide Children’s Hospital. She wasn’t well qualified to read the slides, used inferior video equipment under poor lighting conditions, and had access to the treatment code (though she told me she didn’t look at it). I’m not sure she ever claimed she was blinded to sequence – only blinded to patient #.

The data on the right side are from the 3 veterinary pathologists, who did a masked read that was also masked to sequence. Given the importance of these data, I analyzed them myself and plotted the results (below).

Let me know if you have Qs.

Ellis

	Nationwide Children’s Hospital analysis				Re-analysis by 3 blinded readers				
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48	Week 180 (n=11)
30 mg/kg (n=4)	18		41	70	14		27	23	17
50 mg/kg (n=4)	11	12		54	15	17		25	
Placebo to 30 mg/kg (n=2)	24		24	58	10		10	9	
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		10	



Temple, Robert

eteplirsan

From: Rao, Ashutosh
Sent: Friday, May 13, 2016 12:11 PM
To: Unger, Ellis
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert; Farkas, Ronald; Bhattaram, Atul
Subject: RE: WB question
Attachments: EU_WB text.doc

Hi Ellis,

I have made some suggested changes and have some comments in the attached document with tracked changes. The table below provides the raw data for the actual values that were BLOQ from the Sponsor. The blue column with RSD values from the raw numbers was generated by me.

Ash

Table 1: Individual Eteplirsan-Treated Subject Samples (% normal dystrophin)

Subject Number	Gel 1	Gel 2	Average (Arithmetic)	Average (Per Protocol)	RSD
002	0.02*	0.28	0.15	0.14	122.5
003	0.19*	0.16*	0.18	0.00	12.1
004	1.22	0.69	0.96	0.96	39.2
006	2.83	2.11	2.47	2.47	20.6
007	0.17*	0.15*	0.16	0.00	8.8
008	0.93	1.02	0.98	0.98	6.5
009	0.58	0.46	0.52	0.52	16.3
010	1.45	1.78	1.62	1.62	14.4
012	0.75	0.24*	0.50	0.38	72.8
013	Failed gel	1.15	1.15	1.15	n/a
015	2.43	1.67	2.05	2.05	26.2

* = BLOQ; values are estimated and are BLOQ for the validated assay.
Source: Listing A.1.1 and laboratory notebooks

From: Unger, Ellis
Sent: Friday, May 13, 2016 10:23 AM
To: Rao, Ashutosh
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert; Farkas, Ronald; Bhattaram, Atul
Subject: RE: WB question

Thanks, Ash.

What do you think of this text??

Two blocks were prepared from each patient sample. Sections from both blocks were pooled during homogenization for lysate preparation, and Western blots were run in duplicate.

The individual (anonymized) values for the Western blot analysis are shown in Table 3. As reported by the review team, the analysis showed a mean dystrophin value of $0.93\% \pm 0.84\%$ of normal (mean $\pm$ standard deviation) after 3 to 3.5 years of eteplirsen treatment (3 years in patients initially randomized to placebo; 3.5 years in the other patients). Mean values were virtually the same for the lower (30 mg/kg/week) and higher (50 mg/kg/week) dose groups.

Of note, the Western blot values are (b) (5), both between patients and between duplicate runs *within* patients (i.e., repeatability; intra-assay precision), Table 3.

Mean (b) (5) values range from a maximum of 2.47% in Patient J, to near-zero in Patient H, to zero in 2 patients (E and G). For some patients, there were considerable discrepancies between duplicate runs (the intra-assay difference was $>0.5\%$ in Patients B, C, D, and J). Aside from patients with zero or near-zero dystrophin, only 3 patients showed reasonable intra-assay agreement: Patients F, L, and K.



Table 3: Week 180 Western Blot Analysis – Study 201/202

The content of Table 3 is completely redacted with a solid grey fill. A small "(b) (5)" label is visible in the top right corner of the redacted area.

From: Rao, Ashutosh
Sent: Friday, May 13, 2016 9:37 AM
To: Unger, Ellis; Farkas, Ronald; Bhattaram, Atul
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Subject: RE: WB question

Hi Ellis,

For values that were below LOQ and reported as 0 for those two patients, I am not sure those numbers are interpretable for statistical tests. In my opinion, we really need more data to do a meaningful precision/intermediate precision analyses from treated samples but I am not a statistician so it might be best to check with one.

I apologize for the over-simplification; by 'this table' I meant all the data that led to this table including the loading controls, standard curve samples, precision and *intermediate* precision samples. Here is further clarification on the precision and intermediate precision calculations. The items below are either from IR responses to specific questions we asked the sponsor about the %RSD and acceptance criterion on October 2015, the validation report, or the WB protocol. From the WB protocol pasted below, the Sponsor included the actinin loading control values for the %RSD calculations. Here is what they say –

(b) (4)



This table shows a template data sheet, if it would be useful, we could ask for the raw data sheets for patients 002 and 012 to see how they reported it.

Here are the average %RSD values for precision that they got during validation –

Table 8: Precision and Repeatability

Replicate Number	Band Intensity		
	4% Normal	2% Normal	0.5% Normal
1	309394	154357	11619
2	113067	140813	10801
3	243552	62242	15740
4	342239	75818	9359
Mean	252063	108315	11881
SD	101342	46032	2737
%RSD	40.21	42.50	23.03
Acceptance Criteria	Less than (b) (4) % RSD	Less than (b) (4) % RSD	Less than (b) (4) % RSD
Pass/Fail	Pass	Pass	Pass

The acceptance criteria for intermediate precision (between two analysts) was an RSD of (b) (4)%. Here is what they showed during method validation.

Table 9: Intermediate Precision

Day	Analyst	Band Intensity		
		4% Normal	2% Normal	0.5% Normal
1	1	309394	154357	11619
1	2	103067	140843	10807
1	1	234552	62242	9359
1	2	342239	75818	15740
2	1	409173	123085	35574
2	2	308968	197527	18599
2	1	162301	52595	7705
2	2	378141	126949	31447
Mean		283304	116677	17600
SD		103408	49895	10469
%RSD		36.5	42.8	59.5
Acceptance Criteria		Less than (b) (4) % RSD	Less than (b) (4) % RSD	Less than (b) (4) % RSD
Pass/Fail		Pass	Pass	Pass

Using a (b) (4)% RSD criteria for the two replicates for patients 002 and 012 and using the actual values (instead of 0), we get %RSDs of 72.8 (0.75 and 0.24) and 122.5% (0.02 and 0.28). Again, I am not sure one could use a BLOQ value for RSD calculation and we really need more data points (I think) but there may be others with more statistics background who might disagree.

From: Unger, Ellis
Sent: Thursday, May 12, 2016 6:33 PM
To: Rao, Ashutosh; Farkas, Ronald; Bhattaram, Atul
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Subject: RE: WB question

Thanks Ash. I'm having some trouble. You say "An RSD > (b) (4) % was considered a "fail" so the numbers in the table you have were all within (b) (4) % RSD."

But there are 2 patients with both a zero value and a non-zero value;

Patient 1002 – values are 0 and 0.28

Patient 1012 – values are 0.75 and 0

For these 2 patients, the ratio of the SD/mean = 1.414214. The other patients have an RSD (b) (4), as you say.

How can those two patients be included, given that their RSD = 1.414, which is > (b) (4)

Thanks,
Ellis

From: Rao, Ashutosh

Sent: Thursday, May 12, 2016 9:19 AM

To: Farkas, Ronald; Unger, Ellis; Bhattaram, Atul

Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert

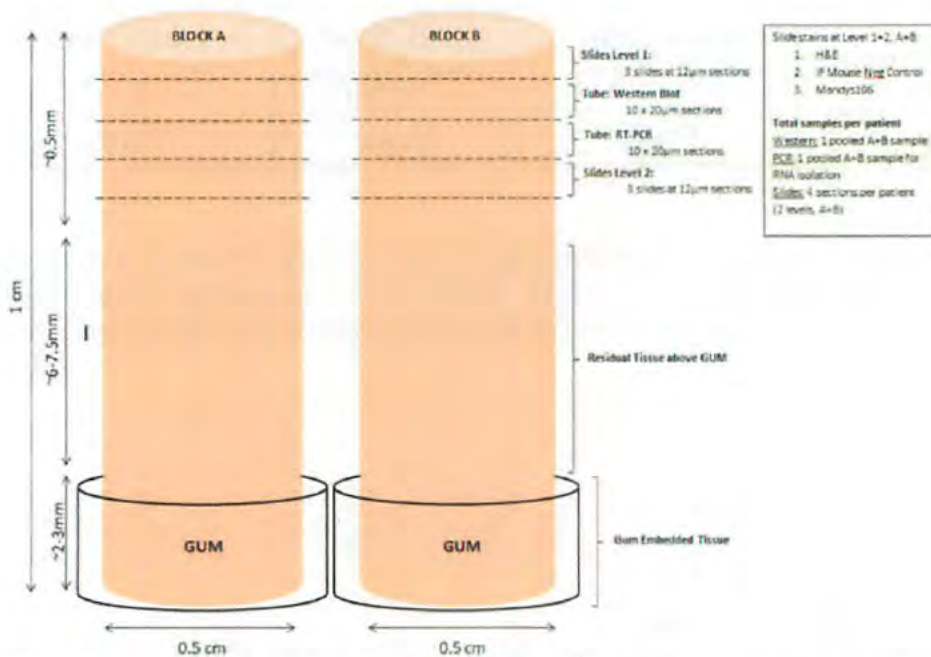
Subject: RE: WB question

Hi Ellis,

My understanding of their WB tissue allocation and replicates is summarized below. We can discuss further if that helps; although, we may need to ask the sponsor if the points below from the attached report don't address our concerns.

Two blocks (A and B) are prepared for each patient sample. Each block was sectioned for a western blot sample. See illustration below from SR-CR-15-003 (tissue allocation protocol, attached). The 20 micron sections from both blocks are pooled during homogenization to provide sufficient tissue for lysate preparation and run in duplicate for western blot.

Figure 2: Patient Sample Tissue Allocation Plan



Biopsy blocks were sectioned as indicated in Figure 1. Gum Tagacanth is used to attach the biopsy block to the cryostat chuck. Block A and B represent two blocks obtained from each patient participating in the Week 180 biopsy. Tissue sections from Block A and B were pooled for Western blot and RT-PCR analysis.

The assay precision for their validated WB was (b) (4)%, which is not unheard of for a primary human tissue-based WB. An RSD > (b) (4)% was considered a "fail" so the numbers in the table you have were all within (b) (4)% RSD. An RSD close to or less than (b) (4)% is better, especially if this was a clonally expanded cell line or homogenous primary tissue sample, but in this disease condition where there is known heterogeneity and ongoing degeneration of the tissue I don't know if it's possible to get a very high precision – so heterogeneity and a (b) (4)% RSD here might be reflective of the biology of the sample and not the assay itself. For instance, you can see the % RSD recommended for tissue in this paper (20-50% - http://www.nature.com/gt/journal/v12/n1s/fig_tab/3302627t3.html#figure-title). One could even argue that WB isn't a fully quantitative method to expect high precision, compared to say HPLC or mass spec method, which is why we had tried to get them to do the quantitative mass spec method that Hoffman had developed.

Keep in mind that the "failed" gels from their validation report were related to the calibration curve's linearity and not necessarily due to the inter-sample precision. The assay was validated such that the gel was considered a "fail" if the healthy standard curve's linearity was < (b) (4)%.

From: Farkas, Ronald
Sent: Thursday, May 12, 2016 8:22 AM
To: Unger, Ellis; Bhattaram, Atul; Rao, Ashutosh
Cc: Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Subject: RE: WB question

It isn't clear to me whether a single homogenate was divided in 2, or if 2 separate sets of cryosections were separately homogenized –

Ash, do you know?

Below is some text from the protocol:



From: Unger, Ellis
Sent: Thursday, May 12, 2016 12:17 AM
To: Bhattaram, Atul; Rao, Ashutosh
Cc: Farkas, Ronald; Breder, Christopher D; Bastings, Eric; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert
Subject: WB question

Dear All,

The agreement between gels 1 and 2 seems poor, at least for many patients (see table).

If gel 1 and gel 2 are run from different cuts of a single muscle sample, then the difference could be from heterogeneity within the sample, i.e., some differences would be expected.

BUT -- if they prepare a lysate from a single muscle sample, divide it, and run two gels on the same lysate, then these differences suggest that the assay has poor precision.

I've never run a Western blot and have very little knowledge, so if my question is naïve, I won't be offended!

Thoughts...

Treatment at Week 180	Subject	4th Biopsy Gel #1	4th Biopsy Gel #2	Average for 4th Biopsy; BLOQ set to 0	Average for 4th Biopsy Actual Values
30 mg/kg	002	BLOQ	0.28	0.14	0.15
	006	2.83	2.11	2.47	2.47
	007	BLOQ	BLOQ	0	0.16
	008	0.93	1.02	0.98	0.98
	009	0.58	0.46	0.52	0.52
	010	1.45	1.78	1.62	1.62
50 mg/kg	003	BLOQ	BLOQ	0	0.18
	004	1.22	0.66	0.96	0.96
	005 ⁹	NA	NA	0	0
	012	0.75	BLOQ	0.38	0.5
	013	NA	1.15	1.15	1.15
	015	2.43	1.67	2.05	2.05

Source: nda206488_0024_m1_us_111-info-amend_clinpharm-20151204.pdf

Temple, Robert

From: Jenkins, John K
Sent: Tuesday, May 17, 2016 12:24 PM
To: Unger, Ellis
Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy; Rao, Ashutosh
Subject: RE: First draft of Office Director Memo on Eteplirsen - NDA 206488

We can discuss more at 4. My view is that the Promovi data may allow us to have confidence that the drug is leading to dystrophin production, the first step in using it as a surrogate for AA. So, I'd like to have it to support a "substantial evidence" finding. If the data were to confirm a clear increase in dystrophin, even if small, I think we would be hard pressed not to grant AA given the current treatment options and severity of the disease. Then we would need to turn to how to confirm clinical benefit through either another exon or low-dose/high-dose randomization in the Promovi trial.

The dose ranging for this drug is clearly inadequate and will need to be addressed, but it is likely that will be post-marketing given the way the winds are blowing now.

From: Unger, Ellis
Sent: Tuesday, May 17, 2016 9:16 AM
To: Jenkins, John K
Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy; Rao, Ashutosh
Subject: RE: First draft of Office Director Memo on Eteplirsen - NDA 206488

John,

Having slept on this, I continue to have some reservations about the potential plan to use biopsy data from the ongoing Promovi study to provide evidence of effectiveness for eteplirsen.

The Promovi study is a baseline-controlled study. Presumably, if the applicant is correct and eteplirsen produces dystrophin, we should expect to see a dystrophin value of ~0.9% in the post-treatment samples.

The problem with the baseline-controlled analysis is that we have no idea whether there is degradation of dystrophin or loss of immunoreactivity during storage. I doubt whether anyone has ever banked muscle samples and analyzed them serially to assess this possibility. If there were loss of immunoreactive dystrophin at an absolute rate of, say, 0.1% per month, they could detect a difference on the basis of systematic error. (This seems like a "textbook" case of systematic error.) Of course degradation is conjecture at this point, and even if there is degradation, it could be much less than say, 0.1% per month. But this is why we demand studies with adequate controls.

One approach to allay concerns about changes with storage (though not perfect by any means) would be to consider all of the baseline samples, presumably obtained at different calendar dates, and see if there is a trend that suggests that the longer the samples were frozen, the lower the value. What would constitute "degradation" would be a judgment call.

Another approach would be a non-randomized comparison between the Week 24(?) samples from these patients who are now on treatment to the pre-treatment samples of the next *N* boys who enroll.

In any case, we need to think this through in advance.

The other problem I have is that I believe it would be unconscionable to approve a dose of 30 mg/kg/week, presumably leading to a dystrophin level of only ~0.9%, when we know that this dose fails to prevent decline in physical function. This would not be a problem if there were significant toxicity. But there is no known clinical

toxicity, and much higher doses might actually stabilize these patients and prevent progression. Optimistically speaking – higher doses, started early in life, might lead to a near-normal lifespan.

Finally, if we were to work out some kind of accelerated approval, we would have to engineer a way for the company to verify the clinical benefit, even though I recognize there is virtually no way to get the drug off the market once the genie is out of the bottle – even if benefit is not verified. A study with a different morpholino oligomer in boys with a different mutation, even if somehow persuasively positive, would only serve to prove the concept that this type of treatment can be effective. I don't see how one can consider two genetic defects and two oligomers to be interchangeable.

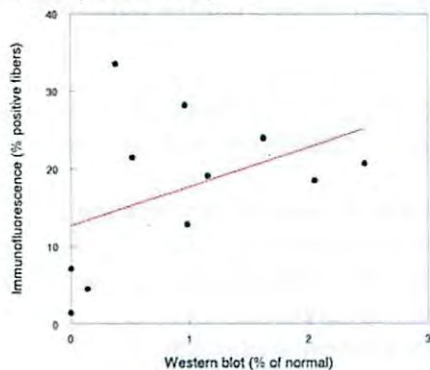
My suggestion, again, is to randomize patients in the ongoing Promovi study to remain on 30 mg/kg or have their dose significantly increased. The new treatment assignment would be double-blind. If there is more dystrophin with the higher vs. the lower dose, it is a win-win. And we'd have the answer within a year

Ellis

From: Unger, Ellis
Sent: Tuesday, May 17, 2016 8:08 AM
To: Jenkins, John K; Rao, Ashutosh
Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy; Farkas, Ronald; Breder, Christopher D; Bhattaram, Atul; Hawver, David; Freed, Lois M
Subject: RE: First draft of Office Director Memo on Eteplirsen - NDA 206488

Yes, the R-value was 0.42.

Figure 1: Correlation between Two Methods Used to Quantify Dystrophin in Skeletal Muscle: Patients from Study 201/202 (Week 180)



From: Jenkins, John K
Sent: Tuesday, May 17, 2016 8:00 AM
To: Unger, Ellis; Rao, Ashutosh
Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy; Farkas, Ronald; Breder, Christopher D; Bhattaram, Atul; Hawver, David; Freed, Lois M
Subject: RE: First draft of Office Director Memo on Eteplirsen - NDA 206488

Ellis

Another thought that occurred to me, has anyone looked at the correlation between the IHC and Western data for individual patients? In other words, for those at 180 weeks with the highest Western levels reported did they also have the highest % positive fibers?

John

From: Unger, Ellis
Sent: Monday, May 16, 2016 11:17 PM
To: Jenkins, John K; Rao, Ashutosh
Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy; Farkas, Ronald; Breder, Christopher D; Bhattaram, Atul; Hawver, David; Freed, Lois M
Subject: RE: First draft of Office Director Memo on Eteplirsen - NDA 206488

Thanks to both of you for the comments.

Monkey data - I'm verifying this, but to the best of my knowledge, the monkey data are based on some kind of quantitative PCR, with the goal to quantify mRNA. They seem to use the terms "splicing" and "skipping" interchangeably.

Bioquant data – My recollection of my observations in Columbus is consistent with the operations manual they submitted in the IND. This was not a particularly good way to analyze the immunohistochemistry slides, in my opinion (and I performed quantitative image analysis at NIH for a number of years). What they call "Bioquant" is essentially the same analysis as the fiber counting, and so I don't think it needs emphasis in my memo. (Realize that "Bioquant" is the name of a company, not the name of any kind of specific image analysis.)

Ash - on the Western blot, I wrote: "the intra-assay difference was >0.5% in Patients B, C, D, and J."

You said "The %RSD was : (b) (4) % for only one patient - 002, which I believe is subject H in your table. But, these values were below LOQ, I am not sure we could meaningfully interpret variability outside the validated range, it would defeat the purpose of validating a range."

But I wasn't referring to the %RSD, I was just talking about the absolute difference, the delta, between the two gels. Does that make sense?

John - I can write something about the samples in the freezer, but before I write, I want to see how this plays out over the next couple of days. If Sarepta believes that they can somehow get an approval letter without analyzing the samples, they will refuse to provide these analyses within a reasonable length of time. As much as they might like to give us definitively positive data within a brief time frame, they will be worried sick that if they analyze the samples and the analyses are negative, they will never get an approval. And if the samples are properly analyzed, they know that could happen.

Ellis

From: Jenkins, John K
Sent: Monday, May 16, 2016 9:58 PM
To: Rao, Ashutosh; Unger, Ellis; Bastings, Eric; Dunn, Billy; Farkas, Ronald; Breder, Christopher D; Bhattaram, Atul; Hawver, David; Freed, Lois M
Cc: Temple, Robert; Choy, Fannie (Yuet); Jenkins, John K
Subject: RE: First draft of Office Director Memo on Eteplirsen - NDA 206488

Here are some edits/comments on top of Ash's comments. As noted earlier, we need to resolve the technical issues that Ash raised.

I think you should also mention the availability of a substantially larger set of pre/post biopsy specimens that could be assayed to better evaluate dystrophin production. Leaving these data "in the freezer" when contemplating an AA based on scan dystrophin data does not make sense. While regulatory flexibility can be

used in making decisions, it is not wise to ignore data, particularly in a case like this one where the data in the NDA are so limited.

John

From: Rao, Ashutosh
Sent: Monday, May 16, 2016 2:56 PM
To: Unger, Ellis; Bastings, Eric; Dunn, Billy; Farkas, Ronald; Breder, Christopher D; Bhattaram, Atul; Hawver, David; Freed, Lois M; Jenkins, John K
Cc: Temple, Robert; Choy, Fannie (Yuet)
Subject: RE: First draft of Office Director Memo on Eteplirsen - NDA 206488

Dear Ellis,

Please see attached document with some suggested edits. Hope you find them useful. My apologies if some of the suggestions are naïve or addressed in other memos.

Best,
Ash

From: Unger, Ellis
Sent: Sunday, May 15, 2016 9:52 PM
To: Bastings, Eric; Dunn, Billy; Farkas, Ronald; Breder, Christopher D; Rao, Ashutosh; Bhattaram, Atul; Hawver, David; Freed, Lois M; Jenkins, John K
Cc: Temple, Robert; Choy, Fannie (Yuet)
Subject: First draft of Office Director Memo on Eteplirsen - NDA 206488

All,

Here's a draft of my eteplirsen memo. I am recommending a CR. Your thoughts are welcome.

As the story is still being written, there is no summary/conclusions section yet (and no benefit-risk framework).

My plan is to have this in Dr. Woodcock's inbox on Tuesday 5/17, as promised. Then I'll be away on leave: leaving mid-day on 5/18, returning the morning of 5/24 (and I won't have much time to do any FDA work).

Thanks in advance,

Ellis

Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Tuesday, May 17, 2016 7:49 PM
To: Woodcock, Janet
Cc: Jenkins, John K; Unger, Ellis; Temple, Robert; Dunn, Billy; Bastings, Eric; Choy, Fannie (Yuet)
Subject: Eteplirsen Package (NDA 206488)

Dr. Woodcock:

Attached please find the reviews and memos for NDA 206488 / eteplirsen for your review.

Office Director Memo	Director Memo	(b) (5)
 Eteplirsen (NDA 206488) Office Director Memo	 Eteplirsen (NDA 206488) Director Memo	
Clinical Review	Biostat Review	OCP Review
 Eteplirsen (NDA 206488) Clinical Review	 Eteplirsen (NDA 206488) Biostat Review	 Eteplirsen (NDA 206488) OCP Review

Thank you,
Fannie

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

Temple, Robert

From: Farkas, Ronald
Sent: Wednesday, May 18, 2016 5:32 PM
To: Dunn, Billy
Cc: Bastings, Eric; Unger, Ellis; Choy, Fannie (Yuet); Temple, Robert
Subject: RE: Sarepta: missing goal date language

I don't think this matters, but just to be clear, there was baseline tissue from 4 patients, but not for each assay: for the Western blot, baseline tissue from patients 5, 13 and 15 was used, but for the IF baseline tissue from patients 8, 13, and 15 was used. I don't know the reason, but I suppose it might be speculated that for patients 5 and 8 there was not enough to do both types of assays, so they used all the remaining tissue for patient 5 for the Western, and all the remaining tissue from patient 8 for the IF (As an aside, the IF for patient 8 was similar to the external controls, about 2% positive fibers, and about 10% of normal by Bioquant, so presumably it would have given a low reading if Western blot had been done instead of IF)

From: Jenkins, John K
Sent: Wednesday, May 18, 2016 5:21 PM
To: Farkas, Ronald; Dunn, Billy
Cc: Bastings, Eric; Unger, Ellis; Temple, Robert; Choy, Fannie (Yuet); Jenkins, John K
Subject: RE: Sarepta: missing goal date language

Thanks. I had missed the fact that the 180 week biopsies were from a different muscle group. I had only synapsed on the fact that the external control biopsies were from a different muscle group.

From: Farkas, Ronald
Sent: Wednesday, May 18, 2016 7:06 AM
To: Dunn, Billy; Jenkins, John K
Cc: Bastings, Eric; Unger, Ellis; Temple, Robert; Choy, Fannie (Yuet)
Subject: RE: Sarepta: missing goal date language

There were only 3 baseline samples available. The table I just sent a minute ago, which was Sarepta's, listed four, but the table below, which is also Sarepta's, lists the 3. Patient 15 and 13 were the two who also had biopsies at Week 180.

Thanks

Ron

Donor ¹	Anatomical Location	Dystrophin Mutation	Gender/Age (age at biopsy)	Source	
DMD	Biceps	Δ45-50	Male – 10 yrs	4658-us-201	
DMD	Biceps	Δ50	Male – 7 yrs		
DMD	Biceps	Δ52	Male – 9 yrs		
DMD	Deltoid	Δ45-50	Male – 7 yrs	4658-301	
DMD	Biceps	Δ45-50	Male – 15 yrs		
DMD	Biceps	Δ48-50	Male – 9 yrs		
DMD	Biceps	Δ48-50	Male – 9 yrs		
DMD	Biceps	Δ49-50	Male – 9 yrs		
DMD	Biceps	Δ52	Male – 9 yrs		
BMD	Quadriceps	Δ45-51	Male – 15 yrs		(b) (4)
BMD	Deltoid	Unknown	Male – 22 yrs		
BMD	Quadriceps	point mutation exon 14: c.2380G>A, p.E794K	Male – 4 yrs		
Non-B/DMD	Quadriceps	None	Male – 6 yrs		
Non-B/DMD	Unknown	None	Female – 12 yrs		
Non-B/DMD	Deltoid	None	Male – 46 yrs		

From: Farkas, Ronald
Sent: Wednesday, May 18, 2016 7:00 AM
To: Dunn, Billy; Jenkins, John K
Cc: Bastings, Eric; Unger, Ellis; Temple, Robert; Choy, Fannie (Yuet)
Subject: RE: Sarepta: missing goal date language

The week 180 biopsies were from deltoid. The control biopsies are listed in the table below. The three biopsies that were matched "by patient" were not matched by muscle group. Of the other 6 external samples 5 were biceps and one was deltoid.

APPENDIX 10. 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	8	Biceps	Δ45-50	421 m	
DMD #3	15	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	

From: Dunn, Billy
Sent: Tuesday, May 17, 2016 10:14 PM
To: Jenkins, John K
Cc: Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: Re: Sarepta: missing goal date language

That was Ron's edit. If he doesn't weigh in tonight, we'll get an answer to you first thing tomorrow.

Billy

From: Jenkins, John K
Sent: Tuesday, May 17, 2016 9:11 PM
To: Dunn, Billy
Cc: Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: RE: Sarepta: missing goal date language

Is it correct that the 180 week biopsies in the boys from Study 201/202 were from a different muscle group that then prior biopsies?

John

From: Dunn, Billy
Sent: Tuesday, May 17, 2016 7:35 PM
To: Jenkins, John K
Cc: Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: RE: Sarepta: missing goal date language

John,

Attached is the document revised by DNP and ODE1.

Billy

From: Jenkins, John K
Sent: Tuesday, May 17, 2016 5:36 PM
To: Choy, Fannie (Yuet)
Cc: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Jenkins, John K
Subject: RE: Sarepta: missing goal date language

Here is my proposed draft. I suggest DNP/ODE1 develop coordinated edits (rather than a stream of individual edits) so we can try to get this to JW tonight or tomorrow with a goal of scheduling a telecon this week.

John

From: Choy, Fannie (Yuet)
Sent: Tuesday, May 17, 2016 4:43 PM
To: Jenkins, John K
Cc: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: Sarepta: missing goal date language

Here's the proposed language for missing the PUDFA goal date:

(b) (5)

Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Wednesday, May 18, 2016 6:53 PM
To: Temple, Robert
Subject: FW: Sarepta: missing goal date language
Attachments: Message to Sarepta_EU RF_RT.DOC

[Here's the version that was printed.](#)

From: Dunn, Billy
Sent: Tuesday, May 17, 2016 7:35 PM
To: Jenkins, John K
Cc: Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: RE: Sarepta: missing goal date language

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[Attached is the document revised by DNP and ODE1.](#)

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To: Choy, Fannie (Yuet)
Cc: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Jenkins, John K
Subject: RE: Sarepta: missing goal date language

[Here is my proposed draft. I suggest DNP/ODE1 develop coordinated edits \(rather than a stream of individual edits\) so we can try to get this to JW tonight or tomorrow with a goal of scheduling a telecon this week.](#)

John

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Sent: Tuesday, May 17, 2016 4:43 PM
To: Jenkins, John K
Cc: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: Sarepta: missing goal date language

[Here's the proposed language for missing the PUDFA goal date:](#)

(b) (5)

Thanks
Fannie



Temple, Robert

From: Bastings, Eric
Sent: Friday, May 20, 2016 6:06 PM
To: Jenkins, John K; Temple, Robert; Unger, Ellis; Dunn, Billy
Subject: RE:

My position is that we first need to establish substantial evidence that dystrophin is increased. This is critical.

Then the question whether that evidence is reasonably likely to predict benefit is a more subjective decision, which will depend on the levels of dystrophin identified, among other things.

I can't say I know now where I sit yet, so the "(b) (5)" is overstated, for me.

ERic

From: Jenkins, John K
Sent: Friday, May 20, 2016 4:51 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE:

I think we want them to do Western and Immunohistochemistry, so I would add that to #1.

From: Temple, Robert
Sent: Friday, May 20, 2016 3:08 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject:

This is what I plan to send to JW with the proposed communication. Comments welcome:

JW,

Attached is the communication to Serepta proposed by the Division, ODE 1, and OND. It is clearly more insistent than what you suggested in your E-mail of May 8. There are 2 main reasons for this. We believe, based on the reviews by Ellis, Ash, and others, that:

1. The existing biopsy samples can be tested by Western blot in a short time (a few weeks to a month) and we would plan to work very closely with them to accomplish this. The contention that 3-6 months are needed for IRB clearance (with more time afterward to do the samples) is not credible
2. Good evidence of increased dystrophin is critical to the possible accelerated approval. There can be judgment as to the "reasonably likely to predict outcome" part of AA but the evidence for the surrogate should be strong and there are, as the reviews show, substantial doubts about whether the existing data show this. The new data should leave no uncertainty at all, either way. I should note that, without saying what the final reviews will say, that there is considerable support for the pathway you proposed at the AC meeting (AA based on dystrophin with various sources of support for reasonable likelihood) even if the dystrophin levels are not very high. The proposed message to Serepta more or less says that and it should be quite encouraging, if they are convinced that the levels are indeed increased.

What do you think?

Temple, Robert

From: Shamim Ruff <SRuff@Sarepta.com>
Sent: Friday, May 20, 2016 2:12 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Temple, Robert; Ed Kaye; Frank J. Sasinowski
Subject: Dystrophin Results
Attachments: Dystrophin PDPF Results For JW 20 may 2016.pptx

Dear Dr. Woodcock,

We would like to request a meeting as soon as possible to ensure that you are provided with an overview of the dystrophin data for eteplirsen. We believe that a full understanding of the complete dystrophin data set, especially the Week 180 biopsies, is critical to enable an informed decision. Given the gravity of the situation, we would request the opportunity to meet, either in person or by telephone.

Frank Sasinowski has brought to our attention that there is still confusion regarding the dystrophin data, in particular Table 1, Page 4 of the FDA Briefing Document (Slide # 3 in the attached deck). We would like to bring to your attention that the percent dystrophin positive fibers (PDPF) results may have been misinterpreted by Dr Farkas as detailed below.

The FDA slide shows the following; dystrophin positive fibers (PDPF) analyzed by (i) Nationwide Children's Hospital (NCH), (ii) Re-analysis by 3 blinded readers and the (iii) Week 180 biopsy samples.

Please note the following key points:

- Time-points for the first 3 biopsies were: 1) baseline 2) Weeks 12 or 24 and 3) Week 48
- In Study 201, baseline and on treatment samples (Wks 12 or 24) were processed at the same time
- In Study 202, the Week 48 samples were processed at a later date and separately from the Study 201 baseline samples
 - FDA recommendation was to disregard Wk 48 images.
 - FDA advised Sarepta that Wk 48 samples should not be re-read by the 3 blinded readers as the images had "a noticeably different background fluorescence than baseline, Wk 12 and Wk 24 images"
- In contrast, Study 202 Wk 180 biopsies were processed and analyzed simultaneously with the baseline/untreated control samples
 - Methods were in accordance with FDA agreed upon protocols
 - **Untreated samples** included the use of both Study 201 baseline (in patients with excess archived tissue) and untreated samples from the PROMOVI study.
 - Sarepta **did NOT initiate** or testing until the protocols were fully vetted by FDA.
- FDA's slide incorrectly compared the PDPF results of the Wk 180 treated samples to baseline samples from the original 201 biopsies.
 - **This is inappropriate** – as the Wk 180 treated samples should be compared to the untreated samples that were processed at the same time, using the same protocol.
 - The Wk 180 biopsy PDPF results demonstrate **17.39% for eteplirsen treated vs. 1.12% for baseline/untreated controls with a difference of 16.27%**

Please find attached the following slides:

Slide 3. FDA slide – misinterpreting the PDPF data

Slide 4. As FDA slide above – with baseline/untreated data included for Wk 180

Slide 5. Wk 180 biopsy data for the 3 baseline and 6 PROMOVI untreated samples. You will see that the results are very similar and distinctly lower than the treated sample.

Slide 6: Wk 180 results demonstrating de-novo dystrophin by 3 complementary methods

Slide 7: FDA communication recommending exclusion of Week 48 biopsy results

Background Information

Slide 9: Wk 180: Individual patient PDPF results for eteplirsen treated and untreated

Finally, it appears that FDA is suggesting that Sarepta had previously inflated the dystrophin results. This is not the case. The initial NCH results for PDPF were re-analyzed by 3 blinded readers as requested by the FDA. The NCH Wk 24 PDPF results (41% for 30 mg/kg treated patients vs 18% for baseline), were consistent with NCH Wk 180 PDPF results (37.3 % for eteplirsen vs 5.0 for untreated). According to FDA request, the Wk 24 and Wk 180 samples were re-analyzed by the 3 blinded readers and although numerically lower, at both time-points confirmation of a significant increase in dystrophin was demonstrated.

Please note that there were no interpretable Western Blot data for the first 3 biopsies; only the 4th biopsy/Week 180 samples had WB results. Although WB results confirmed dystrophin production, the numerical results were not expected to be similar to PDPF, as these were 2 distinct assays.

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

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**Clarification for
FDA Briefing Document
Table 1 page 4**

20 MAY 2016

Content

- FDA's slide (Table 1, P4 of BD) – excludes Week 180 baseline/untreated results
- Slide including baseline/untreated results for Week 180
- Week 180: Individual PDPF results for 3 Baseline and 6 Untreated PROMOVI samples
- Week 180 Dystrophin Results by 3 Different Methods
- FDA Communication To Disregard Week 48 Results



Standardized Reading by the 3 Blinded Readers (blue) Gave Much Lower Estimates Than the Original Reading (grey)

	Nationwide Children's Hospital analysis					Re-analysis by 3 blinded readers					eteplirsen 17
	Baseline	Week 12	Week 24	Week 48	Week 180 (n=11)	Baseline	Week 12	Week 24	Week 48	Week 180 (n=11)	
30 mg/kg (n=4)	18		41	70	14		27	23			
50 mg/kg (n=4)	11	12		54	15	17		25			
Placebo to 30 mg/kg (n=2)	24		24	58	10		10	9			
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		10			

Week 180 PDPF: Correct Interpretation of Eteplirsen Result Requires Comparison To Appropriate Baseline/Untreated Results

	Nationwide Children's Hospital analysis				Re-analysis by 3 blinded readers				
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48	Week 180 (n=11)
30 mg/kg (n=4)	18		41	70	14		27	23	eteplirsen 17 Baseline 1.12
50 mg/kg (n=4)	11	12		54	15	17		25	
Placebo to 30 mg/kg (n=2)	24		24	58	10		10		
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		10	

Week 180
Change from Baseline
 $17.39\% - 1.12\% = 16.27\%$

Week 180 PDPF: Comparable Results Between Study 201/202 Baseline and PROMOVI Untreated Samples

Baseline/Untreated Samples	Individual PDPF Results	Mean PDPF
<i>201/202 Baseline Samples</i>		
201/202 (Patient # 08)	1.09	1.29
201/202 (Patient #15)	0.19	
201/202 (Patient # 13)	2.58	
<i>Untreated PROMOVI – first 6 patients -biopsy samples</i>		
Patient # 1	0.15	1.04
Patient #2	0.29	
Patient # 3	3.95	
Patient #4	0.39	
Patient #5	0.36	
Patient #6	1.11	
<i>Mean of All 9 Samples</i>		1.12

Week 180 Biopsy Demonstrated an Increase in Dystrophin by Three Methods

	WB % of Normal	% Intensity	PDPF
MEAN (Baseline/Untreated)	0.08	9.41	1.12
MEAN (Treated—Week 180)	0.93	22.61	17.39
Absolute Difference	+0.85	+13.2	+16.27
Statistical Significance (p-value)	0.007	<0.001	<0.001
Fold Increase	11.6	2.4	15.5

FDA communication: Email 28 October 2014

- ◆ FDA communicated that Week 48 images were not to be re-analyzed
 - No matched control biopsies for Week 48
 - Images at Week 48 had different background than baseline
 - “Week 48 images have noticeably different background fluorescence than the baseline, Week 12, and Week 24 images. Thus, any differences in positive fiber count that might be identified between earlier time points and the Week 48 time point may not be attributable to an effect of eteplirsen, but instead may be due to these confounding factors”
 - “Furthermore, differences in the appearance of the Week 48 images compared to earlier time points may unblind the image readers and introduce additional bias”
 - “Because all patients were being treated with eteplirsen at Week 48, there are no matched control biopsies to help control for these sources of bias. For these reasons, the primary endpoint should not be based on the Week 48 images”

BACKGROUND

Week 180: Eteplisen Treated, Baseline and Untreated: 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 No.	Multi-rater PDPF % Untreated
1	0.15
2	0.29
3	3.95
4	0.39
5	0.36
6	1.11

Temple, Robert

From: Jenkins, John K
Sent: Friday, May 20, 2016 6:53 PM
To: Temple, Robert; Farkas, Ronald; Unger, Ellis
Cc: Dunn, Billy; Bastings, Eric
Subject: Re: Dystrophin Results

All the more reason to address all the issues by waiting to receive the new data.

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

From: Temple, Robert
Sent: Friday, May 20, 2016 6:00 PM
To: Farkas, Ronald; Unger, Ellis
Cc: Dunn, Billy; Bastings, Eric; Jenkins, John K
Subject: RE: Dystrophin Results

Thanks, all that seems like a good reason to do the immunohisto on the new samples as well as W blot.

From: Farkas, Ronald
Sent: Friday, May 20, 2016 5:49 PM
To: Temple, Robert; Unger, Ellis
Cc: Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

Bob,
See below in red
Thanks
Ron

From: Temple, Robert
Sent: Friday, May 20, 2016 4:37 PM
To: Unger, Ellis; Farkas, Ronald
Subject: RE: Dystrophin Results

OK, let me be clear...

The slices were made and stained at the time the samples were obtained...this is one point that can be confusing. In Study 201, all the patients had baseline muscle biopsies from which slices were made, stained, and photographed. These photos were then read under poor conditions by NCH, then later re-read by the 3 blinded readers. That's all separate from anything done at Week 180. These are the numbers shown in slide 37 under the "nationwide" and "re-analysis" headings.

When the 4th biopsy came along, Sarepta said there was actually some baseline tissue left over for a few patients. this unstained old tissue, plus new tissue from patients outside the study, was then processed in parallel, going through staining, photographing, and reading. This 4th biopsy tissue led to the 17% in treated patients vs. the 1% positive fibers in controls.

When we made them do a blinded re-read comparing the week 24 and week 48 with baseline, the differences between baseline and later were much smaller. Yes, that's true, and these are the numbers in slide 37 under "nationwide" and "re-analysis"

Slide 34, e.g., shows values of 49 -70% for all 12 patients at 48 weeks vs 7-24 % for baseline, on original reads. Yes

The blinded re-analysis showed 48 week values of 9-25% at 48 weeks vs 10-15% values for baseline, a much small difference, if, indeed, any difference. yes

Etiplirsen at 180 weeks read 17%, and I can't tell if the baseline samples were re-read,...this is perhaps a part that wasn't clear to you. the baseline samples are newly cut and stained samples, 6 from outside the study entirely, and 3 from old tissue left over from the original baseline biopsies. There is no re-read of these samples, the only number is the 1% positive fibers

but in slide 35 no other control is mentioned so one would assume that the relevant control is the 11-15% values. There are a series of slides, each showing the same table, but pointing to different things. Slide 35 is comparing the original reading of the baseline through week 48 samples to the re-read by the 3 blinded readers of the baseline through week 48 images. It's not until slide 37 that it's pointed out that it's concerning that the original baseline samples had 9-23% positive fibers, whereas the Week 180 control samples had 1% positive fibers; seemingly these numbers should have been more similar.

Now on slide 37 it refers to new controls for the 4th biopsy (why?)...as noted above, the controls for the 4th biopsy were new. It was not a re-reading of the original baseline images

but it does not say what the new controls were...everything can't be on one slide. The methods and controls were explained on other slides, for example slide 18

Shortcomings of Controls Used for 4th Biopsy

- Control samples from different muscle groups used - biceps, quadriceps, deltoid - and data combined for comparison to deltoid samples from 4th biopsy
- Baseline comparator only available from 2 DMD patients and from a different muscle group
- Healthy controls not sex-matched – one female and two male healthy controls combined for mean value
- Dystrophin variability in healthy controls (51%-95%)

18

and the question (difference in method vs difference in controls does not make it clear. ...the key point in what Sarepta is now writing to you is the WE are very clear on where the data and numbers came from. No doubt it's confusing, and difficult to explain in the very limited time we were forced to use because so much time had to be devoted to the open public hearing.

Why would they want new controls and not the same patient controls used all along? ...the percent positive fiber method is very sensitive to the exact staining and rinsing conditions, and probably other things too. Unless slides are processed side-by-side with the exact same solutions and rinses, the immunofluorescence might not be comparable.

And indeed it does say controls were 1%. the Week 180 controls had 1% positive fibers

Slide 38 ignores the 1% and again invites a comparison of 17% (180 week) vs 11-15%. Slide 38 doesn't ignore anything, and none of the other slides, nor anyone in DNP ignores anything. Slide 37 describes our concern that, even considering differences that can arise from processing, the original baseline samples and Week 180 controls are 17-fold difference, a huge difference. Slide 38 then describes our concern that the Week 180 eteplirsen-treated samples, which should seemingly show much more positive fibers, are not very different from the percent positive fibers in the original baseline samples.

Help!!!

Sent: Friday, May 20, 2016 4:09 PM
To: Temple, Robert; Farkas, Ronald; Dunn, Billy; Bastings, Eric
Subject: Re: Dystrophin Results

We have a datafile fibers1.xpt or fibers2.xpt that has the original reads from baseline, week 12, week24, ?week 48 and week 180 read by the woman at Children's AND the 3 masked readers.

Sent from my BlackBerry.

From: Temple, Robert
Sent: Friday, May 20, 2016 2:56 PM
To: Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

I knew the Western blot 180 week used controls that were mostly new (with only 3 available samples) but I thought the immunofluorescence assessment used the original controls (re-read with the 180 Week samples. So you are saying that (slide 37) the week 180 17% positive was compared with NEW controls that averaged about 1% and there was no comparison with the baseline samples, reread.

From: Farkas, Ronald
Sent: Friday, May 20, 2016 3:32 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

6 are entirely new controls from outside study 201/202. Three are from baseline tissue from study 201/202 patients (patients 8, 13, and 15). It's important to understand that the week 180 numbers are not from a rereading of prior images. Instead, new tissue sections were stained, photographed, and read using the improved methods arrived at with FDA's input. We are impressed that this new tissue gave much lower positive fiber counts than the original tissue. It's not possible to know, however, if the difference in percent positive fibers is the result of a difference in the methodology (different antibody dilutions and washing steps can lead to very different intensities and percent positive fibers), or to differences in the tissue itself. This was all explained in the reviews and at the AC meeting.

Thanks
Ron

From: Temple, Robert
Sent: Friday, May 20, 2016 3:18 PM

To: Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

Are the 4th biopsy controls the original baseline controls, reread properly, or are they new controls (other people). If they are the baseline controls, then there is a 17% vs 1% positive fiber rate. Are we impressed by that?

From: Farkas, Ronald
Sent: Friday, May 20, 2016 3:07 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

We were correct in the way we presented the data. We said the 4th biopsy controls had 1% positive fibers – that is in the title of the slide, and that is what Shamin states in her email.

Thanks
Ron

- The 4th biopsy controls had 1% positive fibers, vs. 10-15% for the original baseline samples (rectangle)
- Difference in methods? Or difference in controls?

	Nationwide Children's Hospital analysis				Re-analysis by 3 blinded readers				
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48	Week 180 (n=11)
30 mg/kg (n=4)	18		41	70	14		27	23	eteplirsen 17
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Placebo to 30 mg/kg (n=2)	24		24	58	10		10	9	
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		10	

37

From: Temple, Robert
Sent: Friday, May 20, 2016 2:23 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald
Subject: FW: Dystrophin Results

This appears to assert that the immunofluorescence slides (180 weeks) with reread baseline data had baseline values of about 1%, not the 14-15% we said. Is that correct?

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, May 20, 2016 2:12 PM
To: Woodcock, Janet

Cc: Moscicki, Richard; Temple, Robert; Ed Kaye; Frank J. Sasinowski
Subject: Dystrophin Results

Dear Dr. Woodcock,

We would like to request a meeting as soon as possible to ensure that you are provided with an overview of the dystrophin data for eteplirsen. We believe that a full understanding of the complete dystrophin data set, especially the Week 180 biopsies, is critical to enable an informed decision. Given the gravity of the situation, we would request the opportunity to meet, either in person or by telephone.

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The FDA slide shows the following; dystrophin positive fibers (PDPF) analyzed by (i) Nationwide Children's Hospital (NCH), (ii) Re-analysis by 3 blinded readers and the (iii) Week 180 biopsy samples.

Please note the following key points:

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- In Study 202, the Week 48 samples were processed at a later date and separately from the Study 201 baseline samples
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 - FDA advised Sarepta that Wk 48 samples should not be re-read by the 3 blinded readers as the images had "a noticeably different background fluorescence than baseline, Wk 12 and Wk 24 images"
- In contrast, Study 202 Wk 180 biopsies were processed and analyzed simultaneously with the baseline/untreated control samples
 - Methods were in accordance with FDA agreed upon protocols
 - **Untreated samples** included the use of both Study 201 baseline (in patients with excess archived tissue) and untreated samples from the PROMOVI study.
 - Sarepta **did NOT initiate** or testing until the protocols were fully vetted by FDA.
- FDA's slide incorrectly compared the PDPF results of the Wk 180 treated samples to baseline samples from the original 201 biopsies.
 - **This is inappropriate** – as the Wk 180 treated samples should be compared to the untreated samples that were processed at the same time, using the same protocol.
 - The Wk 180 biopsy PDPF results demonstrate **17.39% for eteplirsen treated vs. 1.12% for baseline/untreated controls with a difference of 16.27%**

Please find attached the following slides:

Slide 3. FDA slide – misinterpreting the PDPF data

Slide 4. As FDA slide above – with baseline/untreated data included for Wk 180

Slide 5. Wk 180 biopsy data for the 3 baseline and 6 PROMOVI untreated samples. You will see that the results are very similar and distinctly lower than the treated sample.

Slide 6: Wk 180 results demonstrating de-novo dystrophin by 3 complementary methods

Slide 7: FDA communication recommending exclusion of Week 48 biopsy results

Background Information

Slide 9: Wk 180: Individual patient PDPF results for eteplirsen treated and untreated

Finally, it appears that FDA is suggesting that Sarepta had previously inflated the dystrophin results. This is not the case. The initial NCH results for PDPF were re-analyzed by 3 blinded readers as requested by the FDA. The NCH Wk 24 PDPF results (41% for 30 mg/kg treated patients vs 18% for baseline), were consistent with NCH Wk 180 PDPF results (37.3 % for eteplirsen vs 5.0 for untreated). According to FDA request, the Wk 24 and Wk 180 samples were re-analyzed by the 3 blinded readers and although numerically lower, at both time-points confirmation of a significant increase in dystrophin was demonstrated.

Please note that there were no interpretable Western Blot data for the first 3 biopsies; only the 4th biopsy/Week 180 samples had WB results. Although WB results confirmed dystrophin production, the numerical results were not expected to be similar to PDPF, as these were 2 distinct assays.

Regards,
Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality

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e sruff@sarepta.com



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Temple, Robert

From: Dunn, Billy
Sent: Friday, May 20, 2016 6:52 PM
To: Bastings, Eric; Jenkins, John K; Temple, Robert; Unger, Ellis
Subject: RE:

Correct – that is the serial process (first establish substantial evidence, which is what this request is about, then consider reasonable likelihood, which will involve subjectivity) that we all discussed.

Bob – I think deleting [REDACTED] (b) (5)
[REDACTED] (b) (5)
[REDACTED] (b) (5) is reasonable and doesn't change the message you
are conveying.

Billy

From: Bastings, Eric
Sent: Friday, May 20, 2016 6:06 PM
To: Jenkins, John K; Temple, Robert; Unger, Ellis; Dunn, Billy
Subject: RE:

My position is that we first need to establish substantial evidence that dystrophin is increased. This is critical.

Then the question whether that evidence is reasonably likely to predict benefit is a more subjective decision, which will depend on the levels of dystrophin identified, among other things.

I can't say I know now where I sit yet, so the "[REDACTED] (b) (5)" is overstated, for me.

ERic

From: Jenkins, John K
Sent: Friday, May 20, 2016 4:51 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE:

I think we want them to do Western and Immunohistochemistry, so I would add that to #1.

From: Temple, Robert
Sent: Friday, May 20, 2016 3:08 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject:

This is what I plan to send to JW with the proposed communication. Comments welcome:

JW,

Attached is the communication to Serepta proposed by the Division, ODE 1, and OND. It is clearly more insistent than what you suggested in your E-mail of May 8. There are 2 main reasons for this. We believe, based on the reviews by Ellis, Ash, and others, that:

1. The existing biopsy samples can be tested by Western blot in a short time (a few weeks to a month) and we would plan to work very closely with them to accomplish this. The contention that 3-6 months are needed for IRB clearance (with more time afterward to do the samples) is not credible
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What do you think?

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From: Jenkins, John K
Sent: Friday, May 20, 2016 7:23 PM
To: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis
Subject: Re:

Please make sure the statement we propose to send is 100% accurate.

John

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

From: Dunn, Billy
Sent: Friday, May 20, 2016 6:54 PM
To: Bastings, Eric; Jenkins, John K; Temple, Robert; Unger, Ellis
Subject: RE:

Correct – that is the serial process (first establish substantial evidence, which is what this request is about, then consider reasonable likelihood, which will involve subjectivity) that we all discussed.

Bob – I think deleting

(b) (5)

(b) (5)

(b) (5)

is reasonable and doesn't change the message you are conveying.

Billy

From: Bastings, Eric
Sent: Friday, May 20, 2016 6:06 PM
To: Jenkins, John K; Temple, Robert; Unger, Ellis; Dunn, Billy
Subject: RE:

My position is that we first need to establish substantial evidence that dystrophin is increased. This is critical.

Then the question whether that evidence is reasonably likely to predict benefit is a more subjective decision, which will depend on the levels of dystrophin identified, among other things.

I can't say I know now where I sit yet, so the (b) (5) is overstated, for me.

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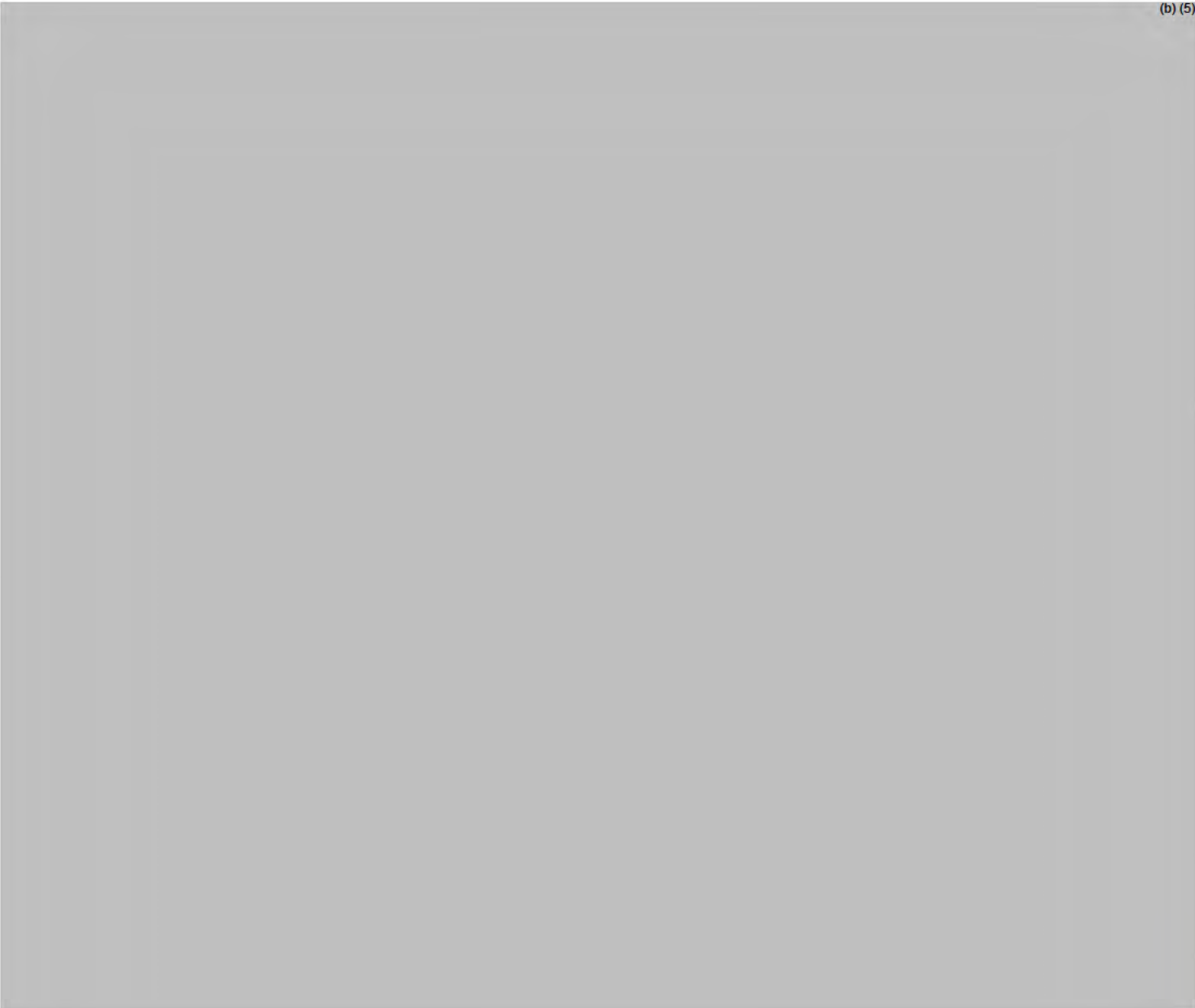
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What do you think?



IW

proposed by the
Division, OAE,
and OND
It is

Attached is the 4. communication
more insistent than what you suggested in
your E-mail of May 8. There are 2
reasons for this: 1. We believe, based on
~~experience~~ ^{the reviews} of Eller, Ash, + others,

1. That the existing biopsy sampler can be
fected ~~for~~ by a wetter blot. in a short
time (2-3 ~~months~~ ^{weeks} at most) The contention
that 3-6 months are needed for IRB
clearance ^(with more time allowed for the assays) is not ^{credible}

2. Good evidence of increased dystrophin is
critical to the possible ~~approval~~ accelerated
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reviews will say, that there is considerable
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The proposed message to Sercepta almost
says that, and should be encouraging
if they are convinced that levels
are indeed increased

you
mentioned
at the
meeting

What do I think

Philips, Howard

From: Bastings, Eric
Sent: Friday, May 20, 2016 8:36 AM
To: Jenkins, John K; Temple, Robert
Cc: Unger, Ellis; Dunn, Billy
Subject: Eteplirsen

Any news about whether we can send our message to Sarepta?

The clock is ticking...

Eric

Philips, Howard

From: Temple, Robert
Sent: Friday, May 20, 2016 5:35 PM
To: Blount, Aprile
Subject: FW:

OK, this is what I want to go to JW, with one change: The first sentence should read: 1. The existing biopsy samples can be tested by Western blot and immunohistochemistry in a short time...

I am still waiting for possible suggestions from Billy, Eric, and Ellis, but this should do it. Can go out on Monday.

From: Temple, Robert
Sent: Friday, May 20, 2016 3:08 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject:

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What do you think?

Philips, Howard

From: Temple, Robert
Sent: Friday, May 20, 2016 2:23 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald
Subject: FW: Dystrophin Results
Attachments: Dystrophin PDPF Results For JW 20 may 2016.pptx.html

This appears to assert that the immunofluorescence slides (180 weeks) with reread baseline data had baseline values of about 1%, not the 14-15% we said. Is that correct?

From: Shamim Ruff [mailto:SRuff@Sarepta.com]
Sent: Friday, May 20, 2016 2:12 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Temple, Robert; Ed Kaye; Frank J. Sasinowski
Subject: Dystrophin Results

Dear Dr. Woodcock,

We would like to request a meeting as soon as possible to ensure that you are provided with an overview of the dystrophin data for eteplirsen. We believe that a full understanding of the complete dystrophin data set, especially the Week 180 biopsies, is critical to enable an informed decision. Given the gravity of the situation, we would request the opportunity to meet, either in person or by telephone.

Frank Sasinowski has brought to our attention that there is still confusion regarding the dystrophin data, in particular Table 1, Page 4 of the FDA Briefing Document (Slide # 3 in the attached deck). We would like to bring to your attention that the percent dystrophin positive fibers (PDPF) results may have been misinterpreted by Dr Farkas as detailed below.

The FDA slide shows the following; dystrophin positive fibers (PDPF) analyzed by (i) Nationwide Children's Hospital (NCH), (ii) Re-analysis by 3 blinded readers and the (iii) Week 180 biopsy samples.

Please note the following key points:

- Time-points for the first 3 biopsies were: 1) baseline 2) Weeks 12 or 24 and 3) Week 48
- In Study 201, baseline and on treatment samples (Wks 12 or 24) were processed at the same time
- In Study 202, the Week 48 samples were processed at a later date and separately from the Study 201 baseline samples
 - FDA recommendation was to disregard Wk 48 images.
 - FDA advised Sarepta that Wk 48 samples should not be re-read by the 3 blinded readers as the images had "a noticeably different background fluorescence than baseline, Wk 12 and Wk 24 images"
- In contrast, Study 202 Wk 180 biopsies were processed and analyzed simultaneously with the baseline/untreated control samples
 - Methods were in accordance with FDA agreed upon protocols
 - **Untreated samples** included the use of both Study 201 baseline (in patients with excess archived tissue) and untreated samples from the PROMOVI study.
 - Sarepta **did NOT initiate** or testing until the protocols were fully vetted by FDA.
- FDA's slide incorrectly compared the PDPF results of the Wk 180 treated samples to baseline samples from the original 201 biopsies.
 - **This is inappropriate** – as the Wk 180 treated samples should be compared to the untreated samples that were processed at the same time, using the same protocol.

- The Wk 180 biopsy PDPF results demonstrate **17.39% for eteplirsen treated vs. 1.12% for baseline/untreated controls with a difference of 16.27%**

Please find attached the following slides:

Slide 3. FDA slide – misinterpreting the PDPF data

Slide 4. As FDA slide above – with baseline/untreated data included for Wk 180

Slide 5. Wk 180 biopsy data for the 3 baseline and 6 PROMOVI untreated samples. You will see that the results are very similar and distinctly lower than the treated sample.

Slide 6: Wk 180 results demonstrating de-novo dystrophin by 3 complementary methods

Slide 7: FDA communication recommending exclusion of Week 48 biopsy results

Background Information

Slide 9: Wk 180: Individual patient PDPF results for eteplirsen treated and untreated

Finally, it appears that FDA is suggesting that Sarepta had previously inflated the dystrophin results. This is not the case. The initial NCH results for PDPF were re-analyzed by 3 blinded readers as requested by the FDA. The NCH Wk 24 PDPF results (41% for 30 mg/kg treated patients vs 18% for baseline), were consistent with NCH Wk 180 PDPF results (37.3 % for eteplirsen vs 5.0 for untreated). According to FDA request, the Wk 24 and Wk 180 samples were re-analyzed by the 3 blinded readers and although numerically lower, at both time-points confirmation of a significant increase in dystrophin was demonstrated.

Please note that there were no interpretable Western Blot data for the first 3 biopsies; only the 4th biopsy/Week 180 samples had WB results. Although WB results confirmed dystrophin production, the numerical results were not expected to be similar to PDPF, as these were 2 distinct assays.

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

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

Philips, Howard

From: Temple, Robert
Sent: Friday, May 20, 2016 5:31 PM
To: Blount, Aprile
Subject: FW: Sarepta: missing goal date language
Attachments: Message to Sarepta_EU RF_RT.DOC.html

Aprile, I want to send JW a note with this attachment (just the attachment, not the rest of it)

From: Jenkins, John K
Sent: Wednesday, May 18, 2016 6:50 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy
Subject: Fw: Sarepta: missing goal date language

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

From: Dunn, Billy <Billy.Dunn@fda.hhs.gov>
Sent: Tuesday, May 17, 2016 7:37 PM
To: Jenkins, John K
Cc: Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: RE: Sarepta: missing goal date language

John,

Attached is the document revised by DNP and ODE1.

Billy

From: Jenkins, John K
Sent: Tuesday, May 17, 2016 5:36 PM
To: Choy, Fannie (Yuet)
Cc: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Jenkins, John K
Subject: RE: Sarepta: missing goal date language

Here is my proposed draft. I suggest DNP/ODE1 develop coordinated edits (rather than a stream of individual edits) so we can try to get this to JW tonight or tomorrow with a goal of scheduling a telecon this week.

John

From: Choy, Fannie (Yuet)
Sent: Tuesday, May 17, 2016 4:43 PM
To: Jenkins, John K
Cc: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: Sarepta: missing goal date language

Here's the proposed language for missing the PUDFA goal date:

Thanks
Fannie

Philips, Howard

From: Farkas, Ronald
Sent: Friday, May 20, 2016 3:32 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

6 are entirely new controls from outside study 201/202. Three are from baseline tissue from study 201/202 patients (patients 8, 13, and 15). It's important to understand that the week 180 numbers are not from a rereading of prior images. Instead, new tissue sections were stained, photographed, and read using the improved methods arrived at with FDA's input. We are impressed that this new tissue gave much lower positive fiber counts than the original tissue. It's not possible to know, however, if the difference in percent positive fibers is the result of a difference in the methodology (different antibody dilutions and washing steps can lead to very different intensities and percent positive fibers), or to differences in the tissue itself. This was all explained in the reviews and at the AC meeting.

Thanks
Ron

From: Temple, Robert
Sent: Friday, May 20, 2016 3:18 PM
To: Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

Are the 4th biopsy controls the original baseline controls, reread properly, or are they new controls (other people). If they are the baseline controls, then there is a 17% vs 1% positive fiber rate. Are we impressed by that?

From: Farkas, Ronald
Sent: Friday, May 20, 2016 3:07 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

We were correct in the way we presented the data. We said the 4th biopsy controls had 1% positive fibers – that is in the title of the slide, and that is what Shamin states in her email.

Thanks
Ron

- The 4th biopsy controls had 1% positive fibers
- 15% for the original baseline samples (rectal)
- Difference in methods? Or difference in controls?

	Nationwide Children's Hospital analysis				Re-analysis by 3 blinded			
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48
30 mg/kg (n=4)	18		41	70	14		27	
50 mg/kg (n=4)	11	12		54	15	17		
Placebo to 30 mg/kg (n=2)	24		24	58	10		10	
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		

From: Temple, Robert
Sent: Friday, May 20, 2016 2:23 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald
Subject: FW: Dystrophin Results

This appears to assert that the immunofluorescence slides (180 weeks) with reread baseline data had baseline values of about 1%, not the 14-15% we said. Is that correct?

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, May 20, 2016 2:12 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Temple, Robert; Ed Kaye; Frank J. Sasinowski
Subject: Dystrophin Results

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Please note that there were no interpretable Western Blot data for the first 3 biopsies; only the 4th biopsy/Week 180 samples had WB results. Although WB results confirmed dystrophin production, the numerical results were not expected to be similar to PDPF, as these were 2 distinct assays.

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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Temple, Robert

From: Jenkins, John K
Sent: Sunday, May 22, 2016 3:15 PM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Temple, Robert
Subject: Re:

We are not going to act before the PDUFA goal date. We need to see JW's memo to understand her rationale for approval. We may want to request a meeting with her to discuss her conclusions and the implications. This is too important a decision to rush an action in 4 days.

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

From: Bastings, Eric
Sent: Sunday, May 22, 2016 2:12 PM
To: Unger, Ellis; Jenkins, John K; Dunn, Billy; Temple, Robert
Subject: RE:

It will be good to know if this is AA or full approval.

I will get a label in shape ASAP.

Section 14 will depend on Dr. Woodcock's memo, so we will have to wait for that.

We can possibly act by the PDFa date, as all of our reviews are complete, and labeling should go very quick.

Eric

From: Unger, Ellis
Sent: Sunday, May 22, 2016 2:10 PM
To: Jenkins, John K; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: Re:

All,

I spoke to Bob. He sent the email and the proposed text for Sarepta to Janet last week. So she'd seen it.

He may try to call her tomorrow.

And I would presume this will be an AA.

Ellis

Sent from my BlackBerry.

From: Jenkins, John K
Sent: Sunday, May 22, 2016 6:49 AM
To: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis

Subject: Re:

What is happening with the communication to Sarepta?

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

From: Jenkins, John K
Sent: Friday, May 20, 2016 7:23 PM
To: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis
Subject: Re:

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John

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Subject: RE:

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Bob – I think deleting

(b) (5)

(b) (5)

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is reasonable and doesn't change the message you are conveying.

Billy

From: Bastings, Eric
Sent: Friday, May 20, 2016 6:06 PM
To: Jenkins, John K; Temple, Robert; Unger, Ellis; Dunn, Billy
Subject: RE:

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Then the question whether that evidence is reasonably likely to predict benefit is a more subjective decision, which will depend on the levels of dystrophin identified, among other things.

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What do you think?

Temple, Robert

From: Jenkins, John K
Sent: Sunday, May 22, 2016 12:51 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy
Subject: Fw: Action

FYI.

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

From: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Sent: Sunday, May 22, 2016 11:13 AM
To: Unger, Ellis
Cc: Jenkins, John K
Subject: Action

I have finished my review of all the Sarepta data and am unchanged in my opinion. Ellis I note your memo is on draft. Do you know when you will finish? I would like to talk to you, tomorrow am if possible.

If you are concerned about precedent here, I would point out 314.126 which authorizes the Center Director to waive certain elements going into an assessment of adequate and well controlled, although the trials must still be controlled

I expect to finalize my decisional memo in the next few days. Jw

Temple, Robert

From: Jenkins, John K
Sent: Monday, May 23, 2016 8:43 AM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Temple, Robert
Cc: Jenkins, John K
Subject: RE:

I have been in communication with JW this morning by e-mail. This is what we have agreed:

1. She plans to send us her draft review memo in the next few days
2. After we receive her review memo she will schedule a time for the review team to meet with her and discuss her conclusions/recommended actions
3. She is not in favor of rushing to ask that the data from the PROMOVI trial be submitted before action. She understands the rationale, but thinks we need to take time to develop a plan for how the data will be analyzed/processed.
4. She agrees we need to communicate to Sarepta that we will miss the PDUFA goal date. I drafted the language below and she concurred
5. She expects Sarepta to call her on receipt of this language and she will tell them to "keep responding to FDA requests."

Here is the draft text I developed. I suggest Billy e-mail this to them this morning.

(b) (5)

Comments?

John

From: Bastings, Eric
Sent: Sunday, May 22, 2016 2:12 PM
To: Unger, Ellis; Jenkins, John K; Dunn, Billy; Temple, Robert
Subject: RE:

It will be good to know if this is AA or full approval.

I will get a label in shape ASAP.

Section 14 will depend on Dr. Woodcock's memo, so we will have to wait for that.

We can possibly act by the PDFA date, as all of our reviews are complete, and labeling should go very quick.

Eric

From: Unger, Ellis
Sent: Sunday, May 22, 2016 2:10 PM
To: Jenkins, John K; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: Re:

All,

I spoke to Bob. He sent the email and the proposed text for Sarepta to Janet last week. So she'd seen it.

He may try to call her tomorrow.

And I would presume this will be an AA.

Ellis

Sent from my BlackBerry.

From: Jenkins, John K
Sent: Sunday, May 22, 2016 6:49 AM
To: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis
Subject: Re:

What is happening with the communication to Sarepta?

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

From: Jenkins, John K
Sent: Friday, May 20, 2016 7:23 PM
To: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis
Subject: Re:

Please make sure the statement we propose to send is 100% accurate.

John

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Sent: Friday, May 20, 2016 6:54 PM
To: Bastings, Eric; Jenkins, John K; Temple, Robert; Unger, Ellis
Subject: RE:

Correct – that is the serial process (first establish substantial evidence, which is what this request is about, then consider reasonable likelihood, which will involve subjectivity) that we all discussed.

Bob – I think deleting [REDACTED] (b) (5)
[REDACTED] (b) (5)
[REDACTED] (b) (5) is reasonable and doesn't change the message you are conveying.

Billy

From: Bastings, Eric
Sent: Friday, May 20, 2016 6:06 PM
To: Jenkins, John K; Temple, Robert; Unger, Ellis; Dunn, Billy
Subject: RE:

My position is that we first need to establish substantial evidence that dystrophin is increased. This is critical.

Then the question whether that evidence is reasonably likely to predict benefit is a more subjective decision, which will depend on the levels of dystrophin identified, among other things.

I can't say I know now where I sit yet, so the [REDACTED] (b) (5) s overstated, for me.

ERIC

From: Jenkins, John K
Sent: Friday, May 20, 2016 4:51 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE:

I think we want them to do Western and Immunohistochemistry, so I would add that to #1.

From: Temple, Robert
Sent: Friday, May 20, 2016 3:08 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject:

This is what I plan to send to JW with the proposed communication. Comments welcome:

JW,

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high. The proposed message to Serepta more or less says that and it should be quite encouraging, if they are convinced that the levels are indeed increased.

What do you think?

Temple, Robert

From: Jenkins, John K
Sent: Monday, May 23, 2016 8:52 AM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Temple, Robert
Cc: Jenkins, John K
Subject: RE:

That change should be OK.

From: Bastings, Eric
Sent: Monday, May 23, 2016 8:47 AM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Temple, Robert
Subject: RE:

My only comment is that we won't have labeling to send until some time tomorrow or Wednesday, so I suggest the following language:

(b) (5)

Eric

From: Jenkins, John K
Sent: Monday, May 23, 2016 8:43 AM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Temple, Robert
Cc: Jenkins, John K
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Subject: RE:

I think we want them to do Western and Immunohistochemistry, so I would add that to #1.

From: Temple, Robert

Sent: Friday, May 20, 2016 3:08 PM

To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric

Subject:

This is what I plan to send to JW with the proposed communication. Comments welcome:

JW,

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What do you think?

Temple, Robert

From: Jenkins, John K
Sent: Monday, May 23, 2016 7:51 AM
To: Unger, Ellis; Woodcock, Janet
Cc: Temple, Robert; Jenkins, John K
Subject: RE: Action

Janet

Given the unusual nature of the eteplirsen situation, I think it would be a good idea for you to meet with the review team to discuss your approach/conclusions related to this application. Such a meeting is specified in the CDER MaPP on Equal Voice. I think this would be best held after the team has a chance to read your draft review.

We will need to communicate to Sarepta that we will not meet the PDUFA goal date. I think Bob communicated the team's proposed text last week that would have included asking that they provide the biopsy data from the ongoing PROMOVI trial before FDA made its decision. I assume that message was not communicated. How do you wish us to communicate the delay to them now?

John

From: Unger, Ellis
Sent: Sunday, May 22, 2016 2:00 PM
To: Woodcock, Janet
Cc: Jenkins, John K; Temple, Robert
Subject: Re: Action

Janet,

I'm in St. Louis now. I'll be driving all day tomorrow (from St. Louis to DC) and expect to get home Monday evening. I can file my memo on Tuesday. Could we talk on Tuesday instead of Monday?

Ellis

Sent from my BlackBerry.

From: Woodcock, Janet
Sent: Sunday, May 22, 2016 10:13 AM
To: Unger, Ellis
Cc: Jenkins, John K
Subject: Action

I have finished my review of all the Sarepta data and am unchanged in my opinion. Ellis I note your memo is on draft. Do you know when you will finish? I would like to talk to you, tomorrow am if possible.

If you are concerned about precedent here, I would point out 314.126 which authorizes the Center Director to waive certain elements going into an assessment of adequate and well controlled, although the trials must still be controlled

Temple, Robert

From: Temple, Robert
Sent: Monday, May 23, 2016 11:22 AM
To: Woodcock, Janet
Cc: Temple, Robert; Blount, Aprile
Subject: Sarepta
Attachments: Message to Sarepta_EU RF_RT.DOC

JW,

This was meant to go Friday, but it did not. It was to explain why I thought it was critical to get the new dystrophin data, which could be done very rapidly. I'm very sorry it did not get out and you probably know all this and have considered these matters. I expect it will be part of any discussions this week, but I did want to state my reasons. As your note said, things can be waived but you still need to conclude that dystrophin levels are increased.

Attached is the communication to Sarepta proposed by the Division, ODE 1, and OND. It is clearly more insistent than what you suggested in your E-mail of May 8. There are 2 main reasons for this. We believe, based on the reviews by Ellis, Ash, and others, that:

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Philips, Howard

From: Temple, Robert
Sent: Monday, May 23, 2016 9:18 AM
To: Blount, Aprile
Subject: FW:

Did we in fact send my memo to JW with the proposed letter

From: Unger, Ellis
Sent: Sunday, May 22, 2016 2:10 PM
To: Jenkins, John K; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: Re:

All,

I spoke to Bob. He sent the email and the proposed text for Sarepta to Janet last week. So she'd seen it.

He may try to call her tomorrow.

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Subject: Re:

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John

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To: Bastings, Eric; Jenkins, John K; Temple, Robert; Unger, Ellis
Subject: RE:

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(b) (5)

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What do you think?

Philips, Howard

From: Unger, Ellis
Sent: Monday, May 23, 2016 11:54 PM
To: Jenkins, John K
Cc: Temple, Robert
Subject: RE: Action

Sorry that I had to disappear during the last few days, but I'm back. Did Janet answer this?

From: Jenkins, John K
Sent: Monday, May 23, 2016 7:51 AM
To: Unger, Ellis; Woodcock, Janet
Cc: Temple, Robert; Jenkins, John K
Subject: RE: Action

Janet

Given the unusual nature of the eteplirsen situation, I think it would be a good idea for you to meet with the review team to discuss your approach/conclusions related to this application. Such a meeting is specified in the CDER MaPP on Equal Voice. I think this would be best held after the team has a chance to read your draft review.

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Janet,

I'm in St. Louis now. I'll be driving all day tomorrow (from St. Louis to DC) and expect to get home Monday evening. I can file my memo on Tuesday. Could we talk on Tuesday instead of Monday?

Ellis

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To: Unger, Ellis
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I expect to finalize my decisional memo in the next few days. Jw

Philips, Howard

From: Woodcock, Janet
Sent: Monday, May 23, 2016 12:28 PM
To: Temple, Robert; Jenkins, John K
Cc: Blount, Aprile
Subject: RE: Sarepta

Thanks Bob. I have considered this course of action (without the memo) and have rejected it, for reasons I detail in my memo.
jw

From: Temple, Robert
Sent: Monday, May 23, 2016 11:22 AM
To: Woodcock, Janet
Cc: Temple, Robert; Blount, Aprile
Subject: Sarepta

JW,

This was meant to go Friday, but it did not. It was to explain why I thought it was critical to get the new dystrophin data, which could be done very rapidly. I'm very sorry it did not get out and you probably know all this and have considered these matters. I expect it will be part of any discussions this week, but I did want to state my reasons. As your note said, things can be waived but you still need to conclude that dystrophin levels are increased.

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Philips, Howard

From: Temple, Robert
Sent: Tuesday, May 24, 2016 2:48 PM
To: Unger, Ellis; Jenkins, John K; Bastings, Eric; Dunn, Billy
Subject: Re:

Looks good

Sent from my BlackBerry 10 smartphone.

From: Unger, Ellis
Sent: Tuesday, May 24, 2016 8:09 AM
To: Jenkins, John K; Bastings, Eric; Dunn, Billy
Cc: Temple, Robert
Subject: RE:

I see. My thought was that their interpretation would be something like "Even though this is not a typical review process..."

In any case, let's send this, which is what Eric proposed in his email from 8:47AM yesterday, but omitting the word (b) (5)

(b) (5)

Also, Bob is out today at a meeting in Philly. My calendar is blocked all day to work on NDAs, but I'm available all day, except from 1-3 when I'll be attending SLT-II.

From: Jenkins, John K
Sent: Tuesday, May 24, 2016 5:36 AM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Temple, Robert
Subject: Re:

The "(b) (5)" comment was intended to avoid a suggestion that our providing labeling comments suggested a pending approval.

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

From: Bastings, Eric
Sent: Tuesday, May 24, 2016 5:25 AM
To: Unger, Ellis; Jenkins, John K; Dunn, Billy; Temple, Robert
Subject: RE:

Can we send the message? Anybody has more edits?

Eric

From: Unger, Ellis
Sent: Monday, May 23, 2016 11:58 PM
To: Jenkins, John K; Bastings, Eric; Dunn, Billy; Temple, Robert
Subject: RE:

Two suggested changes:



From: Jenkins, John K
Sent: Monday, May 23, 2016 8:43 AM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Temple, Robert
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Philips, Howard

From: Temple, Robert
Sent: Tuesday, May 24, 2016 2:53 PM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Jenkins, John K
Subject: Re:

Looked good to me

Sent from my BlackBerry 10 smartphone.

From: Dunn, Billy
Sent: Tuesday, May 24, 2016 10:04 AM
To: Bastings, Eric; Unger, Ellis; Jenkins, John K
Cc: Temple, Robert
Subject: RE:

Before sending this, I think it is wise to do a final double-check for any final thoughts. Bob is out, so John and Ellis, any other considerations before we send this?

Billy

From: Bastings, Eric
Sent: Tuesday, May 24, 2016 9:42 AM
To: Unger, Ellis; Jenkins, John K; Dunn, Billy
Cc: Temple, Robert
Subject: RE:

OK. I will ask the Fanny to send the message.

Eric

From: Unger, Ellis
Sent: Tuesday, May 24, 2016 8:10 AM
To: Jenkins, John K; Bastings, Eric; Dunn, Billy
Cc: Temple, Robert
Subject: RE:

I see. My thought was that their interpretation would be something like "Even though this is not a typical review process..."

In any case, let's send this, which is what Eric proposed in his email from 8:47AM yesterday, but omitting the word "(b) (5)"

[Redacted content]

Also, Bob is out today at a meeting in Philly. My calendar is blocked all day to work on NDAs, but I'm available all day, except from 1-3 when I'll be attending SLT-II.

From: Jenkins, John K
Sent: Tuesday, May 24, 2016 5:36 AM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Temple, Robert
Subject: Re:

The "(b) (5)" comment was intended to avoid a suggestion that our providing labeling comments suggested a pending approval.

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

From: Bastings, Eric
Sent: Tuesday, May 24, 2016 5:25 AM
To: Unger, Ellis; Jenkins, John K; Dunn, Billy; Temple, Robert
Subject: RE:

Can we send the message? Anybody has more edits?

Eric

From: Unger, Ellis
Sent: Monday, May 23, 2016 11:58 PM
To: Jenkins, John K; Bastings, Eric; Dunn, Billy; Temple, Robert
Subject: RE:

Two suggested changes:

(b) (5)

From: Jenkins, John K
Sent: Monday, May 23, 2016 8:43 AM
To: Bastings, Eric; Unger, Ellis; Dunn, Billy; Temple, Robert
Cc: Jenkins, John K
Subject: RE:

I have been in communication with JW this morning by e-mail. This is what we have agreed:

1. She plans to send us her draft review memo in the next few days
2. After we receive her review memo she will schedule a time for the review team to meet with her and discuss her conclusions/recommended actions
3. She is not in favor of rushing to ask that the data from the PROMOVI trial be submitted before action. She understands the rationale, but thinks we need to take time to develop a plan for how the data will be analyzed/processed.
4. She agrees we need to communicate to Sarepta that we will miss the PDUFA goal date. I drafted the language below and she concurred
5. She expects Sarepta to call her on receipt of this language and she will tell them to "keep responding to FDA requests."

Here is the draft text I developed. I suggest Billy e-mail this to them this morning.

(b) (5)

Comments?

John

From: Bastings, Eric
Sent: Sunday, May 22, 2016 2:12 PM
To: Unger, Ellis; Jenkins, John K; Dunn, Billy; Temple, Robert
Subject: RE:

It will be good to know if this is AA or full approval.

I will get a label in shape ASAP.

Section 14 will depend on Dr. Woodcock's memo, so we will have to wait for that.

We can possibly act by the PDFa date, as all of our reviews are complete, and labeling should go very quick.

Eric

From: Unger, Ellis
Sent: Sunday, May 22, 2016 2:10 PM
To: Jenkins, John K; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: Re:

All,

I spoke to Bob. He sent the email and the proposed text for Sarepta to Janet last week. So she'd seen it.

He may try to call her tomorrow.

And I would presume this will be an AA.

Ellis

Sent from my BlackBerry.

From: Jenkins, John K
Sent: Sunday, May 22, 2016 6:49 AM

To: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis
Subject: Re:

What is happening with the communication to Sarepta?

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

From: Jenkins, John K
Sent: Friday, May 20, 2016 7:23 PM
To: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis
Subject: Re:

Please make sure the statement we propose to send is 100% accurate.

John

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

From: Dunn, Billy
Sent: Friday, May 20, 2016 6:54 PM
To: Bastings, Eric; Jenkins, John K; Temple, Robert; Unger, Ellis
Subject: RE:

Correct – that is the serial process (first establish substantial evidence, which is what this request is about, then consider reasonable likelihood, which will involve subjectivity) that we all discussed.

Bob – I think deleting [REDACTED] (b) (5)
[REDACTED] is reasonable and doesn't change the message you are conveying.

Billy

From: Bastings, Eric
Sent: Friday, May 20, 2016 6:06 PM
To: Jenkins, John K; Temple, Robert; Unger, Ellis; Dunn, Billy
Subject: RE:

My position is that we first need to establish substantial evidence that dystrophin is increased. This is critical.

Then the question whether that evidence is reasonably likely to predict benefit is a more subjective decision, which will depend on the levels of dystrophin identified, among other things.

I can't say I know now where I sit yet, so the [REDACTED] (b) (5)" is overstated, for me.

ERic

From: Jenkins, John K
Sent: Friday, May 20, 2016 4:51 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE:

I think we want them to do Western and Immunohistochemistry, so I would add that to #1.

From: Temple, Robert
Sent: Friday, May 20, 2016 3:08 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject:

This is what I plan to send to JW with the proposed communication. Comments welcome:

JW,

Attached is the communication to Serepta proposed by the Division, ODE 1, and OND. It is clearly more insistent than what you suggested in your E-mail of May 8. There are 2 main reasons for this. We believe, based on the reviews by Ellis, Ash, and others, that:

1. The existing biopsy samples can be tested by Western blot in a short time (a few weeks to a month) and we would plan to work very closely with them to accomplish this. The contention that 3-6 months are needed for IRB clearance (with more time afterward to do the samples) is not credible
2. Good evidence of increased dystrophin is critical to the possible accelerated approval. There can be judgment as to the "reasonably likely to predict outcome" part of AA but the evidence for the surrogate should be strong and there are, as the reviews show, substantial doubts about whether the existing data show this. The new data should leave no uncertainty at all, either way. I should note that, without saying what the final reviews will say, that there is considerable support for the pathway you proposed at the AC meeting (AA based on dystrophin with various sources of support for reasonable likelihood) even if the dystrophin levels are not very high. The proposed message to Serepta more or less says that and it should be quite encouraging, if they are convinced that the levels are indeed increased.

What do you think?

Philips, Howard

From: Unger, Ellis
Sent: Tuesday, May 24, 2016 12:59 AM
To: Jenkins, John K; Temple, Robert; Farkas, Ronald
Cc: Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

I want to emphasize a point that Ron has made repeatedly. Muscle samples were obtained from 12 boys from Study 201 back in 2011 when they were treatment-naïve. The samples were stained for dystrophin, and the images were stored. The mean reading by Nationwide Children's Hospital was 15% positive fibers. The 2015 re-read of these stored images by the 3 masked pathologists was 13%.

The applicant obtained muscle tissue from a (mostly different) group of treatment-naïve patients (and different muscles), and analyzed these samples along with muscle tissue from 2 or 3 of the original patients (the latter were frozen for years). For these samples, the reading by the same 3 masked readers was 1%. These results differ by a factor of 10, despite being analyzed by the same readers.

The 10-fold difference has to be related to differences in the staining technique, differences in the patients, differences in the muscle groups assessed, or some combination of all three. The readers were the one constant here.

Irrespective of why there is a 10-fold difference, the huge inconsistency shows that this methodology, as carried out by this applicant, is completely unreliable.

From: Jenkins, John K
Sent: Friday, May 20, 2016 6:53 PM
To: Temple, Robert; Farkas, Ronald; Unger, Ellis
Cc: Dunn, Billy; Bastings, Eric
Subject: Re: Dystrophin Results

All the more reason to address all the issues by waiting to receive the new data.

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

From: Temple, Robert
Sent: Friday, May 20, 2016 6:00 PM
To: Farkas, Ronald; Unger, Ellis
Cc: Dunn, Billy; Bastings, Eric; Jenkins, John K
Subject: RE: Dystrophin Results

Thanks, all that seems like a good reason to do the immunohisto on the new samples as well as W blot.

From: Farkas, Ronald
Sent: Friday, May 20, 2016 5:49 PM
To: Temple, Robert; Unger, Ellis
Cc: Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

Bob,
See below in red
Thanks

Ron

From: Temple, Robert
Sent: Friday, May 20, 2016 4:37 PM
To: Unger, Ellis; Farkas, Ronald
Subject: RE: Dystrophin Results

OK, let me be clear...

The slices were made and stained at the time the samples were obtained...this is one point that can be confusing. In Study 201, all the patients had baseline muscle biopsies from which slices were made, stained, and photographed. These photos were then read under poor conditions by NCH, then later re-read by the 3 blinded readers. That's all separate from anything done at Week 180. These are the numbers shown in slide 37 under the "nationwide" and "re-analysis" headings.

When the 4th biopsy came along, Sarepta said there was actually some baseline tissue left over for a few patients. this unstained old tissue, plus new tissue from patients outside the study, was then processed in parallel, going through staining, photographing, and reading. This 4th biopsy tissue led to the 17% in treated patients vs. the 1% positive fibers in controls.

When we made them do a blinded re-read comparing the week 24 and week 48 with baseline, the differences between baseline and later were much smaller. Yes, that's true, and these are the numbers in slide 37 under "nationwide" and "re-analysis"

Slide 34, e.g., shows values of 49 -70% for all 12 patients at 48 weeks vs 7-24 % for baseline, on original reads. Yes

The blinded re-analysis showed 48 week values of 9-25% at 48 weeks vs 10-15% values for baseline, a much small difference, if, indeed, any difference. yes

Etiplirsen at 180 weeks read 17%, and I can't tell if the baseline samples were re-read,...this is perhaps a part that wasn't clear to you. the baseline samples are newly cut and stained samples, 6 from outside the study entirely, and 3 from old tissue left over from the original baseline biopsies. There is no re-read of these samples, the only number is the 1% positive fibers

but in slide 35 no other control is mentioned so one would assume that the relevant control is the 11-15% values. There are a series of slides, each showing the same table, but pointing to different things. Slide 35 is comparing the original reading of the baseline through week 48 samples to the re-read by the 3 blinded readers of the baseline through week 48 images. It's not until slide 37 that it's pointed out that it's concerning that the original baseline samples had 9-23% positive fibers, whereas the Week 180 control samples had 1% positive fibers; seemingly these numbers should have been more similar.

Now on slide 37 it refers to new controls for the 4th biopsy (why?)...as noted above, the controls for the 4th biopsy were new. It was not a re-reading of the original baseline images

but it does not say what the new controls were...everything can't be on one slide. The methods and controls were explained on other slides, for example slide 18

Shortcomings of Controls Used for 4th Biopsy

- Control samples from different muscle groups used - biceps, quadriceps, deltoid - and data combined for comparison to deltoid samples from 4th biopsy
- Baseline comparator only available from 2 DMD patients and from a different muscle group
- Healthy controls not sex-matched – one female and two male healthy controls combined for mean value
- Dystrophin variability in healthy controls (51%-95%)

18

and the question (difference in method vs difference in controls does not make it clear. ...the key point in what Sarepta is now writing to you is the WE are very clear on where the data and numbers came from. No doubt it's confusing, and difficult to explain in the very limited time we were forced to use because so much time had to be devoted to the open public hearing.

Why would they want new controls and not the same patient controls used all along? ...the percent positive fiber method is very sensitive to the exact staining and rinsing conditions, and probably other things too. Unless slides are processed side-by-side with the exact same solutions and rinses, the immunofluorescence might not be comparable.

And indeed it does say controls were 1%. the Week 180 controls had 1% positive fibers

Slide 38 ignores the 1% and again invites a comparison of 17% (180 week) vs 11-15%. Slide 38 doesn't ignore anything, and none of the other slides, nor anyone in DNP ignores anything. Slide 37 describes our concern that, even considering differences that can arise from processing, the original baseline samples and Week 180 controls are 17-fold difference, a huge difference. Slide 38 then describes our concern that the Week 180 eteplirsen-treated samples, which should seemingly show much more positive fibers, are not very different from the percent positive fibers in the original baseline samples.

Help!!!

Sent: Friday, May 20, 2016 4:09 PM
To: Temple, Robert; Farkas, Ronald; Dunn, Billy; Bastings, Eric
Subject: Re: Dystrophin Results

We have a datafile fibers1.xpt or fibers2.xpt that has the original reads from baseline, week 12, week24, ?week 48 and week 180 read by the woman at Children's AND the 3 masked readers.

Sent from my BlackBerry.

From: Temple, Robert
Sent: Friday, May 20, 2016 2:56 PM
To: Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

I knew the Western blot 180 week used controls that were mostly new (with only 3 available samples) but I thought the immunofluorescence assessment used the original controls (re-read with the 180 Week samples. So you are saying that (slide 37) the week 180 17% positive was compared with NEW controls that averaged about 1% and there was no comparison with the baseline samples, reread.

From: Farkas, Ronald
Sent: Friday, May 20, 2016 3:32 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

6 are entirely new controls from outside study 201/202. Three are from baseline tissue from study 201/202 patients (patients 8, 13, and 15). It's important to understand that the week 180 numbers are not from a rereading of prior images. Instead, new tissue sections were stained, photographed, and read using the improved methods arrived at with FDA's input. We are impressed that this new tissue gave much lower positive fiber counts than the original tissue. It's not possible to know, however, if the difference in percent positive fibers is the result of a difference in the methodology (different antibody dilutions and washing steps can lead to very different intensities and percent positive fibers), or to differences in the tissue itself. This was all explained in the reviews and at the AC meeting.

Thanks
Ron

From: Temple, Robert
Sent: Friday, May 20, 2016 3:18 PM
To: Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

Are the 4th biopsy controls the original baseline controls, reread properly, or are they new controls (other people). If they are the baseline controls, then there is a 17% vs 1% positive fiber rate. Are we impressed by that?

From: Farkas, Ronald
Sent: Friday, May 20, 2016 3:07 PM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

We were correct in the way we presented the data. We said the 4th biopsy controls had 1% positive fibers – that is in the title of the slide, and that is what Shamin states in her email.

Thanks
Ron

- The 4th biopsy controls had 1% positive fibers
- 15% for the original baseline samples (rectal)
- Difference in methods? Or difference in controls?

	Nationwide Children's Hospital analysis				Re-analysis by 3 blinded			
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48
30 mg/kg (n=4)	18		41	70	14		27	
50 mg/kg (n=4)	11	12		54	15	17		
Placebo to 30 mg/kg (n=2)	24		24	58	10		10	
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		

From: Temple, Robert
Sent: Friday, May 20, 2016 2:23 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald
Subject: FW: Dystrophin Results

This appears to assert that the immunofluorescence slides (180 weeks) with reread baseline data had baseline values of about 1%, not the 14-15% we said. Is that correct?

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, May 20, 2016 2:12 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Temple, Robert; Ed Kaye; Frank J. Sasinowski
Subject: Dystrophin Results

Dear Dr. Woodcock,

We would like to request a meeting as soon as possible to ensure that you are provided with an overview of the dystrophin data for eteplirsen. We believe that a full understanding of the complete dystrophin data set, especially the Week 180 biopsies, is critical to enable an informed decision. Given the gravity of the situation, we would request the opportunity to meet, either in person or by telephone.

Frank Sasinowski has brought to our attention that there is still confusion regarding the dystrophin data, in particular Table 1, Page 4 of the FDA Briefing Document (Slide # 3 in the attached deck). We would like to bring to your attention that the percent dystrophin positive fibers (PDPF) results may have been misinterpreted by Dr Farkas as detailed below.

The FDA slide shows the following; dystrophin positive fibers (PDPF) analyzed by (i) Nationwide Children’s Hospital (NCH), (ii) Re-analysis by 3 blinded readers and the (iii) Week 180 biopsy samples.

Please note the following key points:

- Time-points for the first 3 biopsies were: 1) baseline 2) Weeks 12 or 24 and 3) Week 48
- In Study 201, baseline and on treatment samples (Wks 12 or 24) were processed at the same time
- In Study 202, the Week 48 samples were processed at a later date and separately from the Study 201 baseline samples
 - FDA recommendation was to disregard Wk 48 images.
 - FDA advised Sarepta that Wk 48 samples should not be re-read by the 3 blinded readers as the images had “a noticeably different background fluorescence than baseline, Wk 12 and Wk 24 images”
- In contrast, Study 202 Wk 180 biopsies were processed and analyzed simultaneously with the baseline/untreated control samples
 - Methods were in accordance with FDA agreed upon protocols
 - **Untreated samples** included the use of both Study 201 baseline (in patients with excess archived tissue) and untreated samples from the PROMOVI study.
 - Sarepta **did NOT initiate** or testing until the protocols were fully vetted by FDA.
- FDA’s slide incorrectly compared the PDPF results of the Wk 180 treated samples to baseline samples from the original 201 biopsies.
 - **This is inappropriate** – as the Wk 180 treated samples should be compared to the untreated samples that were processed at the same time, using the same protocol.
 - The Wk 180 biopsy PDPF results demonstrate **17.39% for eteplirsen treated vs. 1.12% for baseline/untreated controls with a difference of 16.27%**

Please find attached the following slides:

Slide 3. FDA slide – misinterpreting the PDPF data

Slide 4. As FDA slide above – with baseline/untreated data included for Wk 180

Slide 5. Wk 180 biopsy data for the 3 baseline and 6 PROMOVI untreated samples. You will see that the results are very similar and distinctly lower than the treated sample.

Slide 6: Wk 180 results demonstrating de-novo dystrophin by 3 complementary methods

Slide 7: FDA communication recommending exclusion of Week 48 biopsy results

Background Information

Slide 9: Wk 180: Individual patient PDPF results for eteplirsen treated and untreated

Finally, it appears that FDA is suggesting that Sarepta had previously inflated the dystrophin results. This is not the case. The initial NCH results for PDPF were re-analyzed by 3 blinded readers as requested by the FDA. The NCH Wk 24 PDPF results (41% for 30 mg/kg treated patients vs 18% for baseline), were consistent with NCH Wk 180 PDPF results (37.3 % for eteplirsen vs 5.0 for untreated). According to FDA request, the Wk 24 and Wk 180 samples were re-analyzed by the 3 blinded readers and although numerically lower, at both time-points confirmation of a significant increase in dystrophin was demonstrated.

Please note that there were no interpretable Western Blot data for the first 3 biopsies; only the 4th biopsy/Week 180 samples had WB results. Although WB results confirmed dystrophin production, the numerical results were not expected to be similar to PDPF, as these were 2 distinct assays.

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: Temple, Robert
Sent: Tuesday, May 24, 2016 2:44 PM
To: Unger, Ellis
Subject: Re: Dystrophin Results
Attachments: image001.png.html; image002.png.html

Totally agree

Sent from my BlackBerry 10 smartphone.

From: Unger, Ellis
Sent: Tuesday, May 24, 2016 12:59 AM
To: Jenkins, John K; Temple, Robert; Farkas, Ronald
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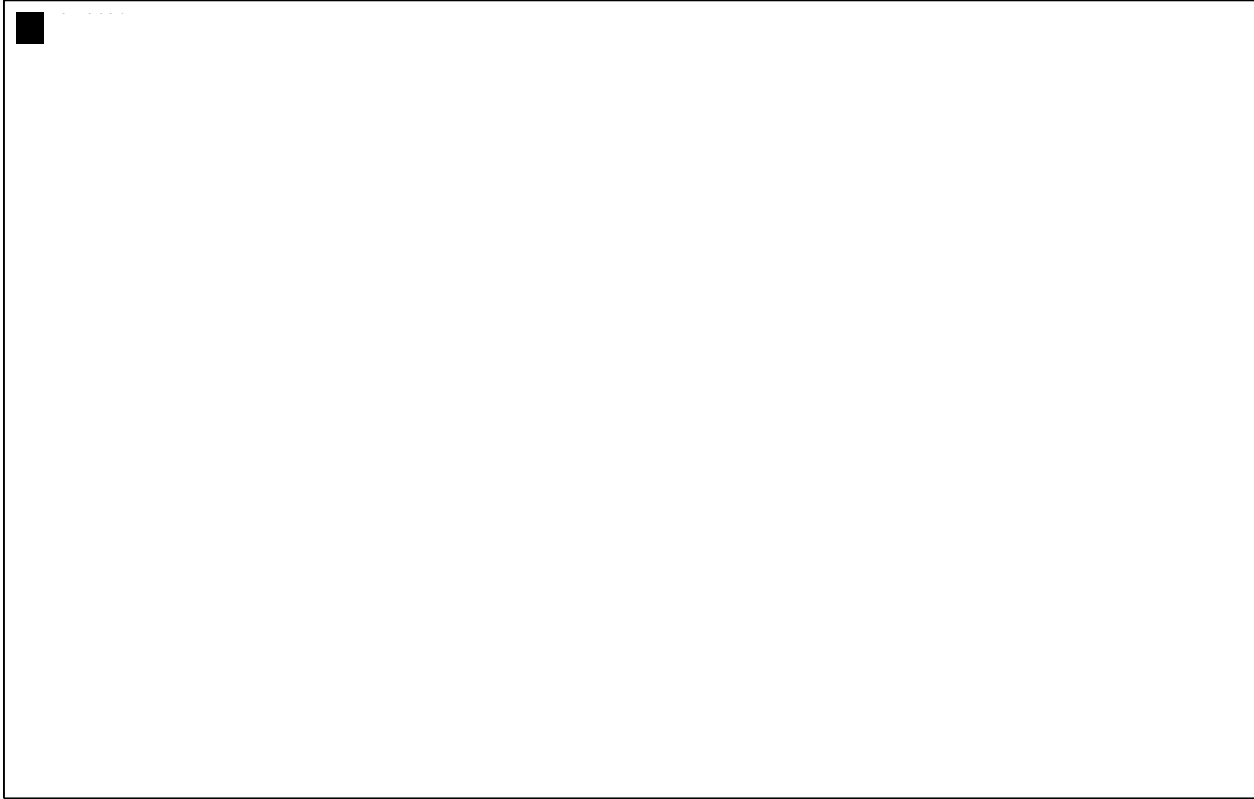
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To: Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: RE: Dystrophin Results

We were correct in the way we presented the data. We said the 4th biopsy controls had 1% positive fibers – that is in the title of the slide, and that is what Shamin states in her email.

Thanks
Ron



From: Temple, Robert
Sent: Friday, May 20, 2016 2:23 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald
Subject: FW: Dystrophin Results

This appears to assert that the immunofluorescence slides (180 weeks) with reread baseline data had baseline values of about 1%, not the 14-15% we said. Is that correct?

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, May 20, 2016 2:12 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Temple, Robert; Ed Kaye; Frank J. Sasinowski
Subject: Dystrophin Results

Dear Dr. Woodcock,

We would like to request a meeting as soon as possible to ensure that you are provided with an overview of the dystrophin data for eteplirsen. We believe that a full understanding of the complete dystrophin data set, especially the Week 180 biopsies, is critical to enable an informed decision. Given the gravity of the situation, we would request the opportunity to meet, either in person or by telephone.

Frank Sasinowski has brought to our attention that there is still confusion regarding the dystrophin data, in particular Table 1, Page 4 of the FDA Briefing Document (Slide # 3 in the attached deck). We would like to bring to your attention that the percent dystrophin positive fibers (PDPF) results may have been misinterpreted by Dr Farkas as detailed below.

The FDA slide shows the following; dystrophin positive fibers (PDPF) analyzed by (i) Nationwide Children's Hospital (NCH), (ii) Re-analysis by 3 blinded readers and the (iii) Week 180 biopsy samples.

Please note the following key points:

- Time-points for the first 3 biopsies were: 1) baseline 2) Weeks 12 or 24 and 3) Week 48
- In Study 201, baseline and on treatment samples (Wks 12 or 24) were processed at the same time
- In Study 202, the Week 48 samples were processed at a later date and separately from the Study 201 baseline samples
 - FDA recommendation was to disregard Wk 48 images.
 - FDA advised Sarepta that Wk 48 samples should not be re-read by the 3 blinded readers as the images had “a noticeably different background fluorescence than baseline, Wk 12 and Wk 24 images”
- In contrast, Study 202 Wk 180 biopsies were processed and analyzed simultaneously with the baseline/untreated control samples
 - Methods were in accordance with FDA agreed upon protocols
 - **Untreated samples** included the use of both Study 201 baseline (in patients with excess archived tissue) and untreated samples from the PROMOVI study.
 - Sarepta **did NOT initiate** or testing until the protocols were fully vetted by FDA.
- FDA's slide incorrectly compared the PDPF results of the Wk 180 treated samples to baseline samples from the original 201 biopsies.
 - **This is inappropriate** – as the Wk 180 treated samples should be compared to the untreated samples that were processed at the same time, using the same protocol.
 - The Wk 180 biopsy PDPF results demonstrate **17.39% for eteplirsen treated vs. 1.12% for baseline/untreated controls with a difference of 16.27%**

Please find attached the following slides:

Slide 3. FDA slide – misinterpreting the PDPF data

Slide 4. As FDA slide above – with baseline/untreated data included for Wk 180

Slide 5. Wk 180 biopsy data for the 3 baseline and 6 PROMOVI untreated samples. You will see that the results are very similar and distinctly lower than the treated sample.

Slide 6: Wk 180 results demonstrating de-novo dystrophin by 3 complementary methods

Slide 7: FDA communication recommending exclusion of Week 48 biopsy results

Background Information

Slide 9: Wk 180: Individual patient PDPF results for eteplirsen treated and untreated

Finally, it appears that FDA is suggesting that Sarepta had previously inflated the dystrophin results. This is not the case. The initial NCH results for PDPF were re-analyzed by 3 blinded readers as requested by the FDA. The NCH Wk 24 PDPF results (41% for 30 mg/kg treated patients vs 18% for baseline), were consistent with NCH Wk 180 PDPF results (37.3 % for eteplirsen vs 5.0 for untreated). According to FDA request, the Wk 24 and Wk 180 samples were re-analyzed by the 3 blinded readers and although numerically lower, at both time-points confirmation of a significant increase in dystrophin was demonstrated.

Please note that there were no interpretable Western Blot data for the first 3 biopsies; only the 4th biopsy/Week 180 samples had WB results. Although WB results confirmed dystrophin production, the numerical results were not expected to be similar to PDPF, as these were 2 distinct assays.

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

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

From: Bastings, Eric
Sent: Tuesday, May 24, 2016 5:24 AM
To: Unger, Ellis; Jenkins, John K; Temple, Robert; Dunn, Billy
Subject: Sarepta

Senate Committee Urges FDA Approval of Duchenne Drug

05/23/2016

The Senate Committee on Homeland Security and Governmental Affairs has written FDA commissioner **Robert Califf** urging the agency to exercise its flexibilities when making a review decision this week on a Sarepta Therapeutics NDA for eteplirsen and its use in treating Duchenne muscular dystrophy. In April, the agency's Peripheral and Central Nervous System Drugs Advisory Committee voted 7 to 6 ([see story](#)) that a Sarepta Therapeutics NDA did not provide substantial evidence from adequate and well controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit in Duchenne patients. The vote was seen as a setback for the company's bid to gain accelerated approval for the drug. A separate 7 to 3 vote by the panel recommended that data were not sufficient to meet traditional approval standards.

The 5/20 [letter](#) to Califf encourages FDA to "prioritize the patient perspective" when making a decision on the submission. It also complains that the questions given to advisory committee member were posed in such a way to make it difficult for them to vote favorably on the NDA. "Patients are crying out for the FDA to hear them: they are engaged and knowledgeable and only want the agency to do what is already within their power," it says. "We fully support their perspective."

Philips, Howard

From: Blount, Aprile
Sent: Wednesday, May 25, 2016 1:35 PM
To: Temple, Robert
Subject: FW: Value of Phase 3 Paper
Attachments: Phase 3Manuscript.docx

FYI

From: Blount, Aprile
Sent: Monday, May 23, 2016 4:26 PM
To: Rovin, Lisa; Witt, Ann M.; Lurie, Peter
Subject: Value of Phase 3 Paper

From Bob: Here are my comments on the first 13 pages. The rest coming soon (on his way to Phil, back on Wed). A few points so far:



PRIVILEGED AND CONFIDENTIAL
Clearance Draft (b) (5)

(b) (5)

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

FDACDER0004476

Philips, Howard

From: Walsh, Sandy
Sent: Wednesday, May 25, 2016 7:32 AM
To: Dunn, Billy; Choy, Fannie (Yuet); Unger, Ellis; Temple, Robert; Jenkins, John K; Farkas, Ronald; Woodcock, Janet; Moscicki, Richard; Bastings, Eric
Cc: Shreeve, Chris; Rawlings, Kimberly; Ikenberry, Sarah; Diggs, Felicia; Ikenberry, Sarah
Subject: FYI Sarepta statement

Good morning -

Sarepta's statement is out:

<http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=2172185>

Sarepta Therapeutics Announces FDA Will Not Complete the Review of the Eteplirsen New Drug Application By The PDUFA Date

CAMBRIDGE, Mass.--(BUSINESS WIRE)--May 25, 2016-- Sarepta Therapeutics, Inc. (NASDAQ:SRPT), a developer of innovative RNA-targeted therapeutics, today announced that the U.S. Food and Drug Administration (FDA) has notified the Company that they are continuing their review and internal discussions related to our pending NDA for eteplirsen and will not be able to complete their work by the Prescription Drug User Fee Act (PDUFA) goal date of May 26, 2016. The FDA has communicated that they will continue to work past the PDUFA goal date and strive to complete their work in as timely a manner as possible.

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



Temple, Robert

To: Jenkins, John K
Cc: Unger, Ellis
Subject: RE: waivers of adequate & well controlled study requirements?

Totally agree, of course, and it would be useful to see if we can make a good estimate of how long it really would take (Ash seemed to be saying a few weeks). I will wait to see her memo before calling, I think.

From: Jenkins, John K
Sent: Thursday, May 26, 2016 2:28 PM
To: Temple, Robert
Cc: Jenkins, John K; Unger, Ellis
Subject: RE: waivers of adequate & well controlled study requirements?

Bob

I floated by Janet again today the points Ellis made in his meeting with her earlier this week on the value to everyone of waiting to get the additional data. She did not say yes, but I think there is value in hitting her from multiple angles if we can. She is supposed to give us her memo tomorrow on how she analyzes the data. I told her the values of waiting include:

1. A clearer science base for making a decision
2. Likely no need to overrule OND since there is greater comfort than before for AA based on even limited, but reliable, dystrophin production
3. Avoid the possibility that the approval will be flawed if the data are reviewed later and do not confirm dystrophin production; i.e., a lot of regulatory and personal credibility risk

Her main objection seems to be that it will take a long time for the sponsor to get a lab lined up to do the analyses (we would not want Mendel to do them) and reach agreement with us on a protocol. I suggested that we could send our staff to monitor the conduct of the experiments so we would not have to go back and inspect later. That could save time and I think we could have an "all-hands-on deck approach to working with Sarepta to move this forward as quickly as possible.

So, you might want to continue to bend her ear about this approach. I pointed out that we can give clear guidance to the sponsor such that (b) (4)

(b) (4) I see it as a win-win, but she is not yet convinced.

John

From: Temple, Robert
Sent: Thursday, May 26, 2016 12:53 PM
To: Jenkins, John K
Subject: RE: waivers of adequate & well controlled study requirements?

Or maybe show there is no case if you read the reg.

From: Jenkins, John K
Sent: Thursday, May 26, 2016 12:41 PM
To: Unger, Ellis
Cc: Joy, David; Temple, Robert
Subject: RE: waivers of adequate & well controlled study requirements?

I too am aware of no examples. I would note for David's sake, that this feels a bit awkward since I suspect this relates to the eteplirsen NDA and we in OND, who are likely to overruled by the Center Director on the action, are being asked to help build the case to overrule us.

From: Unger, Ellis
Sent: Thursday, May 26, 2016 8:22 AM
To: Goldstein, Beth A (Duvall)
Cc: Joy, David; Temple, Robert; Jenkins, John K
Subject: Re: waivers of adequate & well controlled study requirements?

No examples I'm aware of.

Sent from my BlackBerry.

From: Goldstein, Beth A (Duvall)
Sent: Thursday, May 26, 2016 8:18 AM
To: Joy, David
Cc: Sipes, Grail; Jenkins, John K; Temple, Robert; Unger, Ellis; Rosebraugh, Curtis; Parks, Mary H; Beitz, Julie G; Egan, Amy; Ganley, Charles J; Furlong, Lesley-Anne; Cox, Edward M; Farley, John; Pazdur, Richard; CDER-OND-ADRA
Subject: RE: waivers of adequate & well controlled study requirements?

Good morning,

Unfortunately this is not something that is captured in DARRTS. The only way to drum up examples of this (if any) would be to poll divisions' memories. So I've copied the OND ADRA as well as Drs. Jenkins, Temple, and the ODE Directors in case they recall examples.

Beth

From: Joy, David
Sent: Wednesday, May 25, 2016 3:57 PM
To: Goldstein, Beth A (Duvall)
Cc: Sipes, Grail
Subject: waivers of adequate & well controlled study requirements?

Hi Beth,

I'm hoping you can help with a quick question. Have you ever seen us invoke the waiver provision in 21 CFR 314.126 concerning adequate and well controlled studies? 314.126(c) says the Center Director can waive certain requirements for adequate and well controlled studies.

314.126(c) is cross referenced in 314.90, dealing with additional types of waivers NDA & ANDA applicants can request.

I suspect we don't often invoke these provisions, but please let me know if you're aware of any examples.

Temple, Robert

From: Unger, Ellis
Sent: Tuesday, May 31, 2016 7:53 PM
To: Woodcock, Janet
Cc: Jenkins, John K; Temple, Robert; Dunn, Billy; Bastings, Eric
Subject: FW: Message to Sarepta: re: additional dystrophin data

Hi Janet,

Below is our proposed message for Sarepta. Please let us know if you have comments or edits.

Thanks in advance,

Ellis

- - - -



(b) (5)

edplur

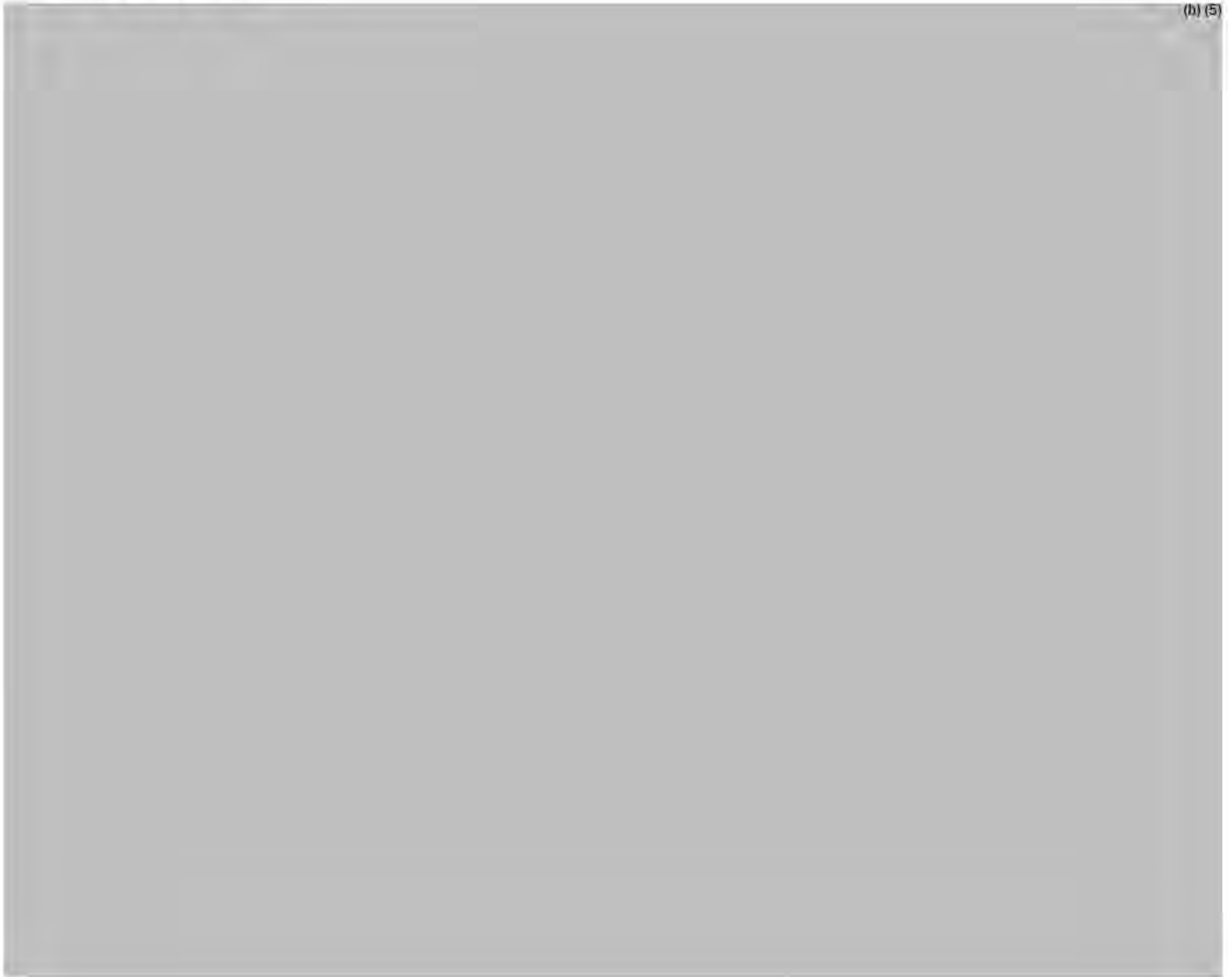
Message to Sarepta:

(b) (5)



Message to Sarepta:

(b) (5)



Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Tuesday, May 31, 2016 3:32 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh
Cc: Choy, Fannie (Yuet)
Subject: Message to Sarepta: re: additional dystrophin data
Attachments: Message to Sarepta_EU RF_RT 051716 (clean).doc

Hello,

Attached please find the language for the message to Sarepta previously circulated. This version was forwarded to Dr. Jenkins on 5/17 and to Dr. Temple on 5/18.

Thanks
Fannie



Temple, Robert

From: Unger, Ellis
Sent: Wednesday, June 01, 2016 8:30 AM
To: Dunn, Billy; Farkas, Ronald; Choy, Fannie (Yuet); Temple, Robert; Bastings, Eric; Rao, Ashutosh
Cc: Jenkins, John K
Subject: RE: Message to Sarepta: re: additional dystrophin data

I ran the statement by Janet. and she wants us to remove the sentence:

(b) (5)

(b) (5)

She also suggested that we call them soon after sending.

Here is the message – ready to send:

(b) (5)

From: Dunn, Billy
Sent: Tuesday, May 31, 2016 6:40 PM
To: Unger, Ellis; Farkas, Ronald; Choy, Fannie (Yuet); Temple, Robert; Bastings, Eric; Rao, Ashutosh
Subject: RE: Message to Sarepta: re: additional dystrophin data

Ellis and I discussed – the attached version is the latest (and possibly final, given that I think everybody has weighed in.)

From: Unger, Ellis
Sent: Tuesday, May 31, 2016 5:03 PM
To: Farkas, Ronald; Dunn, Billy; Choy, Fannie (Yuet); Temple, Robert; Bastings, Eric; Rao, Ashutosh
Subject: RE: Message to Sarepta: re: additional dystrophin data

A few more edits.

Ellis

From: Farkas, Ronald
Sent: Tuesday, May 31, 2016 4:54 PM
To: Dunn, Billy; Choy, Fannie (Yuet); Unger, Ellis; Temple, Robert; Bastings, Eric; Rao, Ashutosh
Subject: RE: Message to Sarepta: re: additional dystrophin data

Billy,
The one suggestion I have is to use throughout the message to Sarepta the term "(b) (5)" in reference to ourselves, and to not use " (b) (5) ," (only used once, in second to last sentence). This request is coming from the ODE- and Office-level, whereas " (b) (5) ," may suggest that request is from the Division-level.
Thanks
Ron

From: Dunn, Billy
Sent: Tuesday, May 31, 2016 3:46 PM
To: Choy, Fannie (Yuet); Unger, Ellis; Temple, Robert; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh
Subject: RE: Message to Sarepta: re: additional dystrophin data

Let's wrap up edits on this today. Fannie will send it to John late today or first thing tomorrow and then we'll get final clearance from Janet.

I made two edits that reflect the conversation we just had.

Billy

From: Choy, Fannie (Yuet)
Sent: Tuesday, May 31, 2016 3:32 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh
Cc: Choy, Fannie (Yuet)
Subject: Message to Sarepta: re: additional dystrophin data

Hello,

Attached please find the language for the message to Sarepta previously circulated. This version was forwarded to Dr. Jenkins on 5/17 and to Dr. Temple on 5/18.

Thanks
Fannie

Philips, Howard

From: Unger, Ellis
Sent: Wednesday, June 01, 2016 8:41 AM
To: Bastings, Eric; Farkas, Ronald; Freed, Lois M; Dunn, Billy; Jenkins, John K; Temple, Robert
Subject: RE: Did Chris McSherry forget she testified AGAINST drisapersen at the drisapersen AC???

Here's what it feels like to be sucker punched by Christine McSherry...

NOVERMBER, 2015 - PCNS AC Meeting:

"Hi. My name is Christine McSherry, and for disclosure, I run an organization, Jett Foundation. Jett Foundation has received educational programming from the sponsor. I am the founder of Jett Foundation, a Duchenne nonprofit started 16 years ago when my now-20-year-old son Jett was diagnosed with Duchenne. I'm here to tell you my story, my family's experience with drisapersen, and why it was not an option for Jett. He, like others but not all, experienced side effects, which you've heard about today from both the company and the agency.

When Jett was diagnosed in 2001, there were no options. Duchenne was terminal, and there were no drugs in the pipeline. When I heard of Prosenza's safety and efficacy trial, we agreed to participate. The year was 2010 and the site was 17 hours by car from our home in Boston. We drove those 17 hours three times between Thanksgiving and Christmas, leaving four other young children at home. During a two-week stay, Jett received three doses over three days, subcutaneous injection into his belly. By the third injection, we knew he was getting drug, as the sites were inflamed and incredibly painful. Even if this was an effective treatment, there was no way Jett could tolerate it, and he said so himself. It was a very long drive home.

Christmas approached and he could no longer walk on his own. And while we waited for words of a promised extension study, it never came. And we knew that even if it did, the risks would not be manageable for Jett.

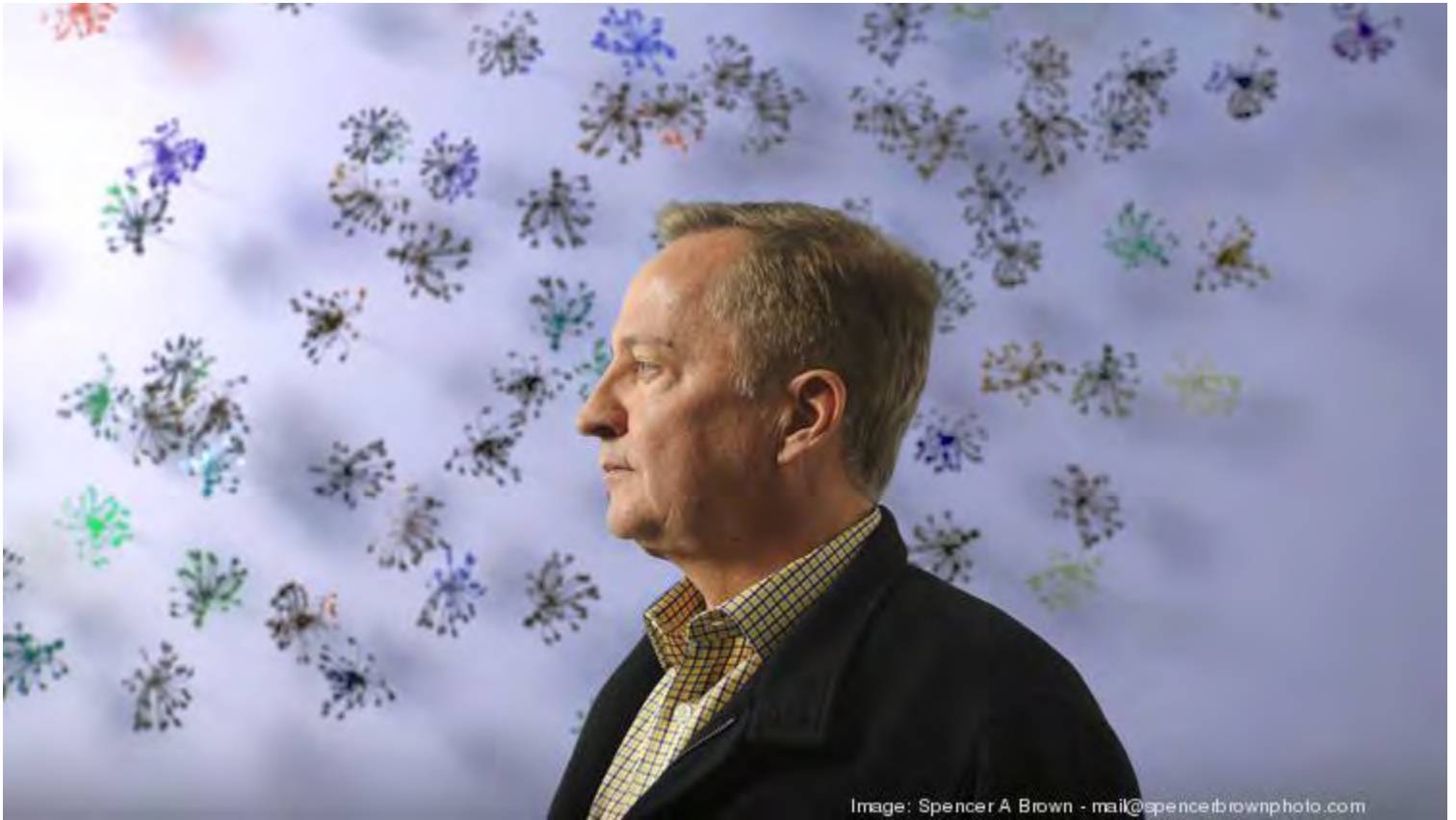
For Jett, what did an injection site reaction actually mean? It meant it was extremely painful when the drug was injected. It meant that the sites immediately turned red and swelled. They stayed that way for months, and then they turned purple. It meant interference with his bathing, his dressing, his transferring, his sleeping, and worst of all, in the summertime, the embarrassment of the purple spots on his belly. Still today, five years later, he has three large hardened welts on his stomach.

Had Jett remained on drug, by my own estimate, he would have 250 of these injection sites. There is no way that Jett could manage those risks. And in the context of all that you've heard today, all these safety risks that we've discussed, these are the least severe. So as you deliberate, please remember, the risk to patients like Jett is not manageable. For patients like Jett who are exon 51-amenable, we need other options. And for those patients in our community who are not exon 51-amenable, the unmet need remains, and it's significant. Thank you"

From: Bastings, Eric
Sent: Wednesday, June 01, 2016 8:23 AM
To: Unger, Ellis; Farkas, Ronald; Freed, Lois M; Dunn, Billy
Subject: Did Chris McSherry forget she testified AGAINST drisapersen at the drisapersen AC???

[BioMarin Pharmaceutical Inc.](#) killed development of an experimental treatment for a rare muscle-weakening disease and a trio of potential follow-on drugs, the company said Tuesday, dealing a blow to patients and advocates pressing for FDA approval of a therapy.

BioMarin (NASDAQ: BMRN) faced regulatory roadblocks in its attempts to win approval for its drug, called drisapersen or Kyndrisa, in the United States and Europe as a treatment for some patients with Duchenne muscular dystrophy.



[Enlarge](#)

BioMarin CEO Jean-Jacques Bienaime

Spencer A Brown

"This feels like (patients have) been sucker punched," said [Christine McSherry](#), executive director of the Kingston, Mass.-based Jett Foundation and the mother of a 20-year-old Duchenne patient.

San Rafael-based BioMarin, led by Chairman and CEO [Jean-Jacques Bienaimé](#), landed drisapersen in its \$680 million acquisition of Prosensa Holding NV. Unlike previous BioMarin deals, it didn't hedge its bet, though, paying the money upfront and promising \$80 million if the drug was approved in the United States and another \$80 million if it won approval in Europe.

Neither of those approvals was likely to happen, though, as the Food and Drug Administration in January issued a "complete response letter," which means the agency would not approve BioMarin's application. A European regulatory committee this month indicated that it would recommend against approval.

Drisapersen's effects, especially the drug's effects on kidneys, were key to regulators.

Duchenne muscular dystrophy is a genetic condition that causes muscle weakness. It typically affects one in every 3,500 to 5,000 boys, though girls may carry the defective gene and have symptoms. Patients get progressively weaker, losing muscle strength in their hips, legs, shoulders and arms, and they develop heart and respiratory problems, and typically die by their mid-20s.

In addition to discontinuing work on drisapersen and withdrawing the company's application for European approval, BioMarin said it would stop work on three first-generation follow-on drugs — BMN-044, BMN-045 and BMN-053 — that were in mid-stage studies.

In a statement, Bienaimé called the company's decision "difficult but necessary" and thanked families and caregivers of Duchenne patients.

BioMarin is continuing research in next-generation Duchenne drugs, the company said. Those drugs, however, aren't even considered preclinical by the company, so they would take years to traverse the drug-approval process.

BioMarin was in a race with Cambridge, Mass.-based Sarepta Therapeutics (NASDAQ: SRPT) to develop a Duchenne drug, but both have had a rough time convincing regulators that their drugs are either safe or effective. [The FDA last week delayed a decision on Sarepta's drug](#), called eteplirsen, and an advisory committee in April voted 7-6 against recommending accelerated approval of the drug.

But BioMarin's decision now would seem to help Sarepta's attempts to win approval, given that there is no other drug approved for treating Duchenne.

"There's only one standing now," McSherry said. "There would seem to be some sideways pressure (on the FDA) to approve" Sarepta's drug.

The FDA has given no timetable for a decision on eteplirsen.

"There's a whole population of people sitting in the dark," McSherry said.

McSherry's son, Jett, received three doses of BioMarin's drisapersen and had a reaction at the injection site on his belly. He received Sarepta's eteplirsen, was stable after nine weeks and regained some fine motor skills, she said.

Eteplirsen has had few safety concerns. What's more, patients showed varying but generally increased levels of a protein, called dystrophin, that helps build and strengthen muscle fibers.

"Honestly, I think the drug saved his life," McSherry said.

BioMarin stock was up 56 cents, or 0.63 percent, to close Tuesday at \$89.65 per share, but was down \$1.32 in after-hours trading. Sarepta stock was down 26 cents, or 1.23 percent, to close at \$20.93, but it was up 7 cents in after-hours trading.

BioMarin's decision also could translate into layoffs, though it is too early to say how many people could lose their jobs, said spokeswoman Debra Charlesworth. The greatest impact likely will be felt at the company's facility in Leiden in The Netherlands, she said.

Both BioMarin's and Sarepta's drugs are designed as bridges over a genetic mutation — a disrupted segment of a gene known as exon 51 — that codes for the dystrophin protein. About 15 percent of the 15,000 or so people with Duchenne muscular dystrophy have the mutation.

"There's certainly an interest in the field of exon skipping, but it's a blow," McSherry said about BioMarin's decision. "My heart is just broken for kids who traveled and had biopsies (for clinical trials). These kids have a short lifespan to begin with, and they take time away from birthdays and classes. The sacrifices are just surreal.

"And now they've had the rug pulled out from under them."

APPEARS THIS WAY ON ORIGINAL

Philips, Howard

From: Walsh, Sandy
Sent: Thursday, June 02, 2016 11:37 AM
To: Unger, Ellis; Temple, Robert
Subject: follow up on voucher question

Hi Ellis, I've talked to few people in CDER and it sounds like a good possibility that Sarepta would get a Rare Pediatric Disease Priority Review Voucher if approved before Sept. 31. They're eligible and could get a voucher regardless if it was a regular approval or an accelerated approval. Just another interesting twist to this story. I wanted to mention it to you since this would be highly newsworthy and we are trying to prepare for potential questions on multiple topics related to this application.

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: Temple, Robert
Sent: Thursday, June 02, 2016 11:43 AM
To: Blount, Aprile
Subject: FW: Recent piece on Sarepta

Can you copy the attachment? It won't let me. That is happening a lot lately.

From: Unger, Ellis
Sent: Thursday, June 02, 2016 11:33 AM
To: Temple, Robert; Lowy, Naomi
Subject: FW: Recent piece on Sarepta

From: Bastings, Eric
Sent: Thursday, June 02, 2016 10:56 AM
To: Dunn, Billy; Unger, Ellis; Jenkins, John K
Subject: Recent piece on Sarepta

www.streetinsider.com/dr/news.php?id=11700316

Eric Bastings, MD
Deputy Director
Division of Neurology Products
CDER/OND

Philips, Howard

From: Unger, Ellis
Sent: Thursday, June 02, 2016 10:53 AM
To: Jenkins, John K; Temple, Robert; Bastings, Eric; Farkas, Ronald; Breder, Christopher D
Cc: Lowy, Naomi; Choy, Fannie (Yuet); Locicero, Colleen L
Subject: FW: Sarepta

FYI

From: Woodcock, Janet
Sent: Thursday, June 02, 2016 10:44 AM
To: Unger, Ellis; Dunn, Billy; Rao, Ashutosh
Cc: Choy, Fannie (Yuet)
Subject: Sarepta

I spoke to the firm. They would take a long time with the tech transfer (they have a CRO lined up) to do the analysis of 20 WB-10 baseline and 10 48 week. However, I proposed: what if they gave "us" the samples and we had someone run them. They are considering that. Ash, this would mean a lab with some experience would be needed, and would need to drop everything in the next week or so.

They don't have enough normal muscle control left for all the runs. Another normal sample would need to be validated against the current standard and they have enough for that. That would also need to be done by "us".

The samples are all stored by University of Iowa, who may be able to do the blinding before sending.

I propose that the Division hold off talking to them until they determine if they are willing to do this.

I guess I would be ok if NIH did this (if they were willing) under our supervision.

The firm should get back to us "soon"... jw

Philips, Howard

From: Unger, Ellis
Sent: Friday, June 03, 2016 5:51 PM
To: Temple, Robert; Jenkins, John K; Locicero, Colleen L
Subject: Fw: Finalized - NDA-206488 General Advice Letter (COR-NDAIR-10)
Attachments: NDA206488_eteplirsen_FINAL GeneralAdviceLtr_EB-AR-RF-BD_unger_JW.pdf

Sent from my BlackBerry.

From: oasfda@fda.gov
Sent: Friday, June 3, 2016 5:48 PM
To: Kelley, Laurie; Unger, Ellis; Bastings, Eric; Locicero, Colleen L; Farkas, Ronald; Ware, Jacqueline H; Choy, Fannie (Yuet); Woodcock, Janet; Dunn, Billy; Peters, Tracy; Rao, Ashutosh
Subject: Finalized - NDA-206488 General Advice Letter (COR-NDAIR-10)





DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. Do **NOT** send this page with the letter.

Application #(s):	NDA 206488
Communication Type:	Correspondence
Communication Group:	Information Request/Advice
Communication Name:	General Advice Letter
Communication ID:	(COR-NDAIR-10) (COR-SNDAIR-03)(COR-BLAIR-10) (COR-SBLAIR-03)
Drafted by:	Choy
Clearance History:	Bastings, Farkas, Rao, Dunn, Unger; Woodcock
Finalized:	
Filename:	
Signatory Authority:	Chemistry TL, Division Director or Deputy. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	Use to send general advice to the applicant that is not necessarily related to a pending application.
Notes:	

Version: 05/07/2015

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.



NDA 206488

GENERAL ADVICE

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

Dear Ms. Ruff:

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

JANET WOODCOCK
06/03/2016

Philips, Howard

From: Farkas, Ronald
Sent: Friday, June 05, 2015 9:56 AM
To: Rao, Ashutosh; Breder, Christopher D; Tandon, Veneeta; Unger, Ellis; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: Of interest, Wilton (developer of eteplirsen) paper, arguing against drisapersen and some other interesting thoughts of his
Attachments: Wilton emporers dystrohin 2015.pdf

The emperor's new dystrophin: finding sense in the noise

S.D. Wilton^{1,2}, R.N. Veedu^{1,2}, and S. Fletcher^{1,2}

¹Centre for Comparative Genomics, Murdoch University, 90 South Street, Murdoch, WA 6009, Australia

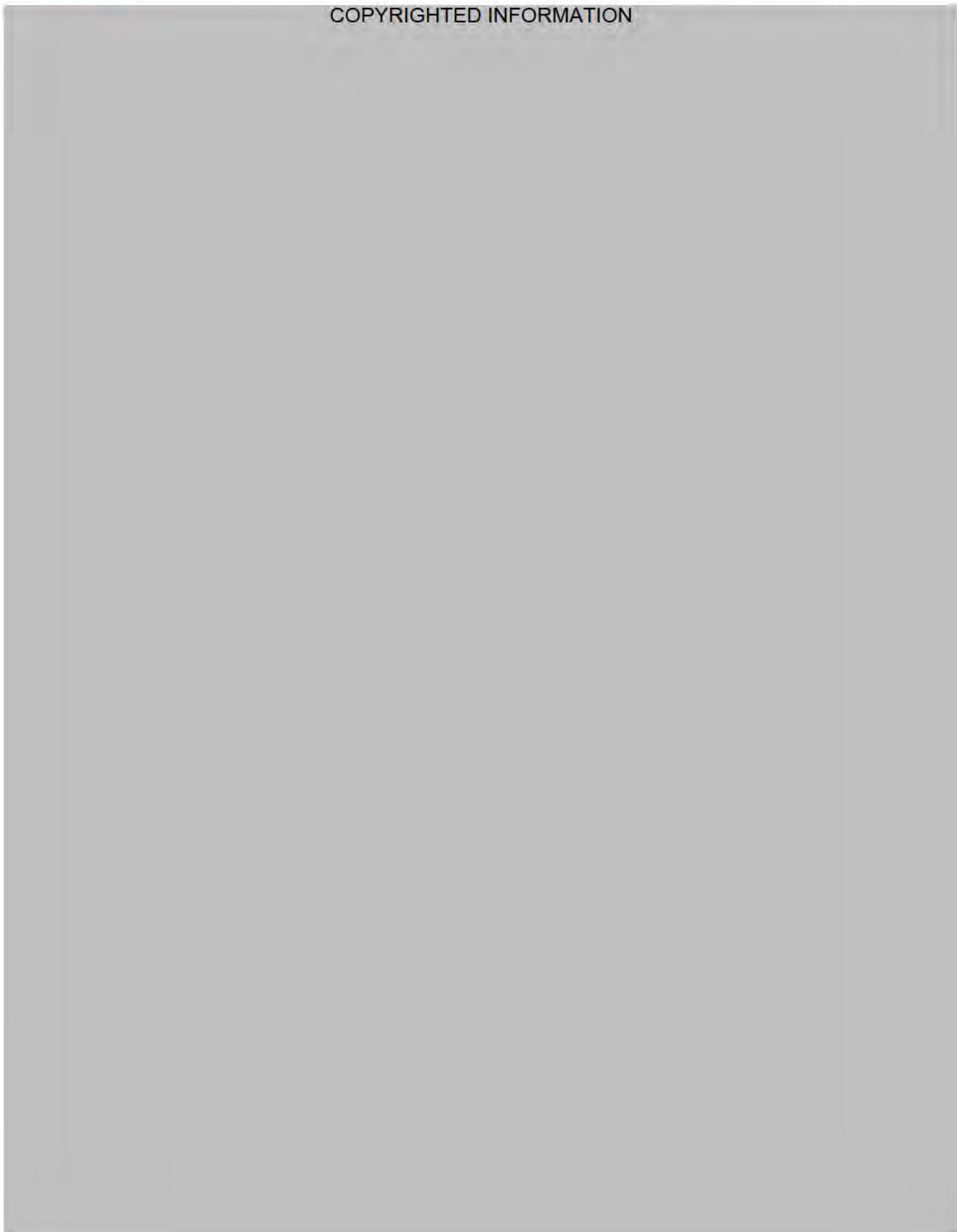
²West Australian Neuroscience Research Institute, Murdoch University, 90 South Street, Murdoch, WA 6009, Australia

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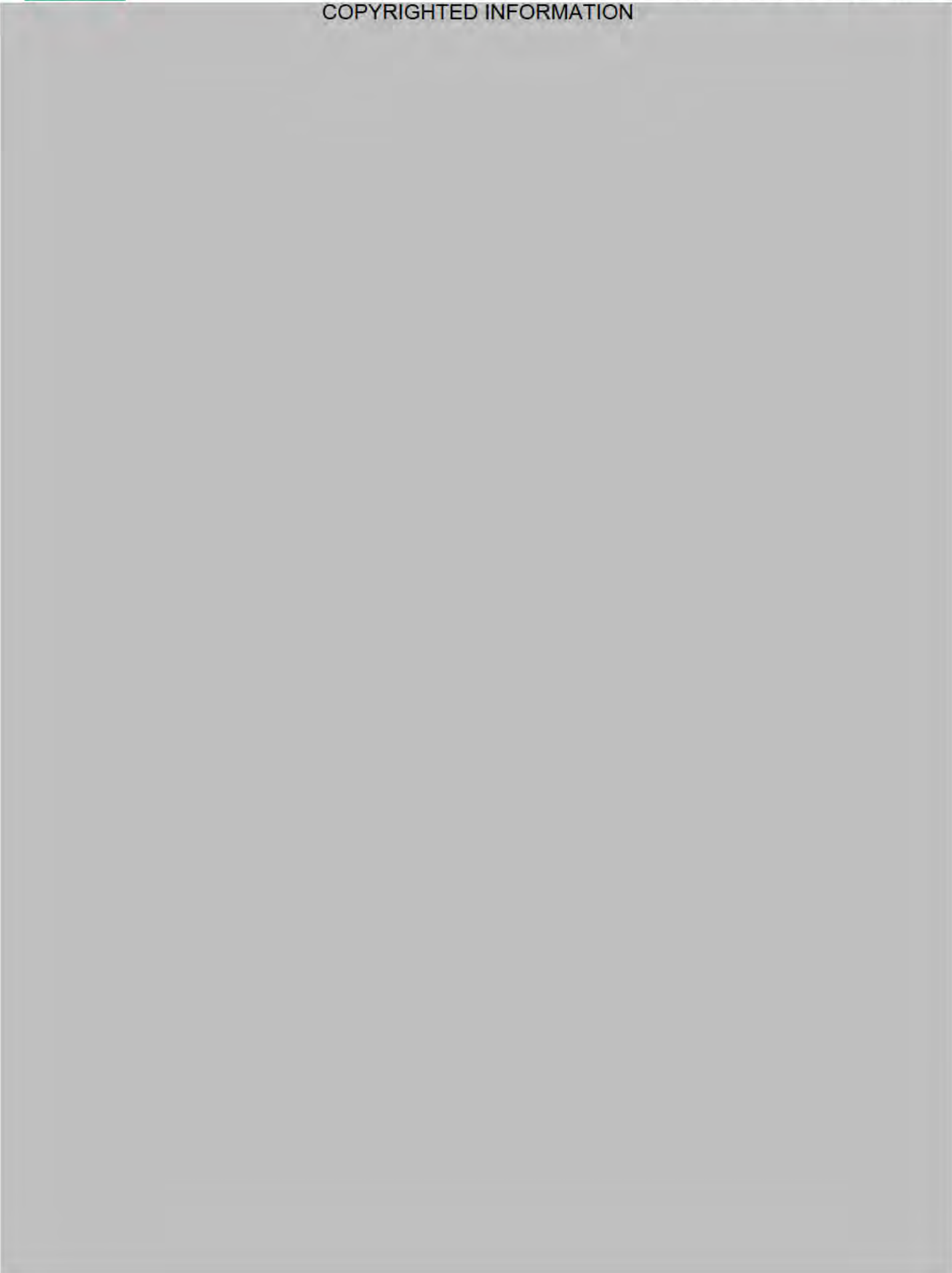
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Temple, Robert

From: Locicero, Colleen L
Sent: Tuesday, June 07, 2016 11:17 AM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Bastings, Eric; Choy, Fannie (Yuet); Farkas, Ronald
Subject: FW: article about Sarepta/eteplirsen

Just FYI, in case you hadn't seen it.

Colleen

From: Goldstein, Beth A (Duvall)
Sent: Tuesday, June 07, 2016 11:10 AM
To: Dubeau, Julieann; Sharma, Khushboo; Locicero, Colleen L; Walsh, Maria R
Subject: article about Sarepta/eteplirsen

From: CDER Trade Press
Sent: Tuesday, June 07, 2016 9:47 AM
To: CDER Trade Press
Subject: CDER Trade Press News Update June 7, 2016

Agony & Ecstasy Of Sarepta: A New FDA Rare Disease Standard?

07 Jun 2016

Donna Young [@ScripDonnaDC donna.young@informa.com](mailto:donna.young@informa.com)

Executive Summary

Even though investors viewed the FDA's willingness to give Sarepta another chance to provide more data as a positive step, most analysts said it was simply delaying the inevitable of rejecting the firm's Duchenne muscular dystrophy drug eteplirsen. Others have cautioned the FDA may be setting a new standard for approving rare disease drugs, in which other companies may demand similar attention.

The FDA has done it again – put off its decision on [Sarepta Therapeutics Inc.](#)'s new drug application (NDA) for its Duchenne muscular dystrophy (DMD) drug eteplirsen, this time telling the firm regulators want dystrophin data, as measured by Western blot, from biopsies already obtained from the company's ongoing PROMOVI confirmatory study.

Sarepta said it would submit data to the FDA "in the coming weeks" from biopsy samples from 13 patients who have completed 48 weeks in PROMOVI, a 96-week, open-label study evaluating the effects of eteplirsen in boys 7 to 16 years amenable to exon 51 skipping.

The news sent shares of Sarepta flying up about 37% in after-hours trading on June 6.

But even though investors viewed the FDA's apparent willingness to give Sarepta another chance as positive, most analysts said the agency – which is under perhaps more political pressure than it's been faced with since the "Vioxx" debacle a little more than a decade ago – was simply delaying the inevitable of rejecting the drug.

"FDA appears to leave no stone unturned in its attempt to explore every possible pathway and scenario under which it could possibly approve a drug that under almost every other circumstance we can think of would have been rejected given the severe weaknesses and deficiencies in its dataset," said RBC Capital Markets analyst Simos Simeonidis. "We definitely view this as a clear signal that the agency wants to exhaust every reasonable avenue to allow the company to provide evidence whether the drug has activity or not."

But several critics have said it would be a mistake for the FDA to put eteplirsen on the US market when its data are insufficient.

Ezekiel Emanuel, vice provost for global initiatives and chair of medical ethics and health policy at the University of Pennsylvania and a former adviser to President Barack Obama, took aim at Sarepta for trying to avoid doing a placebo-controlled trial, which he insisted the company "easily could have done," but opted instead to "put a lot of pressure by families and others" on the FDA to approve eteplirsen based on data from 12 patients, which failed to show efficacy.

"What this company was trying to do was not generate reliable, valid data, but instead use a lot of emotional" arguments, Emanuel charged during an April 26 appearance on *CNBC*.

Emanuel's remarks came a day after an FDA advisory panel voted 7-6 that Sarepta had failed to provide substantial evidence from adequate and well-controlled studies that eteplirsen induced production of dystrophin – a protein essential for normal muscular structure and function and the lack of which is at the heart of DMD – to a level that is reasonably likely to predict clinical benefit (Also see "[Data Trumps Anecdotes, Emotion At Sarepta Panel](#)" – *Scrip*, 26 Apr, 2016).

At the contentious April 25 meeting of the Peripheral and Central Nervous System Advisory Committee, the FDA's reviewers insisted Sarepta's data were weak – declaring the dystrophin levels were on average only about 0.93% after 3.5 years – which were conclusions that appeared to clash with the urging by higher-level regulators, including Janet Woodcock, director of the Center for Drug Evaluation and Research, for the committee to take patients' and advocates testimony backing the drug into account (Also see "[FDA Duchenne Drug Review Smacks Sarepta](#)" – *Scrip*, 15 Jan, 2016, and "[Sarepta Lashed Again; More Duchenne Market Doubt](#)" – *Scrip*, 21 Apr, 2016).

"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 effective," Woodcock said.

But, she told the panelists, "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 borne by patients, who traditionally have little say in how the standards are implemented."

It has yet to be seen whether other makers of rare disease drugs will demand the same kind of attention the FDA appears to be giving Sarepta's eteplirsen.

But some experts have warned the agency may be setting a new precedent – especially if it approves eteplirsen based on its weak data – that may be difficult to reverse (Also see "[High-Ranking Meddling Behind Sarepta Duchenne Drug Delay?](#)" – *Scrip*, 3 Jun, 2016).

Another Chance, But Slim

The request from the FDA on the dystrophin data came about a dozen days after the agency told Sarepta regulators would not complete their review of the eteplirsen NDA by its May 26 *Prescription Drug User Fee Act* action date, although not providing any sort of a timeline as for when to expect a verdict, which led analysts to suspect the agency was trying to find a way to approve the drug (Also see "[Limbo Land For Sarepta, Duchenne And Rare Diseases](#)" – *Scrip*, 25 May, 2016).

Then all hell broke loose on June 2 when the FDA released its final compassionate use guidances, complete with detailed Q&As and a simpler-to-use form for doctors, which led Wall Street to assume the agency was going to reject eteplirsen and had finished up its work on the expanded access documents to have a way for patients to access the drug, while providing regulators some political cover (Also see "[Sarepta Smacked By FDA's Curiously Timed Compassionate Use Revisions](#)" – *Scrip*, 2 Jun, 2016).

Some analysts believed that still to be the case even after the FDA's new request for the dystrophin data.

While dystrophin data from week 48 versus baseline could provide high-quality biomarker data, Jefferies analyst Gena Wang said she still saw only a "slim chance of meaningful improvement in dystrophin level, given the drug mechanism."

Even if some modest dystrophin improvement is observed, the magnitude of improvement likely will not meet the FDA's expectation, Wang added.

Leerink analyst Joseph Schwartz said that while the FDA's request for the dystrophin data reignited optimism for eteplirsen, he said there were several reasons to remain cautious.

First, Schwartz said, different muscle groups can generate different dystrophin expression profiles in different patients receiving different background therapy at different times in the disease and without a clear sense of what muscles were biopsied in the 13 patients and whether the sites were controlled, he said he remained cautious on the interpretability of the data, given the small sample size.

Schwartz also said the fact PROMOVI trial lacks a proper control arm also was a reason to be cautious, since different subpopulations of DMD show varying degrees of dystrophin levels, as was noted at the April 25 advisory committee meeting.

He said there's a "high probability" the dataset will be as "uninterpretable as the first dataset."

Schwartz said it's also unclear what in the 13 samples would constitute a satisfactory dystrophin production by the FDA.

And finally, he said, the "true intentions of the FDA behind this request remain unknown."

The FDA's actions prolonging the eteplirsen review further, Schwartz said, "could simply be designed to acknowledge the demands from all stakeholders, without changing their ultimate stance on the need to employ a proper drug development program."

But, Schwartz said, a decision based "primarily on sympathy" in which the FDA approves a drug that's not efficacious "could face serious reverberations in an already vilified health care space." [\(Return to Top\)](#)

Temple, Robert

From: Walsh, Sandy
Sent: Tuesday, June 07, 2016 10:06 AM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert
Cc: Bolek, Michelle; Choy, Fannie (Yuet); Farkas, Ronald
Subject: FYI Sarepta press release re: new data

Good morning, sharing the Sarepta news release:

<http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=2175522>

News Release

[View printer-friendly version](#)

[Back](#)

Sarepta Therapeutics Announces FDA Request For Dystrophin Data Prior To Making A Decision on Eteplirsen NDA
CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 6, 2016-- Sarepta Therapeutics, Inc. (NASDAQ:SRPT), a developer of innovative RNA-targeted therapeutics, today announced that the U.S. Food and Drug Administration (FDA) has requested that Sarepta provide dystrophin data, as measured by western blot, from biopsies already obtained from the ongoing confirmatory study of eteplirsen (PROMOVI), as part of its ongoing evaluation of the eteplirsen New Drug Application (NDA). The Company plans to submit data from thirteen patient biopsy samples, at baseline and Week 48, to the FDA over the coming weeks to facilitate a prompt decision on the NDA by the Agency.

About Sarepta Therapeutics

Sarepta Therapeutics is a biopharmaceutical company focused on the discovery and development of unique RNA-targeted therapeutics for the treatment of rare, infectious and other diseases. The Company is primarily focused on rapidly advancing the development of its potentially disease-modifying DMD drug candidates, including its lead DMD product candidate, eteplirsen, designed to skip exon 51. Sarepta is also developing therapeutics for the treatment of rare, infectious and other diseases. For more information, please visit us at www.sarepta.com.

About Eteplirsen

Eteplirsen is designed to address the underlying cause of DMD by restoring the dystrophin messenger RNA (mRNA) reading frame, thus enabling the production of a shorter, functional form of the dystrophin protein. Eteplirsen uses Sarepta's proprietary phosphorodiamidate morpholino oligomer (PMO) chemistry and exon-skipping technology to skip exon 51 of the dystrophin gene. Approximately 13 percent of the DMD population is amenable to exon 51 skipping. Data from clinical studies of eteplirsen in DMD patients have demonstrated a consistent safety and tolerability profile and have also shown measurable dystrophin protein expression. Promoting the synthesis of a shorter dystrophin protein is intended to slow the decline of ambulation and mobility seen in DMD patients. There currently is no approved treatment in the United States for DMD and eteplirsen has not been approved by the FDA or any regulatory authority for the treatment of DMD.

About Duchenne Muscular Dystrophy

DMD is an X-linked rare degenerative neuromuscular disorder causing severe progressive muscle loss and

premature death. One of the most common fatal genetic disorders, DMD affects approximately one in every 3,500-5,000 males worldwide. A devastating and incurable muscle-wasting disease, DMD is associated with specific errors in the gene that codes for dystrophin, a protein that plays a key structural role in muscle fiber function. Progressive muscle weakness in the lower limbs spreads to the arms, neck and other areas. Eventually, increasing difficulty in breathing due to respiratory muscle dysfunction requires ventilation support, and cardiac dysfunction can lead to heart failure. The condition is universally fatal, and death usually occurs before the age of 30.

Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. Any statements contained in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Words such as "believes," "anticipates," "plans," "expects," "will," "intends," "potential," "possible" and similar expressions are intended to identify forward-looking statements. These forward-looking statements include statements regarding the FDA's request that the Company provide dystrophin data, as measured by western blot, from biopsies already obtained from the ongoing confirmatory study of eteplirsen (PROMOVI) as part of its ongoing evaluation of the eteplirsen NDA and the expected timelines for the Company submitting this additional data, including the Company's plans to submit data from thirteen patient biopsy samples, at baseline and Week 48, to the FDA over the coming weeks to facilitate a prompt decision on the NDA by the Agency, and the FDA's decision on the eteplirsen NDA.

These forward-looking statements involve risks and uncertainties, many of which are beyond Sarepta's control. Known risk factors include, among others: we may not be able to successfully gather all the data we currently plan to provide to the FDA or may not be able to otherwise comply with FDA requests, to the FDA's satisfaction, with respect to the additional dystrophin data requested by the FDA in a timely manner or at all; even if we provide the FDA with the additional dystrophin data requested, we do not know what the results will show and they could be inconsistent with prior data or result in an FDA finding that the data does not support approval of the eteplirsen NDA, on an expedited timeframe or at all, and the FDA may further delay its approval decision, make additional requests relating to the eteplirsen NDA, provide a complete response letter or otherwise decline to provide marketing approval for eteplirsen; we may not be able to comply with any other FDA requests relating to the eteplirsen NDA submission and the addendums we have submitted to the FDA or with respect to our ongoing or planned clinical trials, in a timely manner or at all; the FDA may further delay its decision on the eteplirsen NDA or may not provide marketing approval for eteplirsen; we may not be able to complete clinical trials required by the FDA for approval of our products or any submissions made in connection with our pipeline of product candidates; the results of our ongoing research and development efforts and clinical trials for our product candidates including eteplirsen and our technologies may not be positive or consistent with prior results or demonstrate a safe treatment benefit or support an NDA filing, positive advisory committee recommendation or marketing approval by the FDA or other regulatory authority; we may not be able to execute on our business plans including meeting our expected or planned regulatory milestones and timelines, clinical development plans and bringing our product candidates to market, including the planned commercialization of eteplirsen, for various reasons, including factors outside of the Company's control, including possible limitations of Company financial and other resources, manufacturing limitations that may not be anticipated or resolved for in a timely manner or at all, and regulatory, court or agency decisions, such as decisions by the United States Patent and Trademark Office with respect to patents that cover our product candidates; and those risks identified under the heading "Risk Factors" in Sarepta's most recent Annual Report on Form 10-K for the year ended December 31, 2015 or Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 filed with the Securities and Exchange Commission (SEC) as well as other SEC filings made by Sarepta which you are encouraged to review.

Any of the foregoing risks could materially and adversely affect Sarepta's business, results of operations and

FDA NEWS RELEASE

For Immediate Release: June xx, 2016

Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

(b) (5)

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

FDACDER0004574

Philips, Howard

From: Walsh, Sandy
Sent: Thursday, June 09, 2016 12:36 PM
To: Dunn, Billy; Unger, Ellis
Cc: Choy, Fannie (Yuet); Bastings, Eric; Bolek, Michelle; Diggs, Felicia; Temple, Robert
Subject: DNP/ODE-1 review of eteplirsen materials
Attachments: eteplirsen KMQA 0601916.doc; eteplirsen PR draft 060916 DNP.doc

Hi, as mentioned yesterday, we are busy preparing for a few possible scenarios around eteplirsen. While we know a decision has not yet been made, we need to go ahead and get materials written. As you know, this will be a major agency announcement if the drug is approved. We'll be planning for a press release, phone press briefing, broadcast TV interviews, and a stakeholder call.

Attached are a draft QA documents and a draft press release. They are written as if it is a "normal" accelerated approval if the new data support approval. We will also work on materials that that reflect other scenarios.

I want to give DNP/ODE-1 the chance to review the draft materials but I understand the sensitivities and the uncertainty around what might happen. Due to the time constraints, we are going to have to write the best drafts that we can and update/replace things as new information becomes available. We especially value your input on the technical accuracy and understand that some responses will need to come directly from Dr. Woodcock.

Ellis, I know you're headed out of town but we'd appreciate your feedback so please let me know if you can squeeze in any time to review this after DNP, or now. Is it possible for DNP to provide feedback by end of day Monday? Let me know if you'd like to discuss this.

Thank you.

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

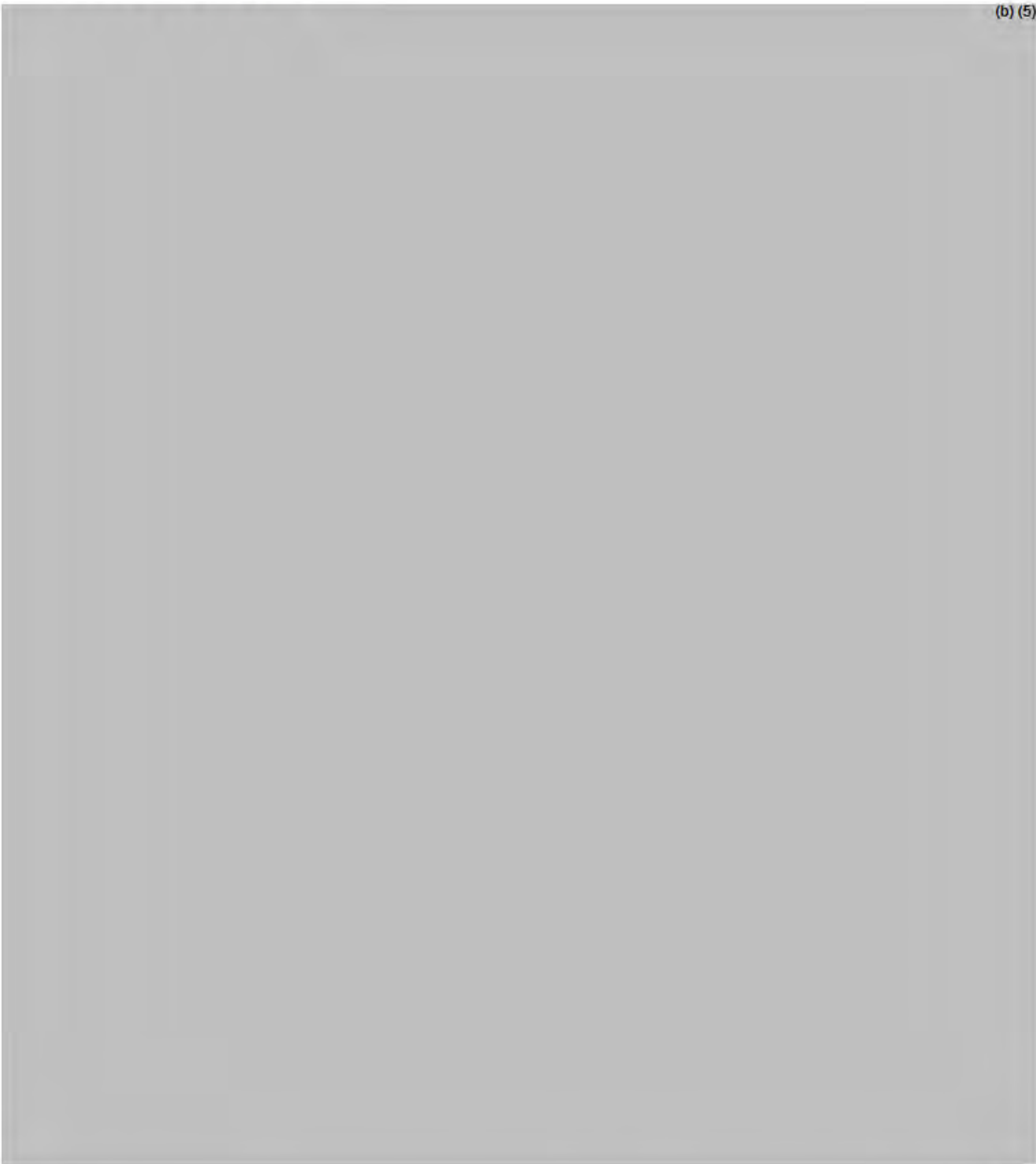


Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

Target date: Late June/Early July

SECTION I: BACKGROUND

(b) (5)



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

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Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

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FDA approves first drug treatment for Duchenne muscular dystrophy, addressing unmet medical need

(b) (5)

(b) (5)

Philips, Howard

From: Blount, Aprile
Sent: Monday, June 13, 2016 5:16 PM
To: Walsh, Sandy; Bastings, Eric
Cc: Dunn, Billy; Choy, Fannie (Yuet); Bolek, Michelle; Diggs, Felicia; Temple, Robert; Unger, Ellis
Subject: RE: DNP/ODE-1 review of eteplirsen materials
Attachments: eteplirsen PR draft RT_EU edits.doc

Here are some additional comments from Bob.

From: Walsh, Sandy
Sent: Monday, June 13, 2016 3:48 PM
To: Bastings, Eric; Blount, Aprile
Cc: Dunn, Billy; Choy, Fannie (Yuet); Bolek, Michelle; Diggs, Felicia; Temple, Robert; Unger, Ellis
Subject: RE: DNP/ODE-1 review of eteplirsen materials

Thanks Eric. I'll clean these up and move them into CDER clearance and we'll update along the way as needed. I'll keep in touch re: next steps and timing.

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



From: Bastings, Eric
Sent: Monday, June 13, 2016 3:46 PM
To: Blount, Aprile; Walsh, Sandy
Cc: Dunn, Billy; Choy, Fannie (Yuet); Bolek, Michelle; Diggs, Felicia; Temple, Robert; Unger, Ellis
Subject: RE: DNP/ODE-1 review of eteplirsen materials

A few edits.

Eric

From: Blount, Aprile
Sent: Friday, June 10, 2016 11:59 AM
To: Walsh, Sandy
Cc: Dunn, Billy; Choy, Fannie (Yuet); Bastings, Eric; Bolek, Michelle; Diggs, Felicia; Temple, Robert; Unger, Ellis
Subject: RE: DNP/ODE-1 review of eteplirsen materials

Hi Sandy,
Here are Ellis' and Bob's comments. I couldn't make out 1 word on pg 2 of the second doc.

From: Walsh, Sandy
Sent: Thursday, June 09, 2016 12:36 PM
To: Dunn, Billy; Unger, Ellis
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Press Officer

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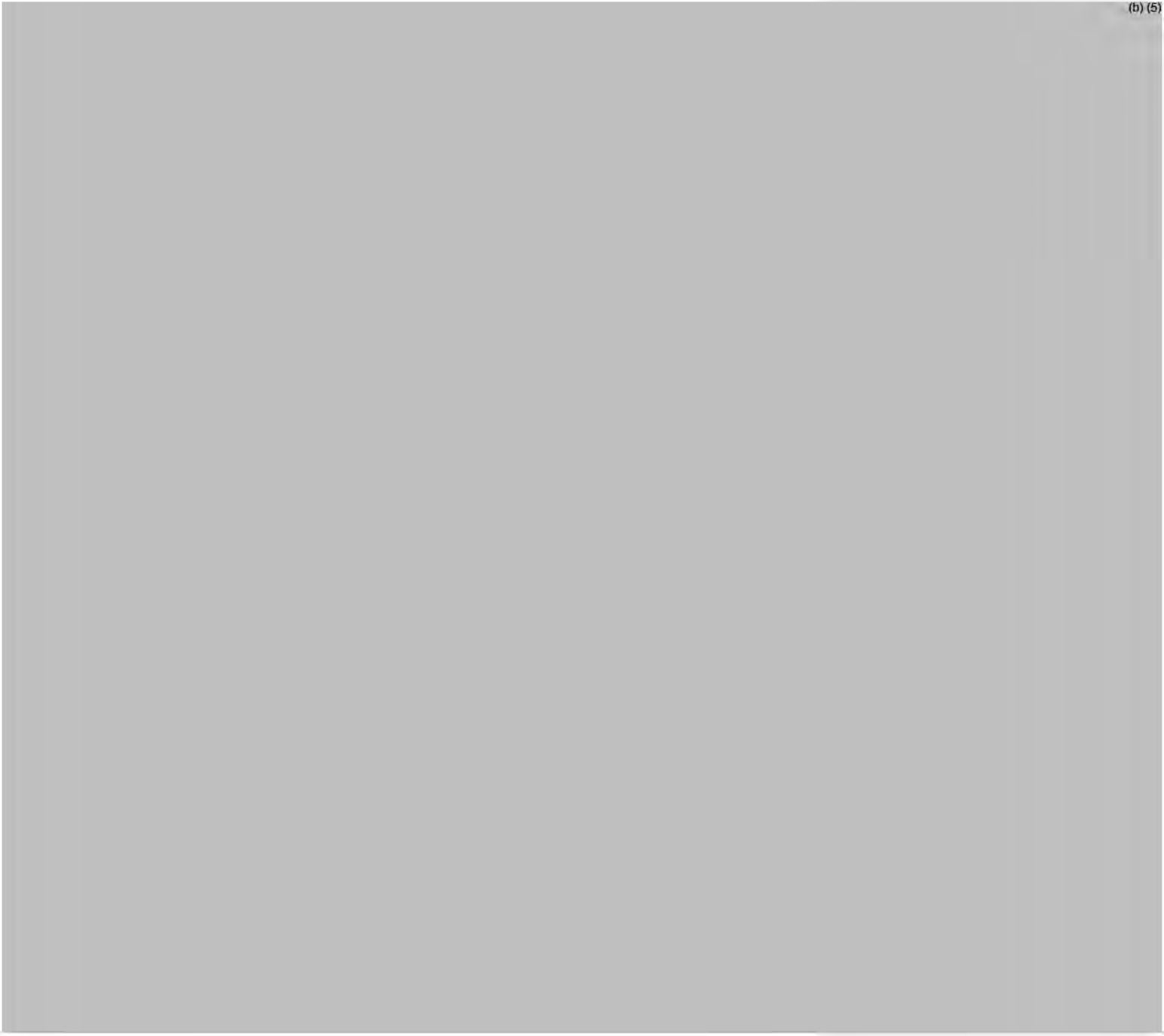
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Subject: RE: DNP/ODE-1 review of eteplirsen materials
Attachments: eteplirsen PR draft RT_EU edits.doc; eteplirsen KMQA_RT_EU edits.doc

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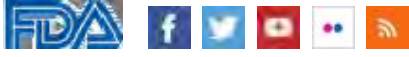
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Thank you.

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



FDA NEWS RELEASE

For Immediate Release: June xx, 2016

Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

(b) (5) (5)

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

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(1)

etp

Elis memo

Not returned endpt

Not broM reasonably likely

Non-clinical quote for buel + no illustration re variability of induced dystrophin by site. Show data, Cited again in Watch blast desc but no data.

Clin Ph wants new study in Ex 57 testing upper + lower body strength age 4-12 and doses > 50

Agree re their AA interpretation

Immunohist table shows 0 effect at 50 ug but no comment (? too soon)

Fig 2 shows NO real increase over time after 48 wks

But doesn't it show > plbo at 24-48 wks

~~Strength~~ Immuno needs close look

Table - intrasession variability not as bad as stated: All pretty close
Quadriceps, G, E, and legs 3

Not just F, H

(2)

Table 4 del 7 but all low
One 0.37, 0.4

New data
base

late

8 0.17 → 1.02

9 0.24 → 1.57

Fig 6, 15 ^{mentioned before fig 8} omitted
(shows up later)

I like argument that doesn't NOT an
enzyme test support

Fig 9 doesn't label groups and to
eval is shown

After fig 9? applicant's argument
for ADA, you say Δ 6 due walk is
SS but give no data

Position A don't say some patients
Say 2/11

Temple, Robert

el-ed wsen

From: Farkas, Ronald
Sent: Wednesday, June 22, 2016 4:29 PM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Breder, Christopher D; Choy, Fannie (Yuet)
Subject: Update from Ash about progress on running Western blots

Ash called just to provide an update. There are no serious problems. The blinding looks good, and most of the Western blots are running well (Ash is favorably impressed by these Sarepta technicians), although a few gels did not meet all the acceptance criteria. Ash thinks these gels may still be usable/interpretable. 6 patients have been run, and the 7 remaining should be run by the end of the day tomorrow. The data is still blinded, but the dystrophin levels are fairly evenly spread out between 0.03% to 1.17% of normal. There are no true zero values, but about half or slightly more of the values are BLOQ at less than 0.25%, and would be considered zero by Sarepta's convention. Sarepta plans to QC the data on Friday and Saturday.

Thanks
Ron

Temple, Robert

From: Farkas, Ronald
Sent: Wednesday, June 22, 2016 3:28 PM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Breder, Christopher D; Choy, Fannie (Yuet); Peters, Tracy
Subject: FW: Eteplirsin/Launch Promotional material
Attachments: MA 2 EXONDYS 51 Launch HCP Sales Aid Annotated C-SRP-51-US-0100.pdf

Attached is Sarepta's sales aid. As you can see, the sales aid [REDACTED] (b) (4) |
talked briefly with Aline from OPDP and under the new legal interpretation about advertising it is not clear that we can
stop Sarepta [REDACTED] (b) (4), but, if I understand correctly, it may still be possible to make them [REDACTED] (b) (4).

Might be good for everyone to look this over now because we'll get the consult from OPDP soon and they will be asking
for a very quick turnaround.

Thanks
Ron

*I note clear net call for
implanted channel
So why do trials need are,*

INDICATION¹

Pl. 05/24/2016, Sec 1, Para 1.

EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping. This indication is approved on a surrogate endpoint demonstrating an increase in dystrophin production. Clinical benefit will be evaluated through confirmatory trials.

IMPORTANT SAFETY INFORMATION¹

Pl. 05/24/2016, Sec 8.6, Para 1, L 1.

EXONDYS 51 has not been studied in patients with renal or hepatic insufficiency. In nonclinical toxicology studies, the kidney was a target organ of toxicity. Any signs or symptoms of potential renal toxicity should be investigated promptly in patients receiving EXONDYS 51.

Pl. 05/24/2016, Sec 5.1, Para 1.

The most common adverse reactions for $\geq 10\%$ of patients treated with EXONDYS 51 that occurred more frequently than in patients treated with placebo were: headache, vomiting, cough, upper respiratory tract infection, arthralgia, and nasopharyngitis. The majority of these events were mild and resolved during continued treatment with EXONDYS 51.

Pl. 05/24/2016, Sec 6.1, Para 3.

There have been reports of mild and transient erythema, flushing (facial), and elevated temperature occurring on the day of EXONDYS 51 infusion. There was no consistent pattern of recurrence of these reactions with subsequent infusions.

Pl. 05/24/2016, Sec 6.1, Para 5.

Please see the accompanying full Prescribing Information for EXONDYS 51.

For more information, please visit EXONDYS51.com.



INSIDE FRONT COVER

Falzarano MS, Scotton C, Passarelli C, Ferlini A. *Molecules*. 2015;20(10):18168-18184. P 18169, Para 1, L 1-3.

ABOUT DUCHENNE AND EXON SKIPPING

DMD IS THE RESULT OF MUTATIONS IN THE DYSTROPHIN GENE^{2,3}

- The dystrophin (*DMD*) gene codes for the production of dystrophin protein

Falzarano MS, Scotton C, Passarelli C, Ferlini A. *Molecules*. 2015;20(10):18168-18184. P 18169, Para 5, L 2-3.

Falzarano MS, Scotton C, Passarelli C, Ferlini A. *Molecules*. 2015;20(10):18168-18184. P 18169, Para 6, L 4-5..

Dystrophin is a key muscle-protecting protein
Dystrophin protects muscle fibers

Falzarano MS, Scotton C, Passarelli C, Ferlini A. *Molecules*. 2015;20(10):



MEET PIETRO.
PIETRO HAS DMD, BUT
TODAY HE IS DOING
FDACDER0004623



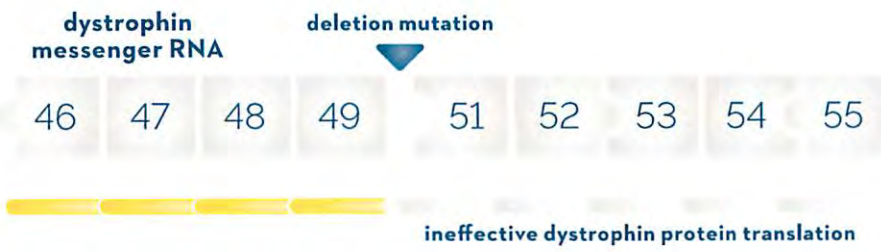
EXONDYS 51™
(eteplirsen) Injection

EXONDYS 51 IS AN EXON-SKIPPING THERAPY^{1,4}

PI. 05/24/2016, Sec 8.1, Para 2, L 1.

- Most people with Duchenne are missing one or more exons in the dystrophin gene

Aartsma-Rus A, Van Deutekom JC, Fokkema IF, Van Ommen GJ, Den Dunnen JT. *Muscle Nerve*. 2006;34(2):135-144. P 137, Col 1, Para 1, L 1-4.



- In patients amenable to exon 51 skipping, EXONDYS 51 restores the messenger RNA (mRNA) reading frame, which results in the production of dystrophin protein

PI. 05/24/2016, Sec 12.1, Para 1, L 3-9.

from mechanical stress during muscle contraction

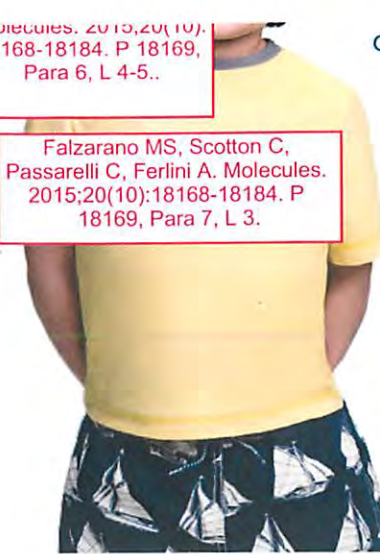
- Mutations causing Duchenne result in little or no dystrophin being produced in muscle tissue

- Lack of dystrophin causes muscle cell damage and deterioration, leading to relentless progression and rapid decline of functional abilities

Ellis JA, Vroom E, Muntoni F. Neuromuscul Disord. 2013;23:682-689. P 682, Col 1, Para 2, L 1-6.

Molecules. 2015;20(10):18168-18184. P 18169, Para 6, L 4-5.

Falzarano MS, Scotton C, Passarelli C, Ferlini A. Molecules. 2015;20(10):18168-18184. P 18169, Para 7, L 3.



ON HIS MIND IS BUILDING
A SAND CASTLE.

Indication¹

Pl. 05/24/2016. Sec 1, Para 1.

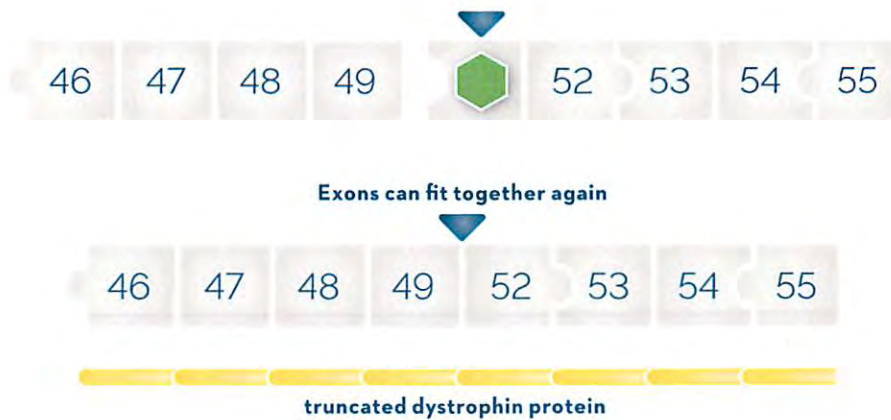
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Pl. 05/24/2016. Sec 8.6, Para 1, L 1.

Pl. 05/24/2016. Sec 5.1, Para 1.



Important Safety Information (continued)¹

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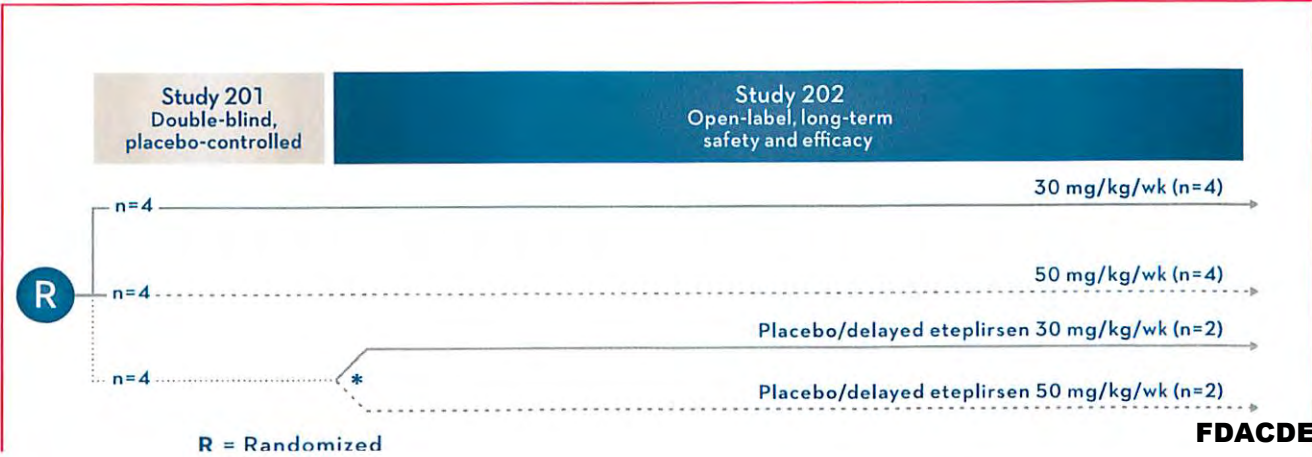
Please see the accompanying full Prescribing Information for EXONDYS 51.



EXONDYS 51 STUDY DESIGN

APPROVAL WAS BASED ON EVALUATION OF 12 PATIENTS, OVER 4 YEARS, COMPARED TO EXTERNAL CONTROLS (N=13)^{1,5}

Pl. 05/24/2015. Sec 14, Para 1, L 1-5 and Table 3, Column 3, Row 1.



Pl. 05/24/2016 3, Row 2.

Pl. 05/24/2016 3, R



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EXONDYS 51 PATIENTS WERE EVALUATED IN COMPARISON TO EXTERNAL CONTROLS^{1,6}

PI. 05/24/2016. Sec 14, Para 1, L 1-7.

PI. 05/24/2016. Sec 14, Table 3, Column 2, Row 1.

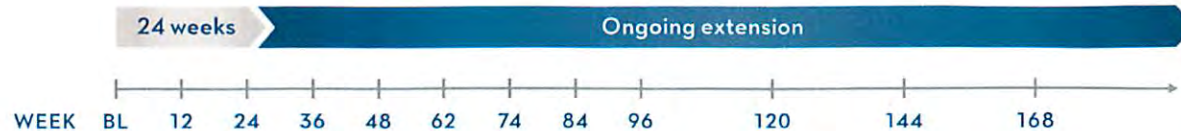
PI. 05/24/2016. Sec 14, Table 3, Column 2, Row 1.

Baseline Characteristics of EXONDYS 51 Treated Patients* and External Controls†

PARAMETER	EXONDYS 51 n=12	EXTERNAL CONTROL n=13
Age (years)		
Mean (SD)	9.4 (1.19)	9.5 (1.45)
Median (Min, Max)	9.7 (7.3, 11.0)	9.0 (7.3, 11.8)
6MWD* (meters)		
Mean (SD)	363 (42.19)	358 (66.75)
Median (Min, Max)	370 (256, 416)	373 (200, 458)

3. Sec 14, Table

1. Sec 14, Table Row 3.



- **Study 201:** Randomized, double-blind, placebo-controlled (24 weeks, n=12)
- **Study 202:** Open-label, long-term safety and efficacy (4 years, n=12)
- In the absence of long-term placebo-controlled data, results from patients treated with EXONDYS 51 were compared to untreated External Control data

*Placebo-controlled group rolled over onto open-label eteplirsen.
Adapted from Mendell. *Ann Neurol.* 2016.

Indication¹

PI. 05/24/2016. Sec 1, Para 1.

Mendell JR, et al. *Ann Neurol.* 2016;79(2):257-271. P 259, Fig 1 chart and copy and P 258, Col 2 Para 2 L 1-6

EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping. This indication is approved on a surrogate endpoint demonstrating an increase in dystrophin production. Clinical benefit will be evaluated through confirmatory trials.

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PI. 05/24/2016. Sec 5.1, Para 1.

PI. 05/24/2016. 3, Row 4

PI. 05/24/2016. Line

. Sec 14, Table and Row 5.	Deletion mutations represented	45-50, 48-50, 49-50, 50, 52	45-50, 48-50, 49-50, 50, 52	PI. 05/24/2016. Sec 14, Para 2, Lines 5-7.
Sec 14, Para 2, s 1-3.	Steroid use at baseline	✓	✓	

*Italian DMD Registry & Leuven Neuromuscular Reference Center (LNMRC).

*ITT pooled analysis across doses (30 mg/kg and 50 mg/kg).

*6-minute walk distance.

Data on File. NDA 2.5 Clinical Overview. P 14, Sec 1.7.1, L 1-7.

Important Safety Information (continued)¹

The most common adverse reactions for ≥10% of patients treated with EXONDYS 51 that occurred more frequently than in patients treated with placebo were: headache, vomiting, cough, upper respiratory tract infection, arthralgia, and nasopharyngitis. The majority of these events were mild and resolved during continued treatment with EXONDYS 51. PI. 05/24/2016. Sec 6.1, Para 3.

There have been reports of mild and transient erythema, flushing (facial), and elevated temperature occurring on the day of EXONDYS 51 infusion. There was no consistent pattern of recurrence of these reactions with subsequent infusions. PI. 05/24/2016. Sec 6.1, Para 5.

Please see the accompanying full Prescribing Information for EXONDYS 51.



CLINICAL STUDY RESULTS¹

EXONDYS 51 ALLOWS FOR THE PRODUCTION OF FUNCTIONAL DYSTROPHIN PROTEIN

Pl. 05/20/2016. Sec 12.1, Para1 , L 6-9.

Pl. 05/24/2016. Sec 14, Table 4.

Dystrophin Levels in EXONDYS 51 Treated Patients after 4 Years of Treatment Compared to Baseline Values/Untreated Patients

	Western Blot % of normal	Intensity* % of normal	Dystrophin Positive Fibers* % of normal
Mean (Baseline/Untreated)	0.08	9.41	1.12
Mean (EXONDYS 51 Treated)	0.93	22.61	17.39

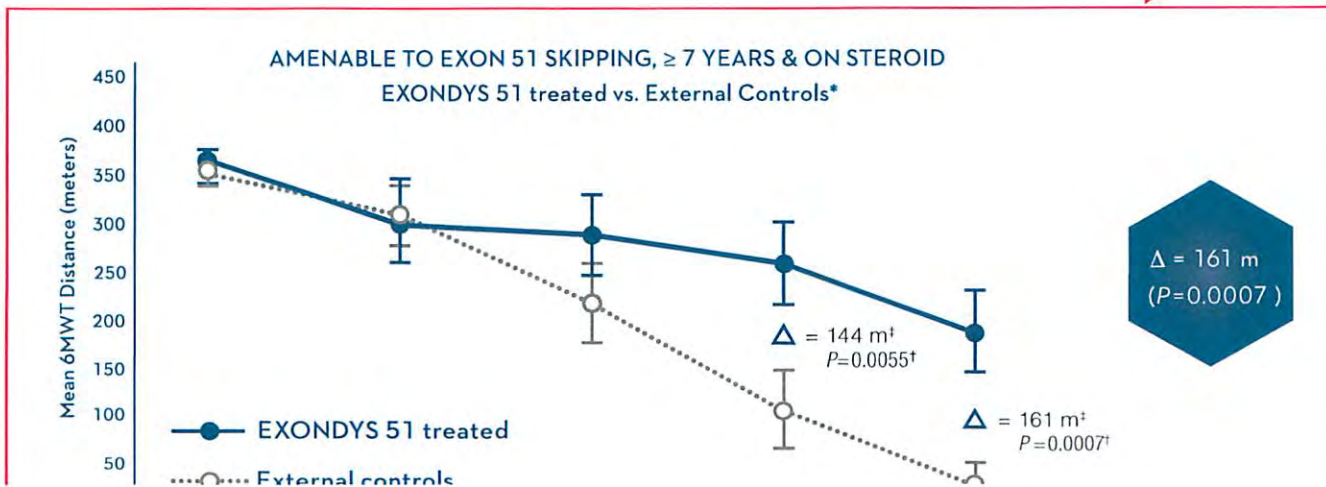


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PI. 05/24/2016. Sec 14,
Para 4, L1-2.

EXONDYS 51 TREATED PATIENTS DEMONSTRATED A SLOWER RATE OF DECLINE AS MEASURED BY 6MWT¹

PI. 05/24/2016. Sec 14, Fig 2.



Absolute Difference	+0.85	+13.2	+16.27
P value	0.007	<0.001	<0.001
Fold increase	11.6	2.4	15.5

* By immunohistochemistry

Indication¹ PI. 05/24/2016. Sec 1, Para 1.

EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping. This indication is approved on a surrogate endpoint demonstrating an increase in dystrophin production. Clinical benefit will be evaluated through confirmatory trials.

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PI. 05/24/2016. Sec 5.1, Para 1.



- At year 4, mean change from baseline favored patients treated with EXONDYS 51 by 161 m

* Baseline: EXONDYS 51 treated [n] = 12; External controls [n] = 13
 * Difference in mean change from baseline after adjusting for baseline
 † ANCOVA model with baseline δ MWT as the covariate
 δ MWT = 6-minute walk test

PI. 05/24/2016. Sec 14, Fig 2.

PI. 05/24/2016. Sec 14, Para 4, L 4-5.

Important Safety Information (continued)¹

The most common adverse reactions for $\geq 10\%$ of patients treated with EXONDYS 51 that occurred more frequently than in patients treated with placebo were: headache, vomiting, cough, upper respiratory tract infection, arthralgia, and nasopharyngitis. The majority of these events were mild and resolved during continued treatment with EXONDYS 51.

PI. 05/24/2016. Sec 6.1, Para 3.

There have been reports of mild and transient erythema, flushing (facial), and elevated temperature occurring on the day of EXONDYS 51 infusion. There was no consistent pattern of recurrence of these reactions with subsequent infusions.

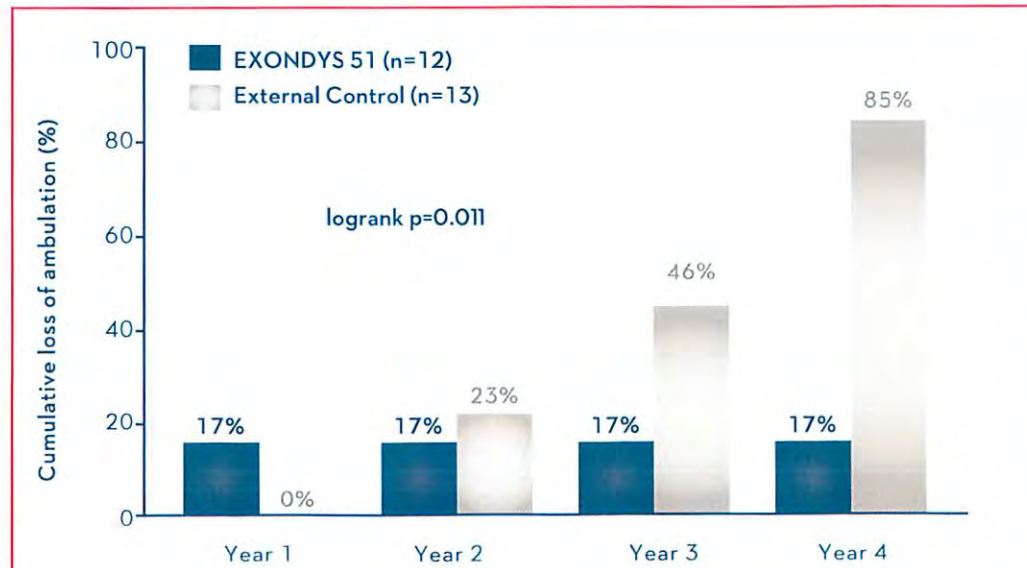
PI. 05/24/2016. Sec 6.1, Para 5.

Please see the accompanying full Prescribing Information for EXONDYS 51.



CLINICAL STUDY RESULTS^{1,5}

Probability of loss of ambulation at year 4, as measured by Kaplan-Meier estimate



Data on File. NDA 2.7.3
Clinical Efficacy
Addendum. P 17, Fig 4.

Data on File. NDA Clinical
Efficacy Addendum. P 17,
Fig 4.

PI.

Mendell JR, et al. Ann
Neurol. 2016;79(2):257-
271. P 264, Fig 4 (B).



SAFETY PROFILE¹

- The safety assessment was based on 114 patients who were exposed to EXONDYS 51
 - Includes 61 patients who were exposed for at least 3 months
 - 36 patients were exposed for at least 6 months
 - 12 patients were exposed for approximately 4 years
- In clinical trials of EXONDYS 51, the most common adverse reactions reported in ≥10% of patients treated with 30 mg/kg or more (n=88) that occurred more frequently than in patients treated with placebo were headache, vomiting, cough, upper respiratory tract infection, arthralgia, and nasopharyngitis
 - The majority of these events were mild and resolved during continued treatment with EXONDYS 51
- One patient with preexisting cardiomyopathy discontinued treatment while receiving EXONDYS 51 (4.0 mg/kg)
- There have been reports of mild and transient erythema, flushing (facial), and elevated

PI. 06/2015. Sec 6.1, Para 2, Lines 1-2.

05/24/2016. Sec 6.1, Para 2, L 2.

PI. 05/24/2016. Sec 6.1, Para 2, L 2.

PI. 05/24/2016. Sec 6.1, Para 2, L 3.

PI. 05/24/2016. Sec 6.1, Para 3, L 1-4.

PI. 05/24/2016. Sec 6.1, Para 3, L 4-5.

PI. 05/24/2016. Sec 6.1, Para 4.

Individual time points missing: ECM2 Year 4, ECG3 Year 3 & 4

- **Probability of loss of ambulation at year 4** was 17% for patients treated with EXONDYS 51 vs. 85% for External Controls PI. 05/24/2016. Sec 14, Para 4, L 5-7.
- **Relative stability of pulmonary function** over 3 years, as assessed by FVC (percent predicted) PI. 05/24/2016. Sec 14, Para 6, L 1-2

FVC = forced vital capacity.
Adapted from Mendell. *Ann Neurol*. 2016.

Indication¹ PI. 05/24/2016. Sec 1, Para 1.

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temperature occurring on the day of EXONDYS 51 infusion. There was no consistent pattern of recurrence of these reactions with subsequent infusions

PI. 05/24/2016. Sec 6.1, Para 5.

- Serial echocardiograms were conducted in Studies 1 and 2. No pattern of decline in left ventricular ejection fraction was observed over 4 years

PI. 05/24/2016. Sec 6.1, Para 6.

- Clinical drug interaction studies have not been conducted with EXONDYS 51

PI. 05/24/2016. Sec 7, Para 1.

Important Safety Information (continued)¹

The most common adverse reactions for $\geq 10\%$ of patients treated with EXONDYS 51 that occurred more frequently than in patients treated with placebo were: headache, vomiting, cough, upper respiratory tract infection, arthralgia, and nasopharyngitis. The majority of these events were mild and resolved during continued treatment with EXONDYS 51.

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PI. 05/24/2016. Sec 6.1, Para 5.

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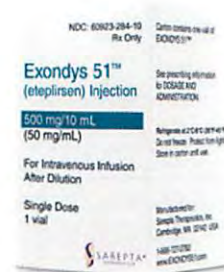


ADMINISTRATION¹

- Administered as a once-weekly infusion of 30 mg/kg over 35 to 60 minutes. Observe patients for reactions to the infusion for one hour after the completion of the infusion
- Application of a topical anesthetic cream to the infusion site prior to administration of EXONDYS 51 may be considered
- Please see full Prescribing Information (section 2) for complete preparation instructions

PI. 06/2015. Sec 2.1, Para and Sec 2.3, Para 2, L

PI. 06/2015. Sec 2.1, Para 2.



PI. 06/2015. Sec 16, Para 1, L 3

FDACDER0004639



1, L 1-2
1-2.

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- 2 Fill out the START form and fax it to 1-800-621-5203
- 3 A dedicated Case Manager will contact your patient soon

-4.

SareptAssist provides each family with a personal Case Manager who can answer



MEET XAVIER.
XAVIER HAS DMD, BUT TODAY,
THE ONE THING ON HIS MIND IS
GETTING IN THE GAME.

Indication¹

PI. 05/24/2016. Sec 1,
Para 1.

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PI. 05/24/2016. Sec 5.1, Para 1.

SareptaAssist provides each family with a personal Case Manager who can answer questions and provide information on:

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- On-site or at-home therapy options
- Out-of-pocket costs
- Financial assistance options
- The prior authorization process
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or visit SareptaAssist.com

Important Safety Information (continued)¹

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EXONDYS 51™

(eteplirsen) Injection

BACK COVER

APPROVED FOR DMD PATIENTS AMENABLE TO EXON 51 SKIPPING¹

PI. 05/20/2016. Sec 1,
Para 1, L 1-2.

- Allows for the production of functional dystrophin protein PI. 05/20/2016. Sec 12.1,
Para 1, L 6-9.
- 161 m difference in distance walked on 6MWT at year 4 PI. 05/24/2016. Sec 14, Fig 2.
- Probability of loss of ambulation at year 4 was 17% for patients treated with EXONDYS 51 vs. 85% for External Controls PI. 05/24/2016. Sec 14, Para 4, L 5-7.
- The safety assessment was based on 114 patients who were exposed to EXONDYS 51 PI. 06/2015. Sec 6.1,
Para 2, Lines 1-2.

SareptAssist™ SUPPORTS PATIENTS AND CAREGIVERS

Visit EXONDYS51.com

References: 1. EXONDYS 51 Draft Prescribing Information. Cambridge, MA: Sarepta Therapeutics, Inc; 2016. 2. Falzarano MS, Scotton C, Passarelli C, Ferlini A. *Molecules*. 2015;20(10):18168-18184. 3. Ellis JA, Vroom E, Muntoni F. *Neuromuscul Disord*. 2013;23:682-689. 4. Aartsma-Rus A, Van Deutekom JC, Fokkema IF, Van Ommen GJ, Den Dunnen JT. *Muscle Nerve*. 2006;34(2):135-144. 5. Mendell JR, et al. *Ann Neurol*. 2016;79(2):257-271. 6. Data on File. NDA.

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Para 1.

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PI. 05/24/2016. Sec 6.1, Para 5.

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05/16 C-SRP-51-US-0100

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EXONDYS 51, the EXONDYS 51 logo, SareptAssist, the SareptAssist logo, and "Support, By Your Patients' Side" are trademarks of Sarepta Therapeutics, Inc.

Philips, Howard

From: Farkas, Ronald
Sent: Wednesday, June 22, 2016 4:29 PM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Breder, Christopher D; Choy, Fannie (Yuet)
Subject: Update from Ash about progress on running Western blots

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Thanks

Ron

Preliminary Report: Western Blot Interim Analysis of Novel Dystrophin Expression in Muscle Biopsy Samples from Week 48 of the Clinical Study 4658-301

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215 First Street
Cambridge MA, 02142 USA

Study Report Number
SR-CR-16-003

June 27, 2016

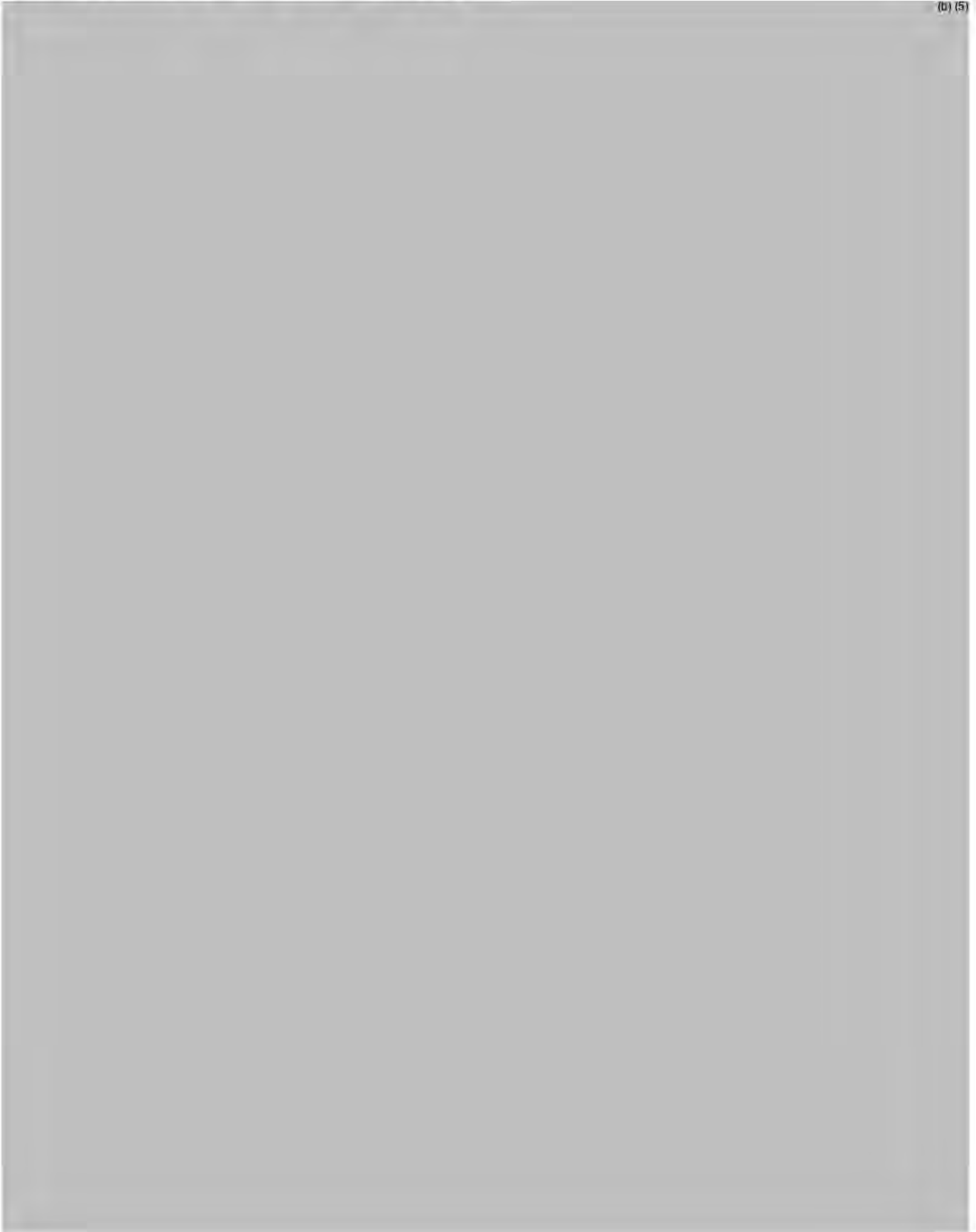
17 pages have been withheld as b(4) (CCI/TS) immediately following this page

Temple, Robert

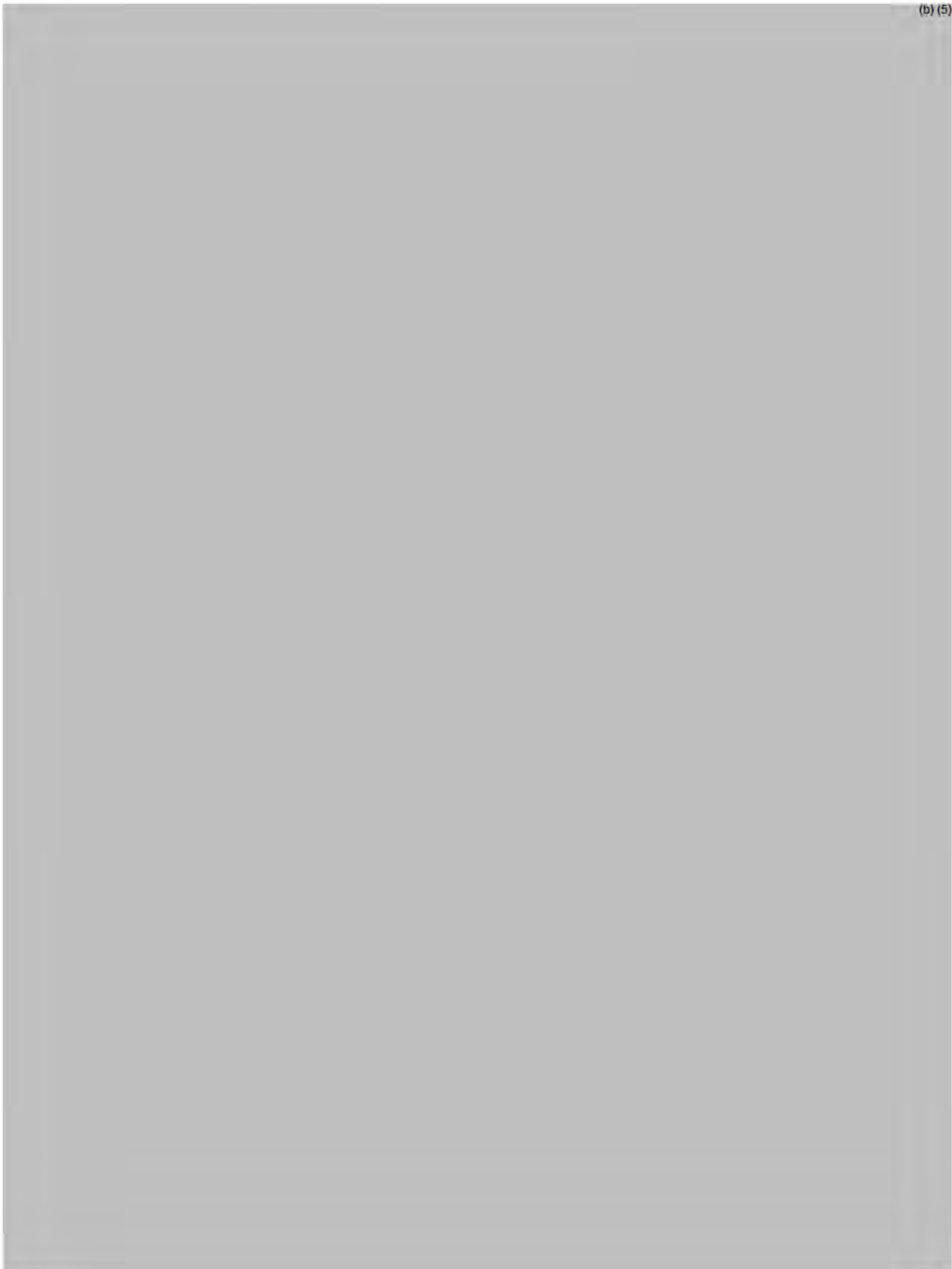
From: Unger, Ellis
Sent: Wednesday, June 29, 2016 2:43 PM
To: Temple, Robert
Subject: Janet's draft memo on etep
Attachments: Woodcock_Sarepta dct.docx

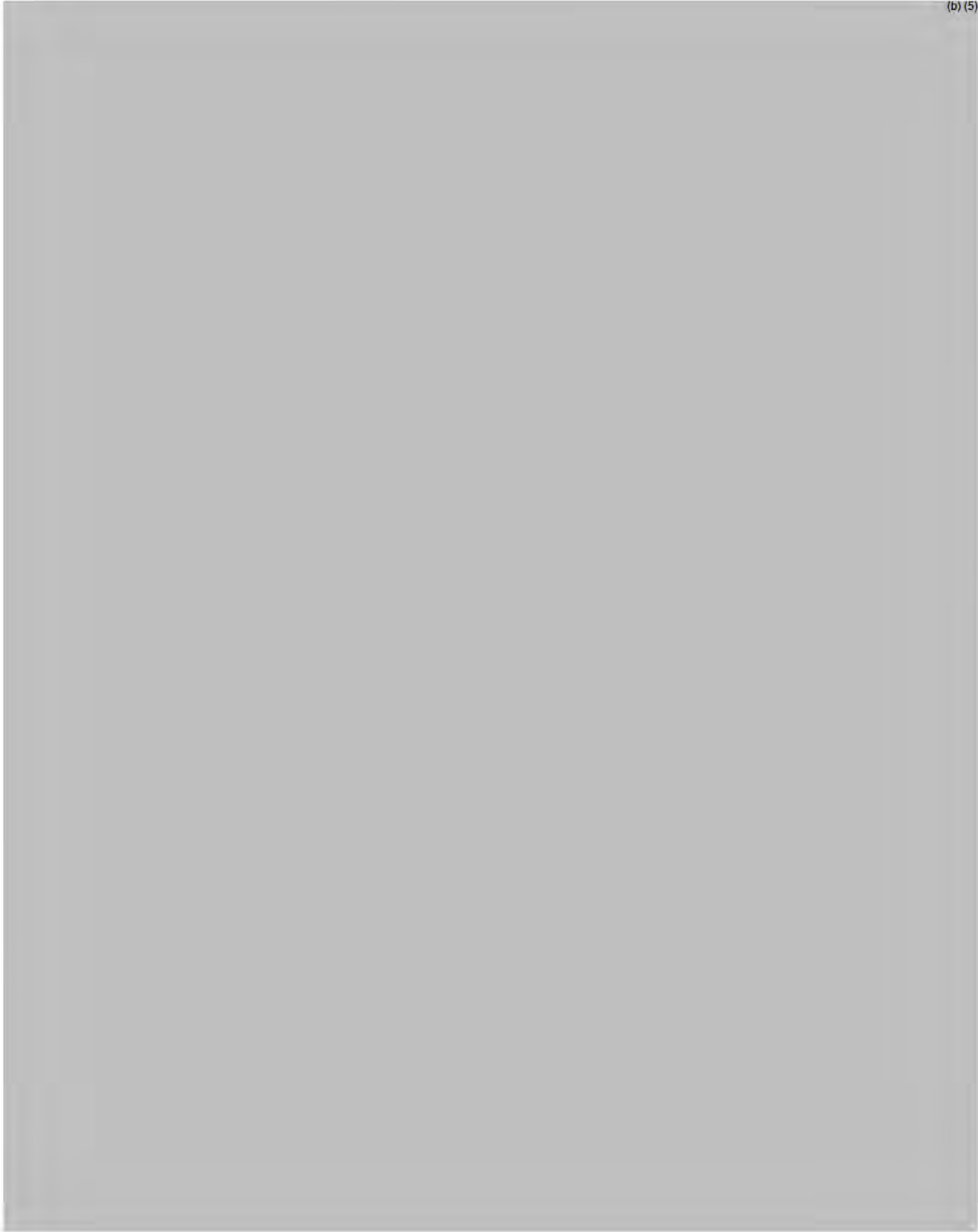
Center Director Decisional Memo DRAFT

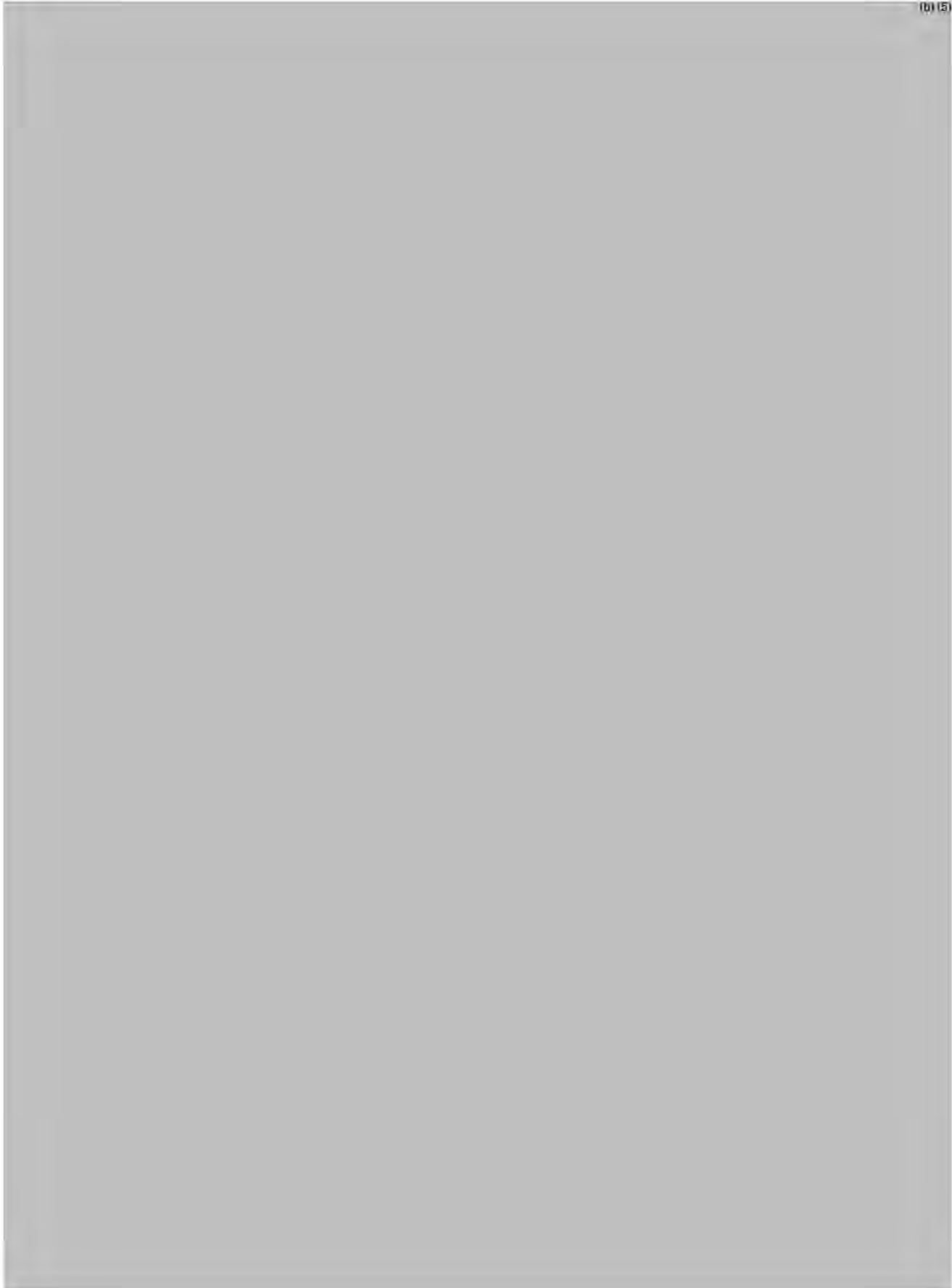
(b) (5)

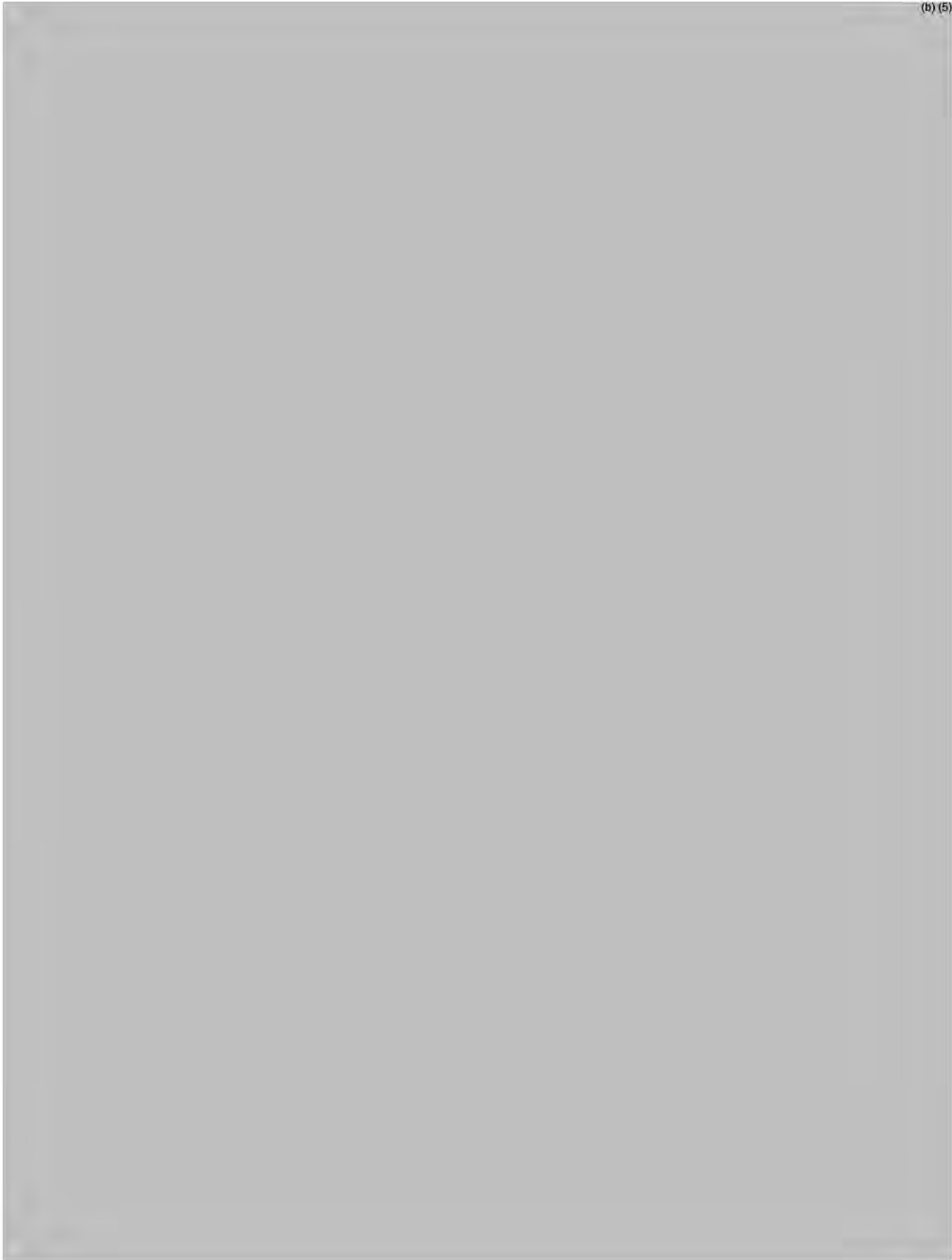


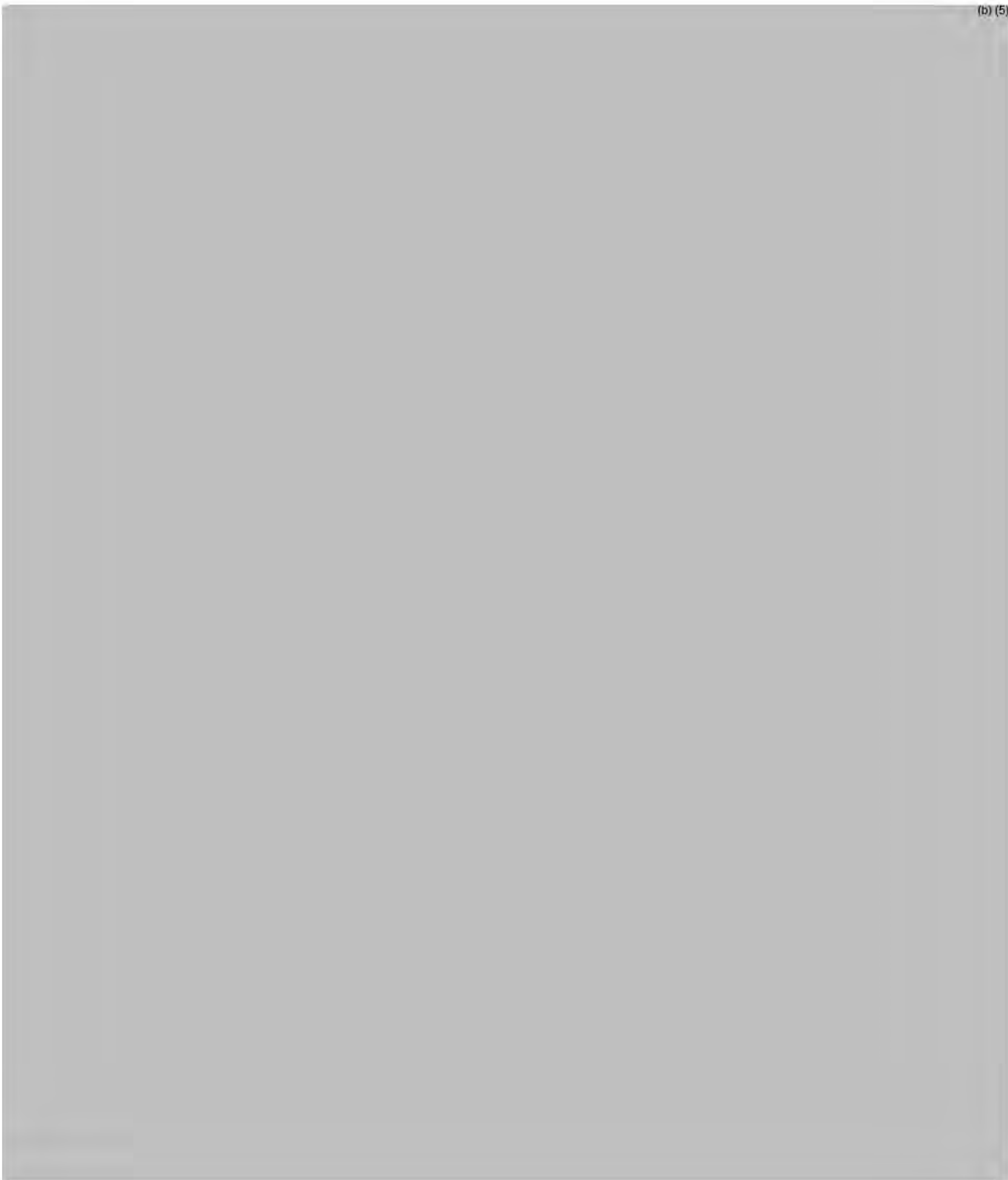
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Philips, Howard

From: Jenkins, John K
Sent: Friday, July 01, 2016 9:50 AM
To: Ligon, Sharnell (CDER)
Cc: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Temple, Robert; Dunn, Billy; Bastings, Eric; Rao, Ashutosh; DeMarco, Devota R
Subject: Meeting to discuss eteplirsen

Sharnell

We need to schedule an urgent meeting with Janet on Tuesday or Wednesday of next week to discuss the ongoing review of the NDA for eteplirsen. At least one hour and preferably 90 minutes is needed.

The main issues for discussion are:

1. The levels of dystrophin observed in 12 DMD patients from the recent interim analysis of an ongoing trial and whether the levels seen can be interpreted to be “reasonably likely to predict clinical benefit” and used as a surrogate endpoint to support accelerated approval.
2. The design of one or more PMR trials to confirm clinical benefit of eteplirsen if it is approved under accelerated approval.
3. Description of the available clinical data in the drug label if approved.

Please include those on the CC list (DNP or Ash may suggest a limited number of additional attendees who are critical to this discussion). We will all be as flexible as possible to accommodate the need to schedule this meeting ASAP. Unfortunately, I need to take my son to a doctor’s appointment on Tuesday afternoon, so I’m hoping you can avoid the 2:30-5 pm time block on that day.

John

Philips, Howard

From: Temple, Robert
Sent: Monday, July 04, 2016 6:31 PM
To: Unger, Ellis
Subject: Re: eteplirsen DRAFT ODE-I memo

More laterbut a few nowm.

(b) (5)

(b) (5)

See ya

Sent from my BlackBerry 10 smartphone.

Original Message

From: Unger, Ellis

Sent: Monday, July 4, 2016 1:04 AM

To: Jenkins, John K; Temple, Robert; Bastings, Eric; Dunn, Billy; Farkas, Ronald; Rao, Ashutosh

Subject: eteplirsen DRAFT ODE-I memo

All,

Here's my draft memo. Ordinarily, I'd go through it and eliminate some redundancy etc., but in the interest of time, here's what I'm thinking at this point. I will continue to revise (perhaps reorganize and shorten), but the messages shouldn't change much. The point is, if you are seeing this email on Tuesday, I will probably have produced a newer and improved version already, so please ask me for the latest draft if you are interested in making specific edits.

I've had a plumbing issue these last two days (water coming through the ceiling of a bedroom) that didn't exactly help me...

Comments welcome.

Ellis

APPEARS THIS WAY ON ORIGINAL

Philips, Howard

From: Unger, Ellis
Sent: Tuesday, July 05, 2016 9:28 AM
To: Jenkins, John K
Cc: Temple, Robert
Subject: RE: CDTL Addendum

I think this is too important for Rob not to be apprised/involved. The question is whether we should discuss this with Janet at the CDB tomorrow, i.e., let her know we think it's important to involve Rob, or go behind her back and arrange a briefing.

I think that the former approach would be far better than the latter, but you are in the best position to judge how best to do this.

Ellis

From: Jenkins, John K
Sent: Tuesday, July 05, 2016 8:49 AM
To: Temple, Robert
Cc: Unger, Ellis
Subject: RE: CDTL Addendum

I don't think there is any chance JW can be convinced to issue a CR and wait for more data, but you are welcome to try to make that argument. Any member of the team is also free to request a meeting with the Commissioner.

From: Temple, Robert
Sent: Monday, July 04, 2016 6:02 PM
To: Jenkins, John K
Cc: Unger, Ellis
Subject: Re: CDTL Addendum

Note also Ellis's suggestion of availability, presumably at 30mg WHILE the D/R study is going on. That study is of course already enrolled.

Sent from my BlackBerry 10 smartphone.

From: Jenkins, John K
Sent: Monday, July 4, 2016 4:58 PM
To: Farkas, Ronald; Bastings, Eric
Cc: Dunn, Billy; Unger, Ellis; Temple, Robert; Jenkins, John K
Subject: RE: CDTL Addendum

I shared the three updated draft memos and the most recent version of the draft label with Janet. I also told her that I am not able to support a conclusion that the dystrophin results are "reasonably likely to predict clinical benefit" and therefore I will not support an approval. Further, I shared my view that this action sets such a precedent for how we consider biomarkers and their ability to serve as surrogates for AA in rare diseases that I think it is important that an approval action come from the Center Director. At this point (prior to reading your revised memos) she is still inclined to proceed with AA. I asked that she be prepared in the meeting on Wednesday morning to share with the team how she reached a conclusion of "reasonably likely to predict clinical benefit." That will be the first focus of the meeting followed by discussion of the PMRs and the clinical sections of the label.

John

From: Farkas, Ronald
Sent: Monday, July 04, 2016 10:48 AM
To: Bastings, Eric; Jenkins, John K
Cc: Dunn, Billy; Unger, Ellis
Subject: CDTL Addendum

Thanks
Ron

From: Bastings, Eric
Sent: Monday, July 04, 2016 8:47 AM
To: Jenkins, John K
Cc: Dunn, Billy; Unger, Ellis; Farkas, Ronald
Subject: RE: Updated memo for eteplirsen

With attachment.

Eric

From: Bastings, Eric
Sent: Monday, July 04, 2016 8:40 AM
To: Jenkins, John K
Cc: Dunn, Billy; Unger, Ellis; Farkas, Ronald
Subject: Updated memo for eteplirsen

John,

Here is my updated draft memo for eteplirsen.

Eric

Philips, Howard

From: Diggs, Felicia
Sent: Wednesday, July 06, 2016 9:03 AM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Jenkins, John K
Cc: Choy, Fannie (Yuet)
Subject: Eteplirsen Information Advisory-Clearance
Attachments: Eteplirsen Information Advisory 6-3-16.doc

Importance: High

Good morning,

Please see attached a draft IA contingent upon the approval of eteplirsen for your clearance and/or edits. I'm uncertain of the status of the application and therefore am sending this document simultaneously for clearance.

We will need to have the document cleared at least 4 days prior to approval. If you could review and return to me asap (today) I will continue to pass this through the OES clearance process. I received word (from OES by way of OMA I believe) that an approval may occur today.

Thank you,

Felicia M. Diggs, RN, BSN, MSN

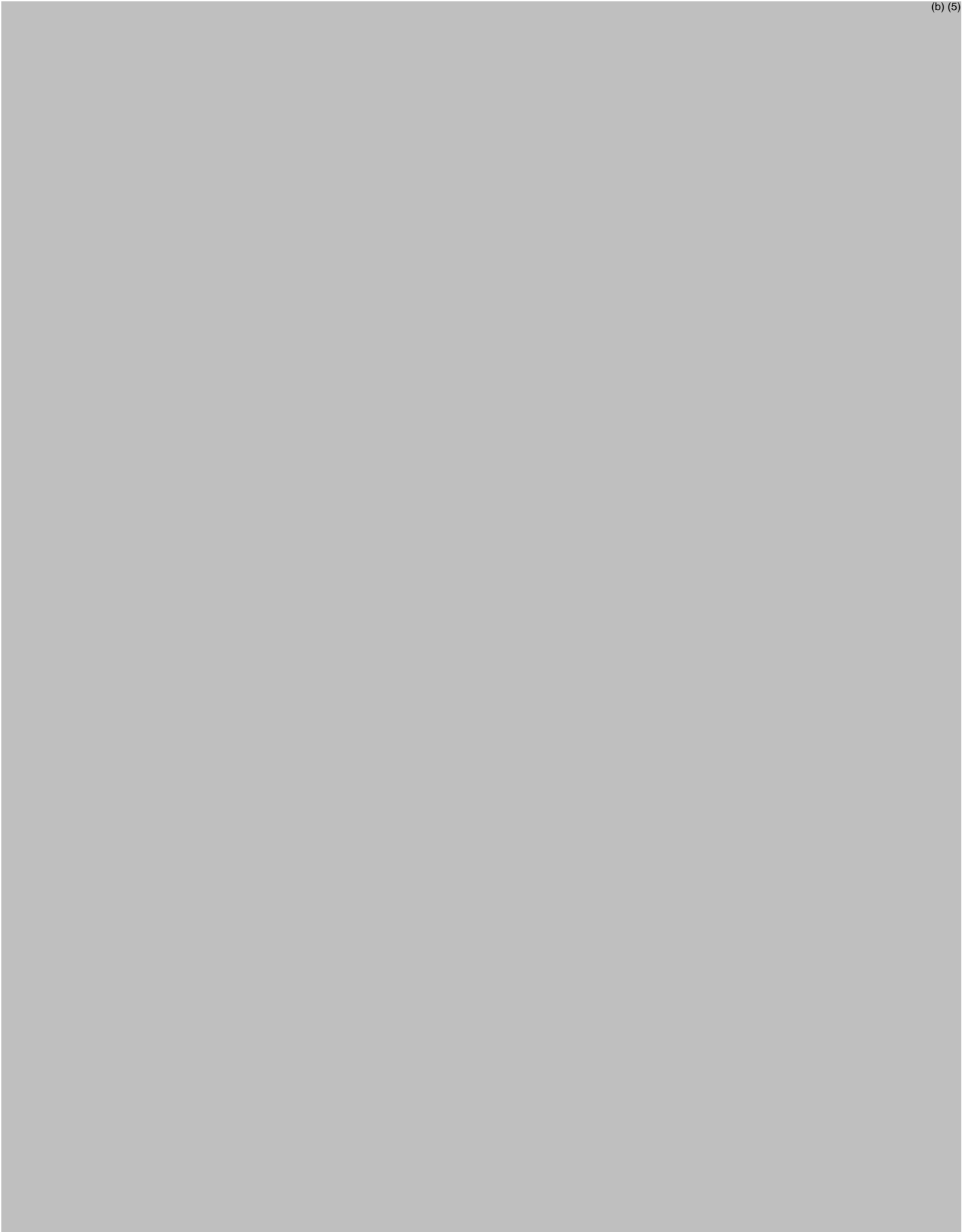
Consumer Safety Officer

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





Philips, Howard

From: Unger, Ellis
Sent: Wednesday, July 06, 2016 2:02 PM
To: Temple, Robert
Subject: FW: Updated memo for eteplirsen
Attachments: Sarepta DD memo (updated).doc

From: Bastings, Eric
Sent: Monday, July 04, 2016 8:47 AM
To: Jenkins, John K
Cc: Dunn, Billy; Unger, Ellis; Farkas, Ronald
Subject: RE: Updated memo for eteplirsen

With attachment.

Eric

From: Bastings, Eric
Sent: Monday, July 04, 2016 8:40 AM
To: Jenkins, John K
Cc: Dunn, Billy; Unger, Ellis; Farkas, Ronald
Subject: Updated memo for eteplirsen

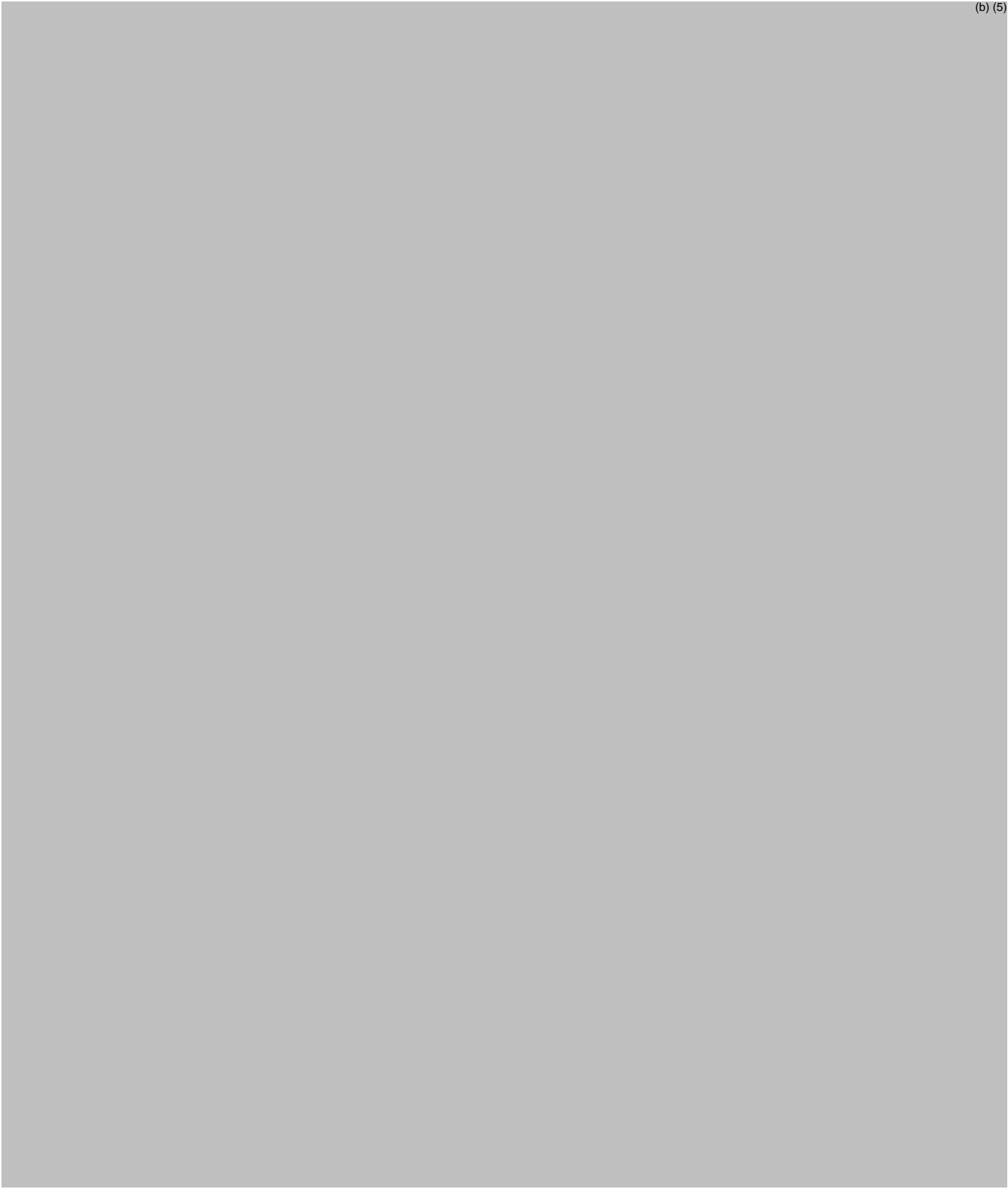
John,

Here is my updated draft memo for eteplirsen.

Eric

Division Director Summary Review for Regulatory Action

(b) (5)



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

Temple, Robert

From: Jenkins, John K
Sent: Thursday, July 07, 2016 10:47 AM
To: Unger, Ellis
Cc: Temple, Robert; Jenkins, John K
Subject: RE: Sarepta and dispute resolution options

I just think they are invalid analyses; these is no isolation of the drug effect from what may have occurred in the absence of drug. My suggestion of imputing baseline values was an attempt to see what a "best case" for such an analysis might be by randomly using true baseline values from 301 for 202. I acknowledge the baseline values tend to be low and might not make much of a difference, but in my mind such an analysis is more valid that just taking the absolute value for dystrophin.

From: Unger, Ellis
Sent: Thursday, July 07, 2016 10:03 AM
To: Jenkins, John K
Cc: Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Thanks John. I sent you my thoughts about the regressions. Both Δ 6MWD vs. Western blot and Δ NSAA vs. Western blot are based on Week 180 Western blot – baseline values are not known but thought to be low.

In any case, if we want to make the point that the Δ 6MWD vs. Western blot shows poor correlation, I don't see how we can summarily reject the Δ NSAA vs. Western blot correlation. Maybe the most salient point is that there aren't a lot of data here, and they are comparing apples to oranges, as you say. Or perhaps they are comparing apples with cores to apples without cores.

In terms of overall involvement of Janet, my sense is that Janet reached the conclusion, perhaps back when the initial exciting immunohistochemistry data were announced, that the drug was effective. She has dialoged with the DMD community, and perhaps she has led them on. Given her strong belief in the drug, her interactions with the DMD community, and her desire to get drugs approved for rare diseases, she is strongly motivated to approve.

But she is trying to fit the data around her conclusions, instead of the other way around. She mostly makes that case that "we don't know" who will respond, or how much dystrophin is needed to cause a response. In essence, she's saying that the drug could be working. We don't know. But that is not the standard.

From: Jenkins, John K
Sent: Thursday, July 07, 2016 7:16 AM
To: Unger, Ellis
Cc: Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Ellis

Nice summary. I think one thing you need to address is Janet's regression analysis. I think it is an invalid analysis and since you show your version of a similar analysis in the slides, I think you should show hers as well and explain the differences. I think it is invalid to compare a delta for an endpoint against an absolute value for a biomarker. That analysis could simply mean that patients who have more dystrophin at baseline have a slower loss of function. She is not isolating any drug effect in the analysis, but it seems to be her major scientific basis for linking the biomarker to the clinical data. A fairer regression would be to randomly impute baseline data from the 301 trial to Janet's regression line

(i.e., subtract actual values randomly selected from the 301 baseline data from the 202 week-180 data and re-run the analysis). That still would not be a valid analysis, but it would be better than simply assuming all the dystrophin present in the 202 week-180 biopsies is the result of drug.

I also do not see any reference to any concerns you may have about the motivation for JW's decision (e.g., inappropriate relationship with sponsor/parents). Perhaps you don't want to put that on a slide, but if you have such concerns, you should voice them.

John

From: Unger, Ellis
Sent: Thursday, July 07, 2016 1:41 AM
To: Behr, Virginia L; Diggs, Felicia
Cc: Temple, Robert; Jenkins, John K
Subject: RE: Sarepta and dispute resolution options

All,

Here's the PowerPoint presentation. Given the rapidity of preparation, no one on the review team has had a chance to look at it, so the actual presentation might have a few changes.

Thanks,

Ellis

From: Unger, Ellis
Sent: Wednesday, July 06, 2016 7:45 PM
To: Behr, Virginia L; Diggs, Felicia
Cc: Temple, Robert; Jenkins, John K; Unger, Ellis
Subject: RE: Sarepta and dispute resolution options

Here it is. Thanks!

From: Behr, Virginia L
Sent: Wednesday, July 06, 2016 7:39 PM
To: Jenkins, John K; Unger, Ellis; Diggs, Felicia
Cc: Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Agreed.

Sent from my BlackBerry 10 smartphone.

From: Jenkins, John K
Sent: Wednesday, July 6, 2016 7:28 PM
To: Unger, Ellis; Diggs, Felicia; Behr, Virginia L
Cc: Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Ellis

I suggest you send the 40 page doc and focus more on slides.

John

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

From: Unger, Ellis
Sent: Wednesday, July 6, 2016 7:07 PM
To: Diggs, Felicia; Behr, Virginia L
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Felicia/Virginia,

I am preparing a powerpoint presentation for Dr. Califf, but won't have it ready until very late tonight.

Would he also want a written backgrounder? If so, I have one I could send now, but it is 40 pages in length (with a fair number of figures and tables). Should I send it, or shorten it first?

Ellis

From: Diggs, Felicia
Sent: Wednesday, July 06, 2016 6:22 PM
To: Unger, Ellis; Behr, Virginia L
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Yes, but we are still waiting for the document to be submitted to OES. Have you all edited the document yet? I haven't received it.

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

From: Unger, Ellis
Sent: Wednesday, July 06, 2016 5:21 PM
To: Diggs, Felicia; Behr, Virginia L
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

We haven't heard anything. Are we 'on' for tomorrow 10:30 to noon?

From: Diggs, Felicia
Sent: Wednesday, July 06, 2016 1:35 PM
To: Jenkins, John K; Behr, Virginia L; Unger, Ellis; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

You will receive an invite for tomorrow at 10:30am -12pm in WO Bldg1, room 2102 sometime today.

Felicia M. Diggs, RN, BSN, MSN
Consumer Safety Officer

From: Jenkins, John K
Sent: Wednesday, July 06, 2016 1:03 PM
To: Diggs, Felicia; Behr, Virginia L; Unger, Ellis; Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Definitely need more than 30 min. At least 60 and preferably 90.

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

From: Diggs, Felicia
Sent: Wednesday, July 6, 2016 11:49 AM
To: Behr, Virginia L; Jenkins, John K; Unger, Ellis; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Good morning,

I've attached a draft summary of the meeting's agenda for your review and edits. If you could make your edits and return the document to me no later than 2pm today that would be very helpful. Also on the agenda it states the meeting will occur tomorrow at 10:30-11:00. I have requested additional time therefore, this date may change but as Virginia stated we are aiming for tomorrow or Friday. I understand we will also need a call-in number and will arrange for such. Please let me know if you have any questions or concerns.

Best regards,

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

From: Behr, Virginia L
Sent: Wednesday, July 06, 2016 11:42 AM
To: Jenkins, John K; Unger, Ellis; Temple, Robert
Cc: Diggs, Felicia
Subject: RE: Sarepta and dispute resolution options

Yes, the briefing is likely to be tomorrow or Friday. Felicia Diggs in CDER's Exec Sec already initiated planning the meeting and she is cc'd on this email. Thank you Felicia! She'll be working with you to find a mutually agreeable time to meet with Dr. Califf. If you think of anyone else who should be invited, please let her know. I plan to attend in person to answer any questions about the formal dispute process, should any arise.

Virginia L. Behr
CDER Ombudsman

(301) 796-3436
WO51, Room 6158
<http://inside.fda.gov:9003/CDER/OfficeofExecutivePrograms/Ombudsman/default.htm>

12³⁰ PM
B1 Rm 2102

Blount, Aprile

Subject: Commissioner Briefing: Eteplirsen
Location: Bldg 1 Rm 2102

Start: Thu 7/7/2016 12:30 PM
End: Thu 7/7/2016 2:00 PM

Recurrence: (none)

Meeting Status: Accepted

Organizer: FDA Commissioner
Required Attendees: Califf, Robert; Kraus, Tom; Dickinson, Elizabeth (FDA); Sherman, Rachel; Tropea, Josephine T.; Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert; Behr, Virginia L
Optional Attendees: Evans, Dana; Pennington, Caitlin; Sennett, Antonia Monique; Diggs, Felicia

A briefing has been scheduled for the Commissioner on Eteplirsen for July 7 at 12:30 pm.

Date: Thursday, July 7, 2016
Time: 12:30 pm – 2:00 pm
Location: White Oak, Building 1, Conference Room 2102

Call-in Information:

Dial in: 1-866-506-7989
Passcode: (b) (4)

Please let me know if you will be joining by phone.

Please do not forward this invitation. If additional participants are needed, please notify Josephine Tropea directly.

Meeting Materials:



COMMISSIONER's
BRIEFING ETEPL...



Eteplirsen



Eteplirsen
Office_Memo_7...

Office of the Executive Secretariat Contact: Josephine Tropea, 301-796-5698

OFFICE OF THE COMMISSIONER

Informational Briefing: Sarepta's New Drug Application Exondys 51 (eteplirsen)
(Thursday, July 7, 2016 @ 10:30 am – 12:00 pm, WO-Bldg 1, Room 2102)

CONFIDENTIAL

Lead(s): Center of Drug Evaluation and Research: Office of Drug Evaluation-I; Division of Neurology Products

Invitees: OC: Robert Califf, Tom Kraus, Elizabeth Dickinson, Rachel Sherman, Josephine Tropea
CDER: John Jenkins, Ellis Unger, Billy Dunn, Eric Bastings, Ron Farkas, Robert Temple, Virginia Behr

Purpose: The Office of Drug Evaluation 1 (ODE1) and Division of Neurology Products are requesting an urgent meeting with the Commissioner to discuss new drug application 206488 Exondys 51 (eteplirsen). Eteplirsen is a modified oligonucleotide drug designed to increase production of truncated but partially functional dystrophin in Duchenne muscular dystrophy (DMD) through the mechanism of exon-skipping. There is a high level of public interest in a number of drugs for DMD that might act by increasing dystrophin production, including drisapersen, eteplirsen, and ataluren. In April, eteplirsen was reviewed by FDA's Peripheral and Central Nervous System Drugs Advisory Committee. The Committee voted seven to three (with three members abstaining) that there was not substantial evidence the drug is effective in providing clinical benefit. The panel also voted seven to six that eteplirsen did not increase production of dystrophin, the critical missing protein, to a level likely to predict clinical benefit. The Prescription Drug User Fee Act goal date originally scheduled for February 26, 2016 was extended to May 26 because of receipt of a major amendment. The review of eteplirsen's application has garnered extensive press and intense interest from patient advocacy groups and Congress. The clinical review team in the Division of Neurology Products, the Office of Drug Evaluation-I, and the Director, the Office of New Drugs have reached the scientific conclusion that the small increase observed in Becker-type dystrophin is not reasonably likely to predict clinical benefit. The Center Director has reached a different conclusion – that the findings are reasonably likely to predict clinical benefit. This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed "reasonably likely to predict clinical benefit." Moreover, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated. ODE1 would like the Commissioner to be aware of the various points of view and consider the potential ramifications of the matter at hand.

Agenda:

- I. Background and Summary of the Data (Dr. Unger) 30 minutes
- II. Clarifying questions 15 minutes
- III. Discussion (all) 45 minutes

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Protecting and Promoting Public Health www.fda.gov

Commissioner Briefing

NDA 206488
Eteplirsen for the Treatment of Duchenne
Muscular Dystrophy in Patients with Mutations
Amenable to Skipping Exon 51

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation-I
Office of New Drugs
CDER

July 7, 2016 1

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Duchenne Muscular Dystrophy (1)

- X-linked recessive muscular disorder
- Caused by mutations of the dystrophin gene
- Affects 1 in ~3,600 boys
- Disrupts the mRNA reading frame
- Absence or near-absence of dystrophin in muscle cells
- Dystrophin maintains structural integrity of sarcolemma
- Connects cytoskeleton to underlying cell matrix

Absence of dystrophin leads to mitochondrial damage, inflammation, myonecrosis, replacement by fat and other connective tissue. 2

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Duchenne Muscular Dystrophy (2)

- Clinical – degeneration of skeletal and cardiac muscle, progressive loss of physical function after childhood and into adolescence
- Death from respiratory/cardiac failure in second to fourth decade
- No approved therapies; steroids thought to delay progression

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Eteplirsen

- A phosphorodiamidate morpholino oligomer (PMO)
- Designed to target the pre-mRNA transcripts of the dystrophin gene
- Intent is to exclude exon 51 from the mature, spliced mRNA ("exon skipping"); restore reading frame
- Goal is to produce a truncated form of dystrophin protein, a form that is produced in Becker Muscular Dystrophy
- Becker form of MD is far less severe than the Duchenne form; many patients do well into adulthood
- Goal is to 'convert' Duchenne patients to Becker patients
- Patients amenable to exon 51 skipping represent 13% of all DMD patients (~1/47,000 boys) – target population 4

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Eteplirsen: Two Potential Lines of Evidence to Support Approval

- Clinical evidence: externally controlled data on physical function
 - Externally-controlled study - no one thinks these data support a conventional approval.
- Biomarker evidence: really the only issue here →

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Lack of Agreement About Biomarker Evidence

All agree:

- Dystrophin is an appropriate surrogate endpoint for Duchenne muscular dystrophy.
 - Disease is well understood
 - Dystrophin is pivotal to the pathogenesis of DMD; on the causal path – all agree endpoint is appropriate.
- There is substantial evidence from 1 adequate and well controlled study that eteplirsen produces dystrophin in skeletal muscle.

The principal question is whether the quantity of dystrophin produced by eteplirsen is reasonably likely to predict clinical benefit.

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1. Eteplirsen development program
2. Biomarker evidence
3. Clinical evidence
4. Safety
5. 'Reasonably likely'
6. Future ramifications
7. Summary

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Study 201

- Planned as a 24-week placebo-controlled study (N = 12)
 - 4 patients – eteplirsen 50 mg/kg/week IV
 - 4 patients – eteplirsen 30 mg/kg/week IV
 - 4 patients – placebo IV
- Primary endpoint: dystrophin expression
- Main secondary endpoint: 6-minute walk distance
- Other secondary endpoints: physical function (several)
- Patients continued in open-label extension (Study 202)

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Study 202

- Open-label extension of Study 201 (N = 12)
- Eligible subjects continued to receive eteplirsen once weekly (50 or 30 mg/kg/week IV) for 164 weeks
- Originally intended to be exploratory
- Later used for comparison to external control group

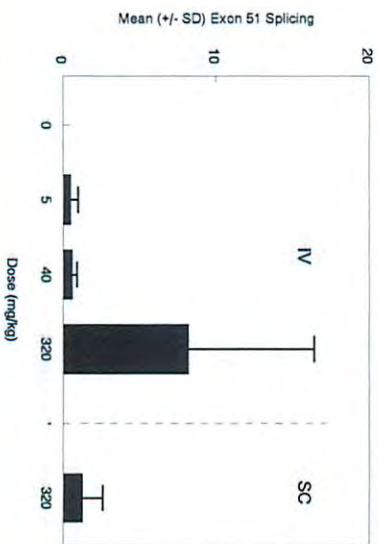
Study 301 (PROMOVI)

- Uncontrolled study, still enrolling
- All subjects receiving eteplirsen 30 mg/kg weekly by IV route

Production of 'Skipped' Messenger RNA

- RT-PCR – used to provide evidence that the desired Becker-type messenger RNA is produced (i.e., exon 51 skipping)
 - Monkey
 - Clinical

Evidence of Exon Skipping in Intact Monkeys



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Exon Skipping / Clinical

- Exon 51 skipping confirmed by RT-PCR analysis in all patients treated with eteplirsen
- PCR is a highly sensitive technique – can detect even a few copies of messenger RNA
- Provides proof of concept that eteplirsen causes at least some degree of exon 51 skipping, as intended
- No controversy or disagreement about this

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Immunohistochemistry / Clinical – Study 201

- Planned as a 24-week placebo-controlled study (N = 12)
 - 4 patients – eteplirsen 50 mg/kg/week IV
 - 4 patients – eteplirsen 30 mg/kg/week IV
 - 4 patients – placebo IV
 - 30 mg/kg/week
 - 50 mg/kg/week

After 24 weeks, 4 patients originally randomized to placebo were switched to eteplirsen 30 (n=2) or 50 (n = 2) mg/kg/week

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Immunohistochemistry / Clinical – Study 201

- Fantastic results: percent positive fibers increase as a function of time
- Published in *Annals of Neurology* and promoted on company's website
- Convinced DMD community that drug was effective
- Patients reluctant to participate in future placebo-controlled trials

Time (weeks)	30 mg/kg (n=4)	50 mg/kg (n=4)	Placebo to 30 mg/kg (n=2)	Placebo to 50 mg/kg (n=2)
0	~20	~10	~20	~10
12	~30	~10	~20	~10
24	~45	~20	~20	~10
48	~75	~55	~55	~45

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Immunohistochemistry / Clinical – Study 201

- FDA inspection: results not reliable; problems with methods, inadequate blinding to sequence
- FDA provided technical advice in advance of a 4th muscle biopsy at Week 180 (3.5 years of treatment)

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Immunohistochemistry / Clinical – Study 201/202

- Blinded read: no increase in dystrophin production at original timepoints; also, no effect at 3.5 years
- No evidence of biological activity per immunohistochemistry data

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Western Blot / Clinical – Study 201/202

- Western blot – standard method used to quantify protein in tissue samples
- Applicant's original analyses at early timepoints in Study 201/202
 - oversaturated gels
 - technically unsatisfactory
 - uninterpretable
- FDA inspection
 - Advice rendered to applicant to improve methods
 - Plan to run Western blot analyses of new muscle biopsies obtained at 180 Weeks

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Western Blot / Clinical – Study 201/202

- Plan had been to compare each patient's Week 180 biopsies to their baseline
- Baseline tissue was inadequate for all but 3 patients
- 6 external controls added to estimate baseline (treatment naïve) dystrophin levels

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Western Blot – Study 201/202, Week 180

Subject	Dose	Western blot		Group Mean±SD	
		gel 1	gel 2	Mean (arithmetic)	Mean (per protocol)
L	30 mg/kg	0.58	0.46	0.52	0.52
K	30 mg/kg	1.45	1.78	1.62	1.62
J	30 mg/kg	2.83	2.11	2.47	2.47
H	30 mg/kg	0.02*	0.28	0.15	0.14
G	Placebo to 30 mg/kg	0.17*	0.15*	0.16	0
F	Placebo to 30 mg/kg	0.93	1.02	0.98	0.98
E	50 mg/kg	0.19*	0.16*	0.18	0
D	50 mg/kg	0.75	0.24*	0.50	0.38
C	50 mg/kg	1.22	0.69	0.96	0.96
B	50 mg/kg	2.43	1.67	2.05	2.05
A	Placebo to 50 mg/kg	1.15	1.15	1.15	1.15

* below limit of quantitation

Dystrophin was 0.93% ± 0.84% of normal (mean ± SD)

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Concerns with Controls Used for Comparison with 4th Biopsy, Study 201/202

- 3 controls were from Study 201 patients but 6 were external
- Control samples generally from different muscle groups
- **With 0.93% ± 0.84% of normal dystrophin present at Week 180, no way to be certain regarding the change from baseline**

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New Western Blot Biopsy Data from Study 301

- Data requested after 5/26/16 PDUFA goal date
- Pre-treatment and post-treatment samples from 13 patients receiving eteplirsen 30 mg/kg/week
- All samples from same muscle group
- Pre- and post-treatment samples run together
- Analyses performed with FDA inspection team on site

Results (n=12):

- pre-treatment 0.16% ± 0.12% of normal dystrophin
- post-treatment 0.44% ± 0.43% of normal (mean ± SD); $p < 0.05$
- **Mean treatment effect is 0.28% of normal**

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New Western Blot Biopsy Data from Study 301

- Study 301 considered adequate and well controlled
- Data provide substantial evidence of a small increase in Becker-type dystrophin.
- Small change; ? clinical significance

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Western Blot: Distribution of Responses, Studies 201/202 and 301

Becker-type Dystrophin Detected (% Normal)	Study 301 change from baseline (%)	Study 201/202 (%)
> 2	0	~18
> 1.75 to 2	0	0
> 1.5 to 1.75	0	~10
> 1.25 to 1.5	~10	0
> 1 to 1.25	~10	~18
> 0.75 to 1	~10	0
> 0.5 to 0.75	~10	~10
> 0.25 to 0.5	~65	~10
< 0.25	0	~25

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Western Blot: Distribution of Responses, Studies 201/202 and 301

- Study 301: 1 of 12 patients (8%) with treatment effect >1%
- Study 201/202: 4 of 11 patients (36%) >1%; 2 of 11 (18%) > 2%
- 61% have < 0.5% dystrophin (combined studies)

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Opinion Leaders: Is Dystrophin Level Reasonably Likely to Predict Benefit?

- Dystrophin levels <3% of those in normal healthy muscle, as identified by WB, have been regarded as diagnostic of DMD with the typical DMD phenotype.
- Based on a wide range of scientific observations, experts suggest that ~10% of normal dystrophin may be the minimum level needed to confer measurable clinical benefit ("...dystrophin levels appear not to be a major determinant of disease severity in BMD, as long as it is above approximately 10%")
- **The threshold needed to predict clinical benefit is unknown, but mean values of 0.93% (Study 201/202) and 0.28% (Study 301) are disappointing.**

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FDA Review

- Since the discovery of revertant fibers and trace dystrophin in DMD, investigators have looked for, but generally not found, a correlation between DMD severity and trace levels of dystrophin
- The applicant's favored example of evidence of a correlation between DMD severity and dystrophin levels, exon 44 skippable patients, suggests that dystrophin levels in patients with "intermediate" severity have dystrophin levels above 10% of normal

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Advisory Committee: Substantial Evidence that Eteplirsen Induces Production of Dystrophin to a Level Reasonably Likely to Predict Benefit?

- 7 'Yes'; 6 'No' (one changed vote from 'No' to 'Yes')
- 5 'No' voters - studies not A&WC, questioned the techniques used to measure dystrophin as well as the appropriateness of the controls
- 4 concerned about the lack of correlation between the dystrophin levels and clinical measures
- 'No' voters agreed that even if some dystrophin was produced, there was no evidence that dystrophin production was at a level that would be reasonably likely to predict clinical benefit.

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Advisory Committee: Substantial Evidence that Eteplirsen Induces Production of Dystrophin to a Level Reasonably Likely to Predict Benefit?

- 6 'Yes' voters included the consumer representative and 2 patient representatives (only 3 professionals in the health sciences voted 'yes').
- Believed that there was some difference in dystrophin production and some evidence of improvement in endpoints.
- 1 'Yes' voter stated he was very troubled by not understanding what constitutes a clinically significant amount, but was impressed by the patients' observations.

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1. Eteplirsen development program
2. Biomarker evidence
3. **Clinical evidence**
4. Safety
5. 'Reasonably likely'
6. Future ramifications
7. Summary

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**Study 201 (Randomized Placebo-Controlled)
Study 202 (Extension, Externally-Controlled)**

- 24-week placebo-controlled study:
 - 4 patients – eteplirsen 50 mg/kg/week
 - 4 patients – eteplirsen 30 mg/kg/week
 - 4 patients – placebo
- Primary endpoint: dystrophin expression
- 6-minute walk distance listed as "exploratory endpoint" in original protocol, later promoted to "secondary endpoint"
- 2 patients in 30 mg/kg group became unable to ambulate early in study, Study 201 results **negative**.

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Sarepta Refused to Conduct a Placebo-Controlled Trial

- Cited problems convincing patients to be randomized to placebo
- Particular problem because muscle biopsies conducted under general anesthesia – no one wanted "saltwater."
- FDA reluctantly considered externally-controlled trial, but cautioned applicant regarding interpretability, need for a large treatment effect.

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Study 202

- Open-label extension of Study 201 (N=12)
- All subjects received once weekly eteplirsen (50 or 30 mg/kg) for 164 weeks
- Multiple iterations of study plan, study patients ultimately compared to an **external control**
- Patients from the Italian DMD Registry database in Rome (n=97) and University Hospitals in Leuven (n=89)
- From these, 13 appropriate controls selected (baseline steroid use, 6WMM, age, genotype)

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Study 202 v. External Controls: 6MWD by Age

6 MWD (meters)

Age (years)

4 eteplirsen patients retain walking ability...but

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Eteplirsen-treated Patients are Following Natural History for Age of Loss of Ambulation*

≈25% of exon 51 boys walking at 16 years

≈15% walking at 18 years

K-M Estimate for Loss of Ambulation

Age (years)

*Data from Cooperative International Neuromuscular Research Group

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The estimate from both CINRG and similar data from CDC indicates about 25% of exon-51 skippable patients ambulant at 16 years, similar to what is expected for the group of eteplirsen-treated patients

6 MWT (meters)

Age (years)

eteplirsen

6MWT

?

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Study 202 v. External Controls: 6MWD by Age

- Concerns about comparability of baseline characteristics (6-minute walk distance and steroid use favored eteplirsen group).
- Concerns about comparability of testing procedures; in eteplirsen group, investigators and patients did whatever they could to obtain the best possible 6-minute walk distance.
- Concerns about the nature of patients left in the registry – these were patients who could not qualify for a clinical trial, or who did not want to participate in a trial.
- No real deviation from reliable natural history data³⁷

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North Star Ambulatory Assessment (NSAA)

- Measure of underlying ambulatory abilities such as ‘rise from floor,’ which support specific activities such as walking
- Although NSAA still susceptible to expectation bias in open-label studies, it may assess disease progression more reliably

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Study 202: North Star Ambulatory Assessment

Time (years)	Eteplirsen (Total Score)	Control (Total Score)
0	25	22
1	20	18
2	18	14
3	15	10
4	10	5

- Similar progression in both groups.

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- Eteplirsen development program
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Eteplirsen Safety

- Small safety database: 114 total patients exposed, 36 for ≥ 24 weeks and 12 for ≥ 1 year
- Most exposures outside placebo-controlled studies, hard to determine drug-relatedness
- Adverse events generally consistent with those expected in DMD
- Patients in Study 201/202 were exposed for a long duration, which provides some reassurance against delayed toxicity
- No immunogenicity reported
- With use of indwelling catheters, infections will happen
- Dose-limiting toxicity *not* observed; could study much higher doses

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Question of Reasonably Likely – There's No Definition

- Two factors that might have supported the question of 'reasonably likely' are a dose-response and a correlation between the amount of dystrophin produced and retention of physical function.
- No dose-response: In Study 201/202, the amount of dystrophin detected with 30 and 50 mg/kg/week was similar.
- Poor correlation between the amount of dystrophin produced and retention of physical function (next slide)

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Study 201/202: Correlations between Quantity of Dystrophin and Physical Function – From Dr. Woodcock

Δ 6MWT

% Dystrophin by Western Blot

Δ NSAA

% Dystrophin by Western Blot

- These compare change in physical performance over time to dystrophin at Week 180, not Δ dystrophin
- Obviously small numbers, correlations driven by 1 or 2 patients

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Responder Analyses

- Defining a responder (arbitrarily) as >1%, ~22% of patients are responders, but even an effect of 1% seems dubious.
- For a 2% level of dystrophin, 9% are responders.

61% have < 0.5% dystrophin

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Ethics of Approving a Dose Known to be Ineffective (on the Basis of Clinical Data)

- Imagine 100 years ago a promising drug called penicillin is discovered – a potential cure for pneumococcal pneumonia – but the drug is difficult to produce and expensive. A dose of 5 mg weekly has been shown to have statistically significant bactericidal effects on *S. pneumoniae*.
- Would it be ethical to give the drug accelerated approval based on this finding and allow marketing of a dose of 5 mg weekly, absent additional information?
- Patients would die.
- It could take years to get the dose right.

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- Eteplirsen development program
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Question of Reasonably Likely

- Amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin.
- If a change of 0.28% is considered adequate to support accelerated approval, then the question arises as to *whether there is any statistically significant change that would be too small to support accelerated approval.*
- Adoption of the concept that any change in an appropriate surrogate endpoint would be a game-changer that would turn the clock back to the days prior to the 1962 Kefauver Harris Amendments
- Damage to the field of evidentiary medicine could be enormous.

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Obvious Need for Higher Doses

- No basis for selecting dose of 30 mg/kg/week
- Lack of efficacy; no safety issues
- Remember monkey data
- Originally, patients treated at study sites; visits more frequently than weekly posed practical limitations.
- Patients now have infusion ports/lines; could be treated more frequently.
- More frequent dosing and/or higher doses could be effective, safe, and practical.

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Summary

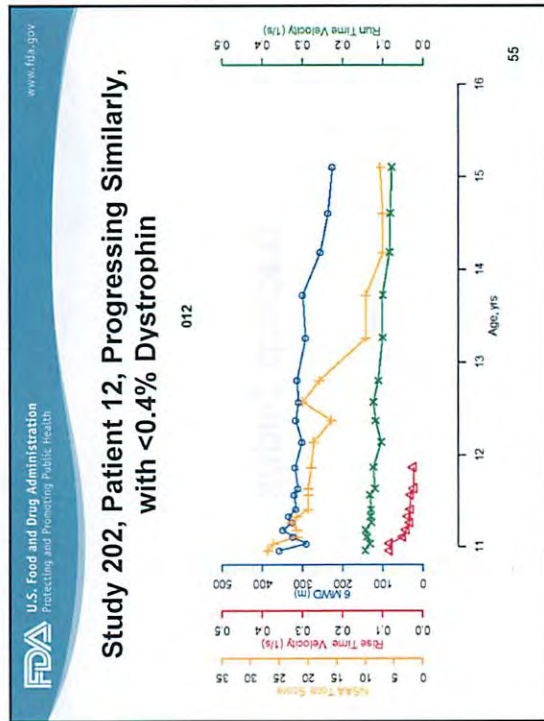
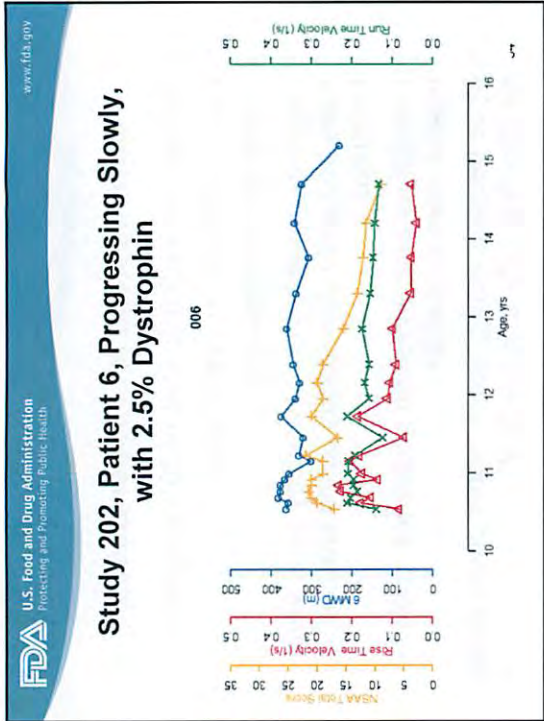
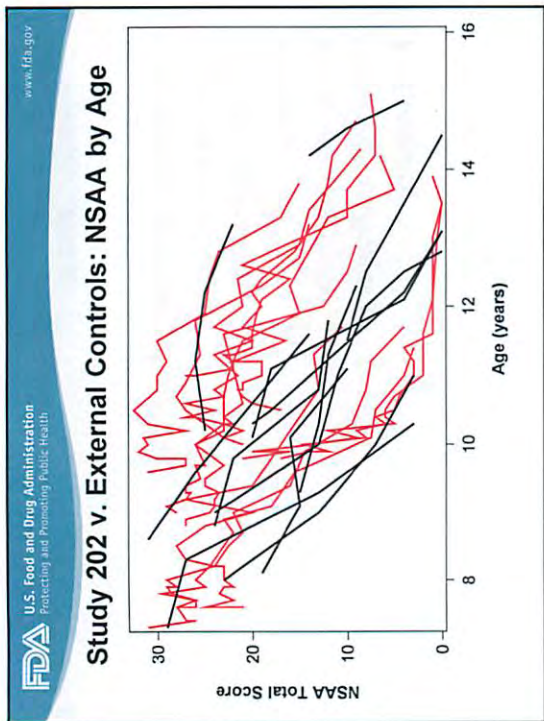
- There is no definition of "reasonably likely"
- Best estimate of quantity of dystrophin produced here = 0.28% of normal = 2.8 parts per thousand
- If you needed to shovel 10" of snow, this quantity would constitute 1/32 of an inch.
- Dystrophin is primarily a structural protein, maybe much less would be needed if this were an enzyme or a cofactor
- If we were willing to be wrong and approve an ineffective drug 15 to 20% of the time, this would not be close.
- If we were willing to approve an ineffective drug 50% of the time, this would not be close.
- Thank you for considering our views.

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Backup Slides

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DRAFT Office of Drug Evaluation-I: Decisional Memo

(b) (5)

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

Office Director Decisional Memo – NDA 206488 – Page 1 of 43

FDACDER0004783

Temple, Robert

From: Unger, Ellis
Sent: Thursday, July 07, 2016 10:03 AM
To: Jenkins, John K
Cc: Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Thanks John. I sent you my thoughts about the regressions. Both Δ 6MWD vs. Western blot and Δ NSAA vs. Western blot are based on Week 180 Western blot – baseline values are not known but thought to be low.

In any case, if we want to make the point that the Δ 6MWD vs. Western blot shows poor correlation, I don't see how we can summarily reject the Δ NSAA vs. Western blot correlation. Maybe the most salient point is that there aren't a lot of data here, and they are comparing apples to oranges, as you say. Or perhaps they are comparing apples with cores to apples without cores.

In terms of overall involvement of Janet, my sense is that Janet reached the conclusion, perhaps back when the initial exciting immunohistochemistry data were announced, that the drug was effective. She has dialoged with the DMD community, and perhaps she has led them on. Given her strong belief in the drug, her interactions with the DMD community, and her desire to get drugs approved for rare diseases, she is strongly motivated to approve.

But she is trying to fit the data around her conclusions, instead of the other way around. She mostly makes that case that "we don't know" who will respond, or how much dystrophin is needed to cause a response. In essence, she's saying that the drug could be working. We don't know. But that is not the standard.

From: Jenkins, John K
Sent: Thursday, July 07, 2016 7:16 AM
To: Unger, Ellis
Cc: Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Ellis

Nice summary. I think one thing you need to address is Janet's regression analysis. I think it is an invalid analysis and since you show your version of a similar analysis in the slides, I think you should show hers as well and explain the differences. I think it is invalid to compare a delta for an endpoint against an absolute value for a biomarker. That analysis could simply mean that patients who have more dystrophin at baseline have a slower loss of function. She is not isolating any drug effect in the analysis, but it seems to be her major scientific basis for linking the biomarker to the clinical data. A fairer regression would be to randomly impute baseline data from the 301 trial to Janet's regression line (i.e., subtract actual values randomly selected from the 301 baseline data from the 202 week-180 data and re-run the analysis). That still would not be a valid analysis, but it would be better than simply assuming all the dystrophin present in the 202 week-180 biopsies is the result of drug.

I also do not see any reference to any concerns you may have about the motivation for JW's decision (e.g., inappropriate relationship with sponsor/parents). Perhaps you don't want to put that on a slide, but if you have such concerns, you should voice them.

John

From: Unger, Ellis
Sent: Thursday, July 07, 2016 1:41 AM
To: Behr, Virginia L; Diggs, Felicia
Cc: Temple, Robert; Jenkins, John K
Subject: RE: Sarepta and dispute resolution options

All,

Here's the PowerPoint presentation. Given the rapidity of preparation, no one on the review team has had a chance to look at it, so the actual presentation might have a few changes.

Thanks,

Ellis

From: Unger, Ellis
Sent: Wednesday, July 06, 2016 7:45 PM
To: Behr, Virginia L; Diggs, Felicia
Cc: Temple, Robert; Jenkins, John K; Unger, Ellis
Subject: RE: Sarepta and dispute resolution options

Here it is. Thanks!

From: Behr, Virginia L
Sent: Wednesday, July 06, 2016 7:39 PM
To: Jenkins, John K; Unger, Ellis; Diggs, Felicia
Cc: Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Agreed.

Sent from my BlackBerry 10 smartphone.

From: Jenkins, John K
Sent: Wednesday, July 6, 2016 7:28 PM
To: Unger, Ellis; Diggs, Felicia; Behr, Virginia L
Cc: Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Ellis

I suggest you send the 40 page doc and focus more on slides.

John

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

From: Unger, Ellis
Sent: Wednesday, July 6, 2016 7:07 PM
To: Diggs, Felicia; Behr, Virginia L
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Felicia/Virginia,

I am preparing a powerpoint presentation for Dr. Califf, but won't have it ready until very late tonight.

Would he also want a written backgrounder? If so, I have one I could send now, but it is 40 pages in length (with a fair number of figures and tables). Should I send it, or shorten it first?

Ellis

From: Diggs, Felicia
Sent: Wednesday, July 06, 2016 6:22 PM
To: Unger, Ellis; Behr, Virginia L
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Yes, but we are still waiting for the document to be submitted to OES. Have you all edited the document yet? I haven't received it.

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

From: Unger, Ellis
Sent: Wednesday, July 06, 2016 5:21 PM
To: Diggs, Felicia; Behr, Virginia L
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

We haven't heard anything. Are we 'on' for tomorrow 10:30 to noon?

From: Diggs, Felicia
Sent: Wednesday, July 06, 2016 1:35 PM
To: Jenkins, John K; Behr, Virginia L; Unger, Ellis; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

You will receive an invite for tomorrow at 10:30am -12pm in WO Bldg1, room 2102 sometime today.

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

From: Jenkins, John K
Sent: Wednesday, July 06, 2016 1:03 PM
To: Diggs, Felicia; Behr, Virginia L; Unger, Ellis; Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Definitely need more than 30 min. At least 60 and preferably 90.

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

From: Diggs, Felicia
Sent: Wednesday, July 6, 2016 11:49 AM
To: Behr, Virginia L; Jenkins, John K; Unger, Ellis; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Good morning,

I've attached a draft summary of the meeting's agenda for your review and edits. If you could make your edits and return the document to me no later than 2pm today that would be very helpful. Also on the agenda it states the meeting will occur tomorrow at 10:30-11:00. I have requested additional time therefore, this date may change but as Virginia stated we are aiming for tomorrow or Friday. I understand we will also need a call-in number and will arrange for such. Please let me know if you have any questions or concerns.

Best regards,

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

From: Behr, Virginia L
Sent: Wednesday, July 06, 2016 11:42 AM
To: Jenkins, John K; Unger, Ellis; Temple, Robert
Cc: Diggs, Felicia
Subject: RE: Sarepta and dispute resolution options

Yes, the briefing is likely to be tomorrow or Friday. Felicia Diggs in CDER's Exec Sec already initiated planning the meeting and she is cc'd on this email. Thank you Felicia! She'll be working with you to find a mutually agreeable time to meet with Dr. Califf. If you think of anyone else who should be invited, please let her know. I plan to attend in person to answer any questions about the formal dispute process, should any arise.

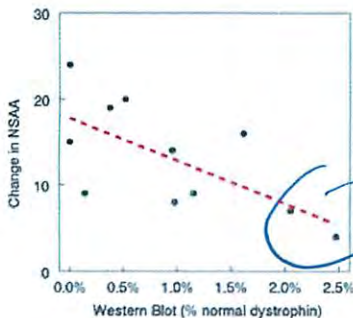
Virginia L. Behr
CDER Ombudsman

(301) 796-3436
WO51, Room 6158
<http://inside.fda.gov:9003/CDER/OfficeofExecutivePrograms/Ombudsman/default.htm>

Temple, Robert

From: Unger, Ellis
Sent: Thursday, July 07, 2016 8:26 AM
To: Jenkins, John K
Cc: Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Here's the plot with all patients. The R-value is 0.66, and so R-squared is about 0.44. The main problem is that it is driven by the 2 patients on the right. Bottom line: not many patients here.



Ellis:

Ever do + calculate
leaving out those
2

From: Jenkins, John K
Sent: Thursday, July 07, 2016 8:09 AM
To: Unger, Ellis
Cc: Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Also not valid to post hoc exclude patients. It is an analysis we would not accept from a sponsor but is the key to her memo.

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

From: Unger, Ellis
Sent: Thursday, July 7, 2016 8:02 AM
To: Jenkins, John K
Cc: Temple, Robert
Subject: Re: Sarepta and dispute resolution options

John, your concern about Janet's NSAA delta v WB regression also applies to the 6MW delta v WB regression.

So if it is valid to say that the 6MW regression fails to show a correlation with WB dystrophin, then it is valid to say that the NSAA regression DOES show a correlation.

She omitted patients 9 and 10 (the two who lost ambulation), but I included. The regression looks the same as hers basically. Also, the baseline dystrophin values are pretty low, and so if we had them, and if we could subtract pre from post, it might not make much difference. I can send plot in a bit

Sent from my BlackBerry.

From: Jenkins, John K
Sent: Thursday, July 7, 2016 7:15 AM
To: Unger, Ellis
Cc: Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Ellis

Nice summary. I think one thing you need to address is Janet's regression analysis. I think it is an invalid analysis and since you show your version of a similar analysis in the slides, I think you should show hers as well and explain the differences. I think it is invalid to compare a delta for an endpoint against an absolute value for a biomarker. That analysis could simply mean that patients who have more dystrophin at baseline have a slower loss of function. She is not isolating any drug effect in the analysis, but it seems to be her major scientific basis for linking the biomarker to the clinical data. A fairer regression would be to randomly impute baseline data from the 301 trial to Janet's regression line (i.e., subtract actual values randomly selected from the 301 baseline data from the 202 week-180 data and re-run the analysis). That still would not be a valid analysis, but it would be better than simply assuming all the dystrophin present in the 202 week-180 biopsies is the result of drug.

I also do not see any reference to any concerns you may have about the motivation for JW's decision (e.g., inappropriate relationship with sponsor/parents). Perhaps you don't want to put that on a slide, but if you have such concerns, you should voice them.

John

From: Unger, Ellis
Sent: Thursday, July 07, 2016 1:41 AM
To: Behr, Virginia L; Diggs, Felicia
Cc: Temple, Robert; Jenkins, John K
Subject: RE: Sarepta and dispute resolution options

All,

Here's the PowerPoint presentation. Given the rapidity of preparation, no one on the review team has had a chance to look at it, so the actual presentation might have a few changes.

Thanks,

Ellis

From: Unger, Ellis
Sent: Wednesday, July 06, 2016 7:45 PM
To: Behr, Virginia L; Diggs, Felicia
Cc: Temple, Robert; Jenkins, John K; Unger, Ellis
Subject: RE: Sarepta and dispute resolution options

Here it is. Thanks!

From: Behr, Virginia L
Sent: Wednesday, July 06, 2016 7:39 PM
To: Jenkins, John K; Unger, Ellis; Diggs, Felicia

Cc: Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Agreed.

Sent from my BlackBerry 10 smartphone.

From: Jenkins, John K
Sent: Wednesday, July 6, 2016 7:28 PM
To: Unger, Ellis; Diggs, Felicia; Behr, Virginia L
Cc: Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Ellis

I suggest you send the 40 page doc and focus more on slides.

John

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

From: Unger, Ellis
Sent: Wednesday, July 6, 2016 7:07 PM
To: Diggs, Felicia; Behr, Virginia L
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Felicia/Virginia,

I am preparing a powerpoint presentation for Dr. Califf, but won't have it ready until very late tonight.

Would he also want a written background? If so, I have one I could send now, but it is 40 pages in length (with a fair number of figures and tables). Should I send it, or shorten it first?

Ellis

From: Diggs, Felicia
Sent: Wednesday, July 06, 2016 6:22 PM
To: Unger, Ellis; Behr, Virginia L
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Yes, but we are still waiting for the document to be submitted to OES. Have you all edited the document yet? I haven't received it.

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

From: Unger, Ellis
Sent: Wednesday, July 06, 2016 5:21 PM

To: Diggs, Felicia; Behr, Virginia L
Cc: Jenkins, John K; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

We haven't heard anything. Are we 'on' for tomorrow 10:30 to noon?

From: Diggs, Felicia
Sent: Wednesday, July 06, 2016 1:35 PM
To: Jenkins, John K; Behr, Virginia L; Unger, Ellis; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

You will receive an invite for tomorrow at 10:30am -12pm in WO Bldg1, room 2102 sometime today.

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

From: Jenkins, John K
Sent: Wednesday, July 06, 2016 1:03 PM
To: Diggs, Felicia; Behr, Virginia L; Unger, Ellis; Temple, Robert
Subject: Re: Sarepta and dispute resolution options

Definitely need more than 30 min. At least 60 and preferably 90.

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

From: Diggs, Felicia
Sent: Wednesday, July 6, 2016 11:49 AM
To: Behr, Virginia L; Jenkins, John K; Unger, Ellis; Temple, Robert
Subject: RE: Sarepta and dispute resolution options

Good morning,

I've attached a draft summary of the meeting's agenda for your review and edits. If you could make your edits and return the document to me no later than 2pm today that would be very helpful. Also on the agenda it states the meeting will occur tomorrow at 10:30-11:00. I have requested additional time therefore, this date may change but as Virginia stated we are aiming for tomorrow or Friday. I understand we will also need a call-in number and will arrange for such. Please let me know if you have any questions or concerns.

Best regards,

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

From: Behr, Virginia L
Sent: Wednesday, July 06, 2016 11:42 AM
To: Jenkins, John K; Unger, Ellis; Temple, Robert

Cc: Diggs, Felicia

Subject: RE: Sarepta and dispute resolution options

Yes, the briefing is likely to be tomorrow or Friday. Felicia Diggs in CDER's Exec Sec already initiated planning the meeting and she is cc'd on this email. Thank you Felicia! She'll be working with you to find a mutually agreeable time to meet with Dr. Califf. If you think of anyone else who should be invited, please let her know. I plan to attend in person to answer any questions about the formal dispute process, should any arise.

Virginia L. Behr
CDER Ombudsman

(301) 796-3436

WO51, Room 6158

<http://inside.fda.gov:9003/CDER/OfficeofExecutivePrograms/Ombudsman/default.htm>



Commissioner Briefing

NDA 206488

Eteplirsen for the Treatment of Duchenne
Muscular Dystrophy in Patients with Mutations
Amenable to Skipping Exon 51

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation-I
Office of New Drugs
CDER

July 7, 2016

1



Duchenne Muscular Dystrophy (1)

- X-linked recessive muscular disorder
- Caused by mutations of the dystrophin gene
- Affects 1 in ~3,600 boys
- Disrupts the mRNA reading frame
- Absence or near-absence of dystrophin in muscle cells
- Dystrophin maintains structural integrity of sarcolemma
- Connects cytoskeleton to underlying cell matrix

Absence of dystrophin leads to mitochondrial damage, inflammation, myonecrosis, replacement by fat and other connective tissue.

2



Duchenne Muscular Dystrophy (2)

- Clinical – degeneration of skeletal and cardiac muscle, progressive loss of physical function after childhood and into adolescence
- Death from respiratory/cardiac failure in second to fourth decade
- No approved therapies; steroids thought to delay progression

3



Eteplirsen

- A phosphorodiamidate morpholino oligomer (PMO)
- Designed to target the pre-mRNA transcripts of the dystrophin gene
- Intent is to exclude exon 51 from the mature, spliced mRNA ("exon skipping"); restore reading frame
- Goal is to produce a truncated form of dystrophin protein, a form that is produced in Becker Muscular Dystrophy
- Becker form of MD is far less severe than the Duchenne form; many patients do well into adulthood
- Goal is to 'convert' Duchenne patients to Becker patients
- Patients amenable to exon 51 skipping represent 13% of all DMD patients (~1/47,000 boys) – target population

4



Eteplirsen: Two Potential Lines of Evidence to Support Approval

- Clinical evidence: externally controlled data on physical function
 - Externally-controlled study - no one thinks these data support a conventional approval.
- Biomarker evidence: really the only issue here →

5



Lack of Agreement About Biomarker Evidence

All agree:

- Dystrophin is an appropriate surrogate endpoint for Duchenne muscular dystrophy.
 - Disease is well understood
 - Dystrophin is pivotal to the pathogenesis of DMD; on the causal path – all agree endpoint is appropriate.
- There is substantial evidence from 1 adequate and well controlled study that eteplirsen produces dystrophin in skeletal muscle.

The principal question is whether the quantity of dystrophin produced by eteplirsen is reasonably likely to predict clinical benefit.

6



1. Eteplirsen development program
2. Biomarker evidence
3. Clinical evidence
4. Safety
5. 'Reasonably likely'
6. Future ramifications
7. Summary

7



Study 201

- Planned as a 24-week placebo-controlled study (N = 12)
 - 4 patients – eteplirsen 50 mg/kg/week IV
 - 4 patients – eteplirsen 30 mg/kg/week IV
 - 4 patients – placebo IV
- Primary endpoint: dystrophin expression
- Main secondary endpoint: 6-minute walk distance
- Other secondary endpoints: physical function (several)
- Patients continued in open-label extension (Study 202)

8



Study 202

- Open-label extension of Study 201 (N = 12)
- Eligible subjects continued to receive eteplirsen once weekly (50 or 30 mg/kg/week IV) for 164 weeks
- Originally intended to be exploratory
- Later used for comparison to external control group

9



Study 301 (PROMOVI)

- Uncontrolled study, still enrolling
- All subjects receiving eteplirsen 30 mg/kg weekly by IV route

10



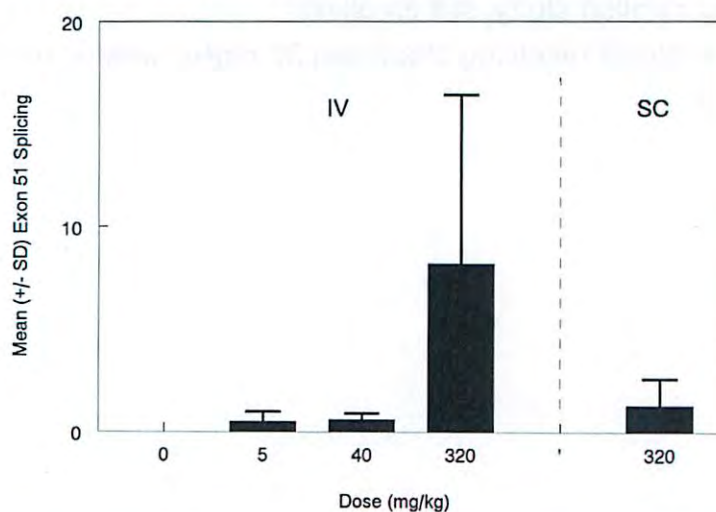
Production of 'Skipped' Messenger RNA

- RT-PCR – used to provide evidence that the desired Becker-type messenger RNA is produced (i.e., exon 51 skipping)
 - Monkey
 - Clinical

11



Evidence of Exon Skipping in Intact Monkeys



12



Exon Skipping / Clinical

- Exon 51 skipping confirmed by RT-PCR analysis in all patients treated with eteplirsen
- PCR is a highly sensitive technique – can detect even a few copies of messenger RNA
- Provides proof of concept that eteplirsen causes at least some degree of exon 51 skipping, as intended
- No controversy or disagreement about this

13



Immunohistochemistry / Clinical – Study 201

- Planned as a 24-week placebo-controlled study (N = 12)
 - 4 patients – eteplirsen 50 mg/kg/week IV
 - 4 patients – eteplirsen 30 mg/kg/week IV
 - 4 patients – placebo IV
 - 30 mg/kg/week
 - 50 mg/kg/week

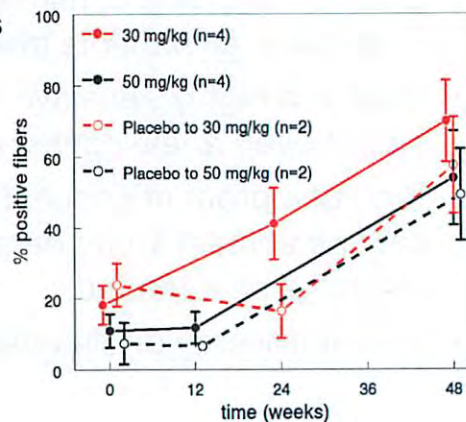
After 24 weeks, 4 patients originally randomized to placebo were switched to eteplirsen 30 (n=2) or 50 (n = 2) mg/kg/week

14



Immunohistochemistry / Clinical – Study 201

- Fantastic results: percent positive fibers increase as a function of time
- Published in *Annals of Neurology* and promoted on company's website
- Convinced DMD community that drug was effective
- Patients reluctant to participate in future placebo-controlled trials



15



Immunohistochemistry / Clinical – Study 201

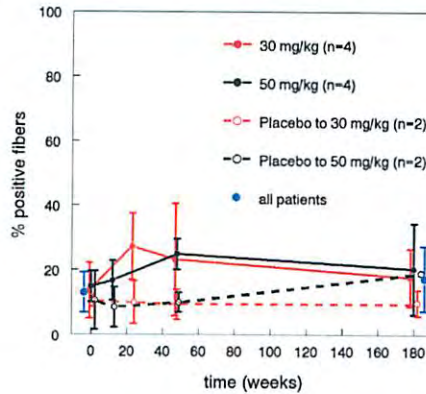
- FDA inspection: results not reliable; problems with methods, inadequate blinding to sequence
- FDA provided technical advice in advance of a 4th muscle biopsy at Week 180 (3.5 years of treatment)

16



Immunohistochemistry / Clinical – Study 201/202

- Blinded read: no increase in dystrophin production at original timepoints; also, no effect at 3.5 years
- No evidence of biological activity per immunohistochemistry data



17



Western Blot / Clinical – Study 201/202

- Western blot – standard method used to quantify protein in tissue samples
- Applicant's original analyses at early timepoints in Study 201/202
 - oversaturated gels
 - technically unsatisfactory
 - uninterpretable
- FDA inspection
 - Advice rendered to applicant to improve methods
 - Plan to run Western blot analyses of new muscle biopsies obtained at 180 Weeks

18



Western Blot / Clinical – Study 201/202

- Plan had been to compare each patient's Week 180 biopsies to their baseline
- Baseline tissue was inadequate for all but 3 patients
- 6 external controls added to estimate baseline (treatment naïve) dystrophin levels

19



Western Blot – Study 201/202, Week 180

Subject	Dose	Western blot				Group Mean±SD
		gel 1	gel 2	Mean (arithmetic)	Mean (per protocol)	
L	30 mg/kg	0.58	0.46	0.52	0.52	No dose-response
K	30 mg/kg	1.45	1.78	1.62	1.62	
J	30 mg/kg	2.83	2.11	2.47	2.47	
H	30 mg/kg	0.02*	0.28	0.15	0.14	
G	Placebo to 30 mg/kg	0.17*	0.15*	0.16	0	
F	Placebo to 30 mg/kg	0.93	1.02	0.98	0.98	
E	50 mg/kg	0.19*	0.16*	0.18	0	No dose-response
D	50 mg/kg	0.75	0.24*	0.50	0.38	
C	50 mg/kg	1.22	0.69	0.96	0.96	
B	50 mg/kg	2.43	1.67	2.05	2.05	
A	Placebo to 50 mg/kg		1.15	1.15	1.15	

* below limit of quantitation

Dystrophin was 0.93% ± 0.84% of normal (mean ± SD) 20



Concerns with Controls Used for Comparison with 4th Biopsy, Study 201/202

- 3 controls were from Study 201 patients but 6 were external
- Control samples generally from different muscle groups
- **With 0.93% $\pm$ 0.84% of normal dystrophin present at Week 180, no way to be certain regarding the change from baseline**

21



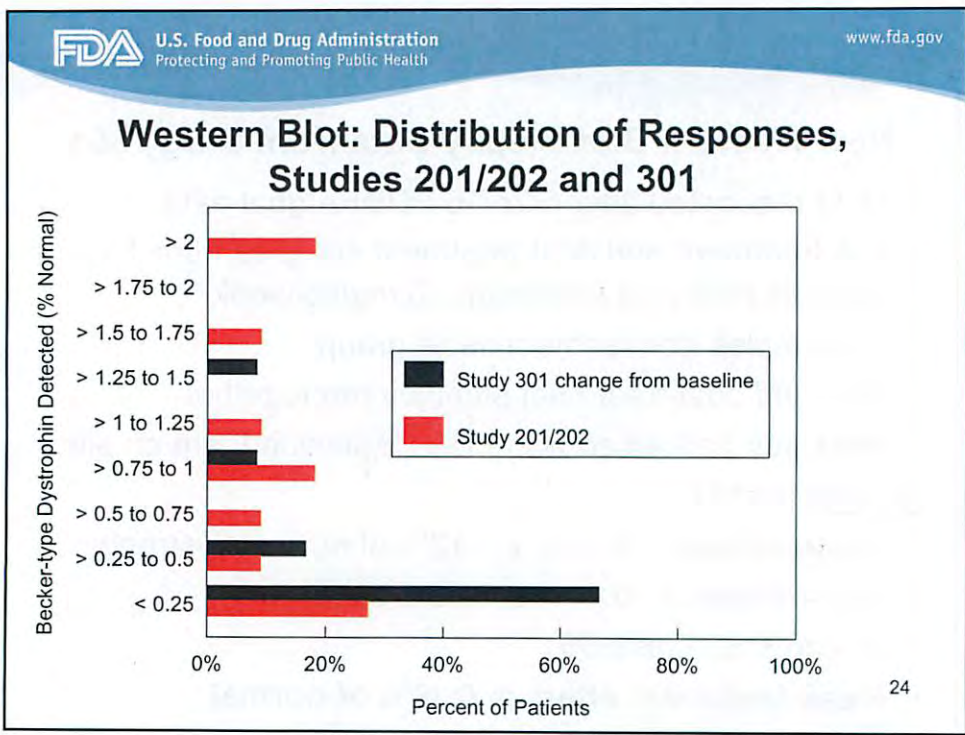
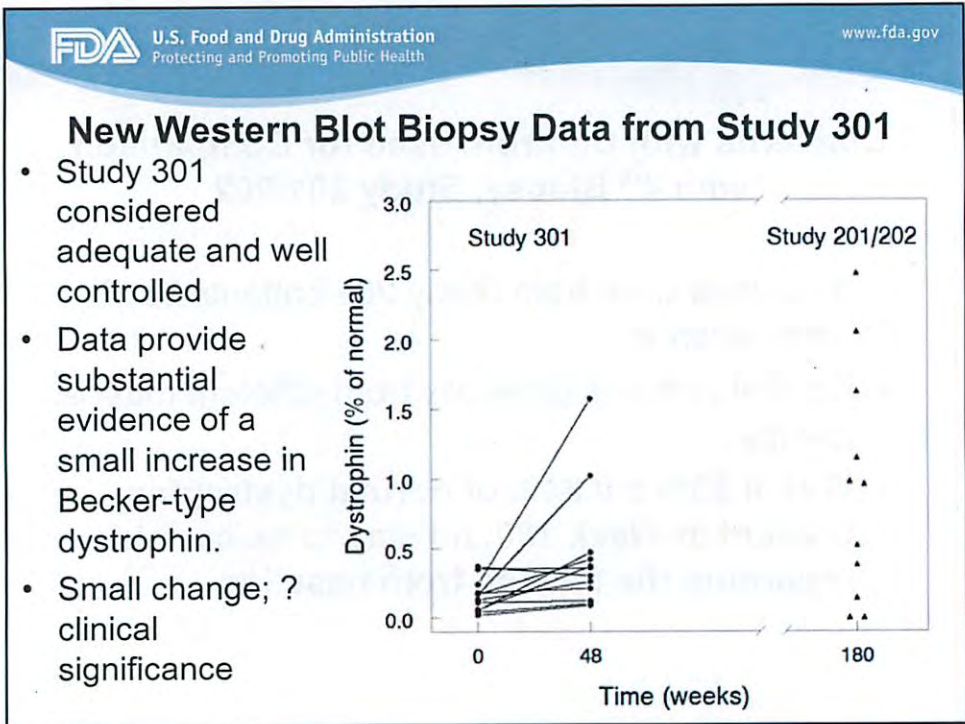
New Western Blot Biopsy Data from Study 301

- Data requested after 5/26/16 PDUFA goal date
- Pre-treatment and post-treatment samples from 13 patients receiving eteplirsen 30 mg/kg/week
- All samples from same muscle group
- Pre- and post-treatment samples run together
- Analyses performed with FDA inspection team on site

Results (n=12):

- pre-treatment 0.16% $\pm$ 0.12% of normal dystrophin
- post-treatment 0.44% $\pm$ 0.43% of normal
(mean $\pm$ SD); $p < 0.05$
- **Mean treatment effect is 0.28% of normal**

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Western Blot: Distribution of Responses, Studies 201/202 and 301

- Study 301: 1 of 12 patients (8%) with treatment effect >1%
- Study 201/202: 4 of 11 patients (36%) >1%;
2 of 11 (18%) > 2%
- 61% have < 0.5% dystrophin (combined studies)

25



Opinion Leaders: Is Dystrophin Level Reasonably Likely to Predict Benefit?

- Dystrophin levels <3% of those in normal healthy muscle, as identified by WB, have been regarded as diagnostic of DMD with the typical DMD phenotype.
- Based on a wide range of scientific observations, experts suggest that ~10% of normal dystrophin may be the minimum level needed to confer measurable clinical benefit (“...dystrophin levels appear not to be a major determinant of disease severity in BMD, as long as it is above approximately 10%”)
- **The threshold needed to predict clinical benefit is unknown, but mean values of 0.93% (Study 201/202) and 0.28% (Study 301) are disappointing.**

26



FDA Review

- Since the discovery of revertant fibers and trace dystrophin in DMD, investigators have looked for, but generally not found, a correlation between DMD severity and trace levels of dystrophin
- The applicant's favored example of evidence of a correlation between DMD severity and dystrophin levels, exon 44 skippable patients, suggests that dystrophin levels in patients with "intermediate" severity have dystrophin levels above 10% of normal

27



Advisory Committee: Substantial Evidence that Eteplirsen Induces Production of Dystrophin to a Level Reasonably Likely to Predict Benefit?

- 7 'Yes;' 6 'No' (one changed vote from 'No' to 'Yes')
- 5 'No' voters - studies not A&WC, questioned the techniques used to measure dystrophin as well as the appropriateness of the controls
- 4 concerned about the lack of correlation between the dystrophin levels and clinical measures
- 'No' voters agreed that even if some dystrophin was produced, there was no evidence that dystrophin production was at a level that would be reasonably likely to predict clinical benefit.

28



Advisory Committee: Substantial Evidence that Eteplirsen Induces Production of Dystrophin to a Level Reasonably Likely to Predict Benefit?

- 6 'Yes' voters included the consumer representative and 2 patient representatives (only 3 professionals in the health sciences voted 'yes').
- Believed that there was some difference in dystrophin production and some evidence of improvement in endpoints.
- 1 'Yes' voter stated he was very troubled by not understanding what constitutes a clinically significant amount, but was impressed by the patients' observations.

29



1. Eteplirsen development program
2. Biomarker evidence
- 3. Clinical evidence**
4. Safety
5. 'Reasonably likely'
6. Future ramifications
7. Summary

30



Study 201 (Randomized Placebo-Controlled) Study 202 (Extension, Externally-Controlled)

- 24-week placebo-controlled study:
 - 4 patients – eteplirsen 50 mg/kg/week
 - 4 patients – eteplirsen 30 mg/kg/week
 - 4 patients – placebo
- Primary endpoint: dystrophin expression
- 6-minute walk distance listed as “exploratory endpoint” in original protocol, later promoted to “secondary endpoint”
- 2 patients in 30 mg/kg group became unable to ambulate early in study, Study 201 results **negative**.

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Sarepta Refused to Conduct a Placebo-Controlled Trial

- Cited problems convincing patients to be randomized to placebo
- Particular problem because muscle biopsies conducted under general anesthesia – no one wanted “saltwater.”
- FDA reluctantly considered externally-controlled trial, but cautioned applicant regarding interpretability, need for a large treatment effect.

32



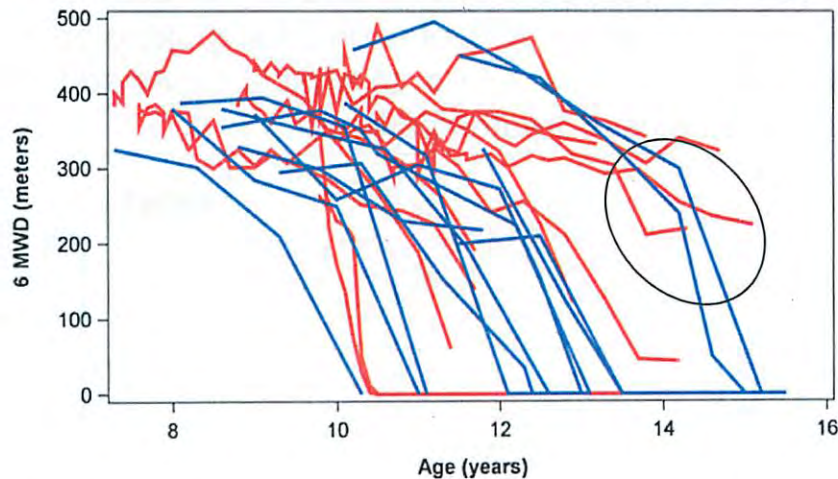
Study 202

- Open-label extension of Study 201 (N=12)
- All subjects received once weekly eteplirsen (50 or 30 mg/kg) for 164 weeks
- Multiple iterations of study plan, study patients ultimately compared to an **external control**
- Patients from the Italian DMD Registry database in Rome (n=97) and University Hospitals in Leuven (n=89)
- From these, 13 appropriate controls selected (baseline steroid use, 6WMM, age, genotype)

33

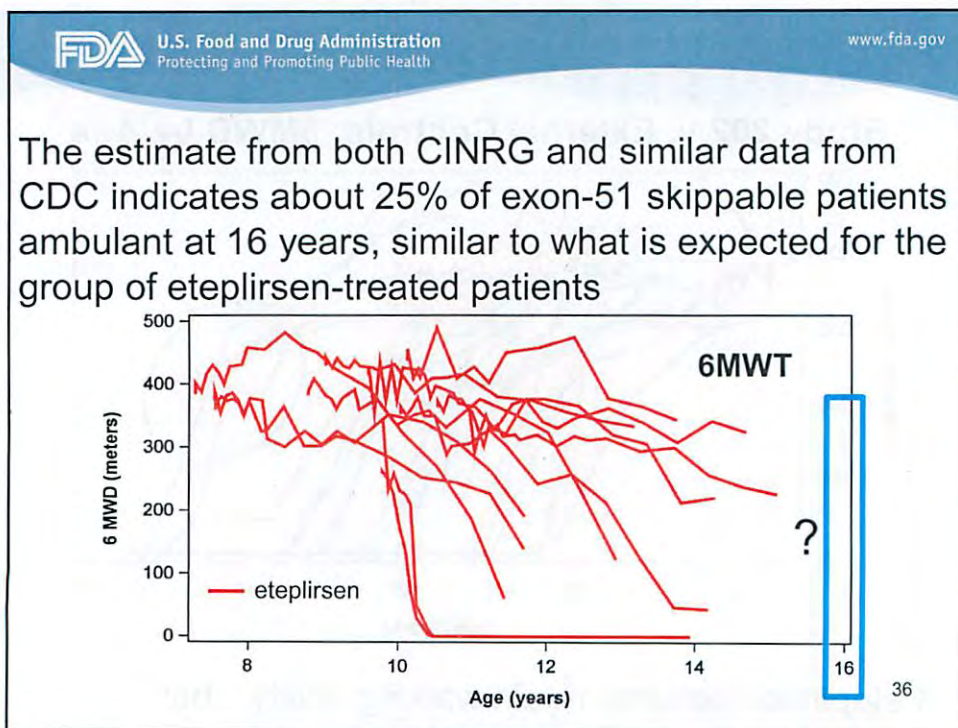
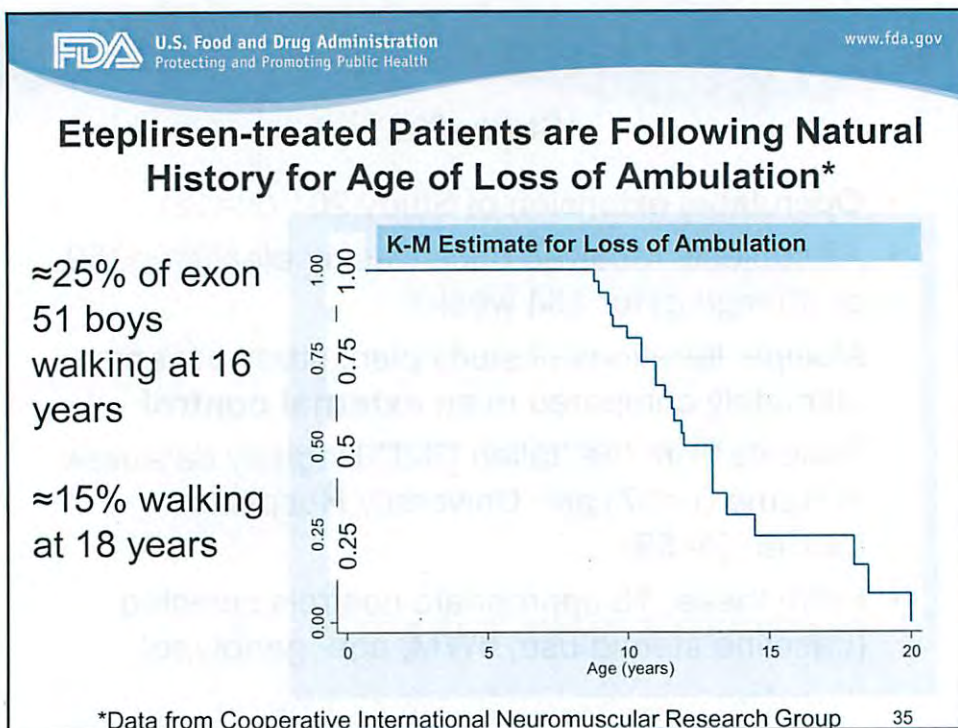


Study 202 v. External Controls: 6MWD by Age



4 eteplirsen patients retain walking ability... but

34





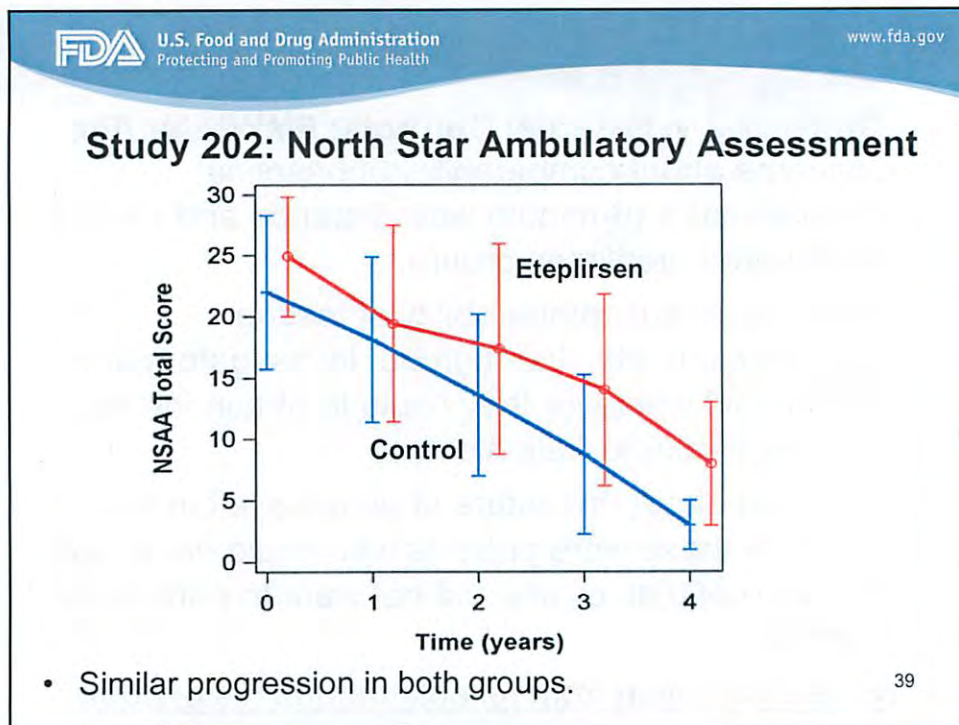
Study 202 v. External Controls: 6MWD by Age

- Concerns about comparability of baseline characteristics (6-minute walk distance and steroid use favored eteplirsen group).
- Concerns about comparability of testing procedures; in eteplirsen group, investigators and patients did whatever they could to obtain the best possible 6-minute walk distance.
- Concerns about the nature of patients left in the registry – these were patients who could not qualify for a clinical trial, or who did not want to participate in a trial.
- No real deviation from reliable natural history data³⁷



North Star Ambulatory Assessment (NSAA)

- Measure of underlying ambulatory abilities such as 'rise from floor,' which support specific activities such as walking
- Although NSAA still susceptible to expectation bias in open-label studies, it may assess disease progression more reliably



- FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov
1. Eteplirsen development program
 2. Biomarker evidence
 3. Clinical evidence
 4. **Safety**
 5. 'Reasonably likely'
 6. Future ramifications
 7. Summary
- 40



Eteplirsen Safety

- Small safety database: 114 total patients exposed, 36 for ≥ 24 weeks and 12 for ≥ 1 year
- Most exposures outside placebo-controlled studies, hard to determine drug-relatedness
- Adverse events generally consistent with those expected in DMD
- Patients in Study 201/202 were exposed for a long duration, which provides some reassurance against delayed toxicity
- No immunogenicity reported
- With use of indwelling catheters, infections will happen
- Dose-limiting toxicity *not* observed; could study much higher doses

41



1. Eteplirsen development program
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- 5. 'Reasonably likely'**
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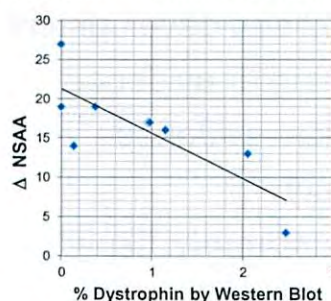
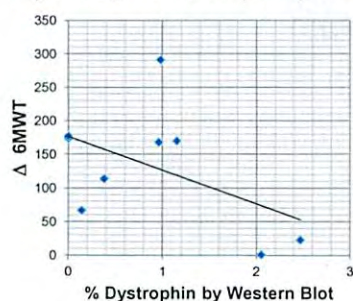
Question of Reasonably Likely – There's No Definition

- Two factors that might have supported the question of 'reasonably likely' are a dose-response and a correlation between the amount of dystrophin produced and retention of physical function.
- No dose-response: In Study 201/202, the amount of dystrophin detected with 30 and 50 mg/kg/week was similar.
- Poor correlation between the amount of dystrophin produced and retention of physical function (next slide)

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Study 201/202: Correlations between Quantity of Dystrophin and Physical Function – From Dr. Woodcock



- These compare change in physical performance over time to dystrophin at Week 180, not Δ dystrophin
- Obviously small numbers, correlations driven by 1 or 2 patients

44



Responder Analyses

- Defining a responder (arbitrarily) as >1%, ~22% of patients are responders, but even an effect of 1% seems dubious.
- For a 2% level of dystrophin, 9% are responders.
- 61% have < 0.5% dystrophin

45



Ethics of Approving a Dose Known to be Ineffective (on the Basis of Clinical Data)

- Imagine 100 years ago a promising drug called penicillin is discovered – a potential cure for pneumococcal pneumonia – but the drug is difficult to produce and expensive. A dose of 5 mg weekly has been shown to have statistically significant bactericidal effects on *S. pneumoniae*.
- Would it be ethical to give the drug accelerated approval based on this finding and allow marketing of a dose of 5 mg weekly, absent additional information?
- Patients would die.
- It could take years to get the dose right.

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1. Eteplirsen development program
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Question of Reasonably Likely

- Amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin.
- If a change of 0.28% is considered adequate to support accelerated approval, then the question arises as to *whether there is any statistically significant change that would be too small to support accelerated approval.*
- Adoption of the concept that any change in an appropriate surrogate endpoint would be a game-changer that would turn the clock back to the days prior to the 1962 Kefauver Harris Amendments
- Damage to the field of evidentiary medicine could be enormous.

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Obvious Need for Higher Doses

- No basis for selecting dose of 30 mg/kg/week
- Lack of efficacy; no safety issues
- Remember monkey data
- Originally, patients treated at study sites; visits more frequently than weekly posed practical limitations.
- Patients now have infusion ports/lines; could be treated more frequently.
- More frequent dosing and/or higher doses could be effective, safe, and practical.

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1. Eteplirsen development program
2. Biomarker evidence
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50



Summary

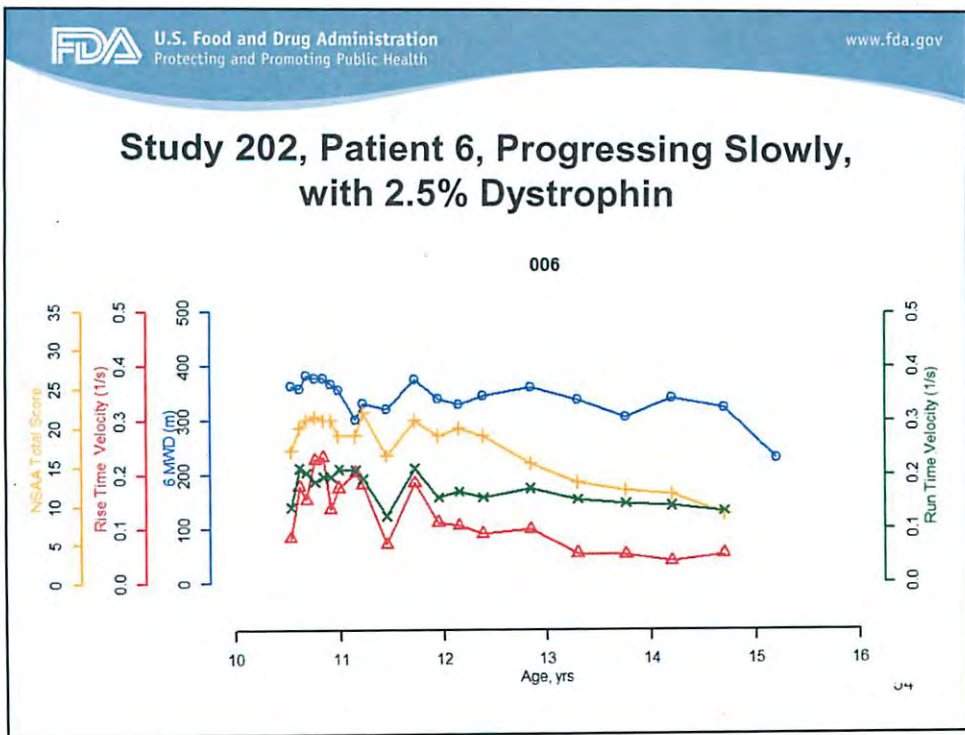
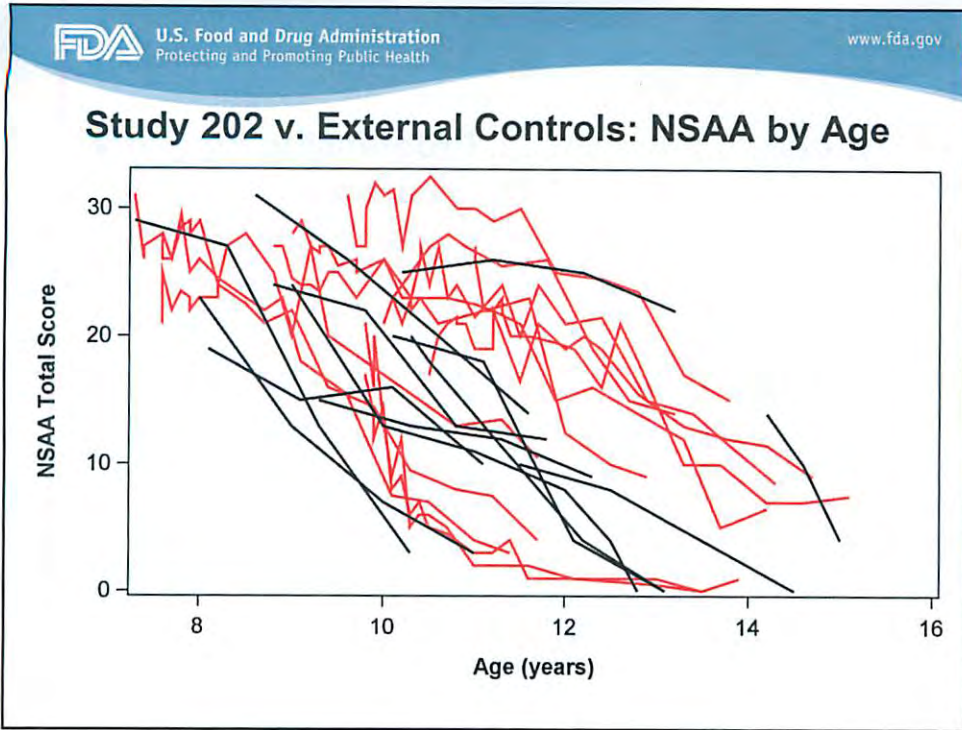
- There is no definition of “reasonably likely”
- Best estimate of quantity of dystrophin produced here = 0.28% of normal = 2.8 parts per thousand
- If you needed to shovel 10” of snow, this quantity would constitute 1/32 of an inch.
- Dystrophin is primarily a structural protein, maybe much less would be needed if this were an enzyme or a cofactor
- If we were willing to be wrong and approve an ineffective drug 15 to 20% of the time, this would not be close.
- If we were willing to approve an ineffective drug 50% of the time, this would not be close.
- Thank you for considering our views.

51



Backup Slides

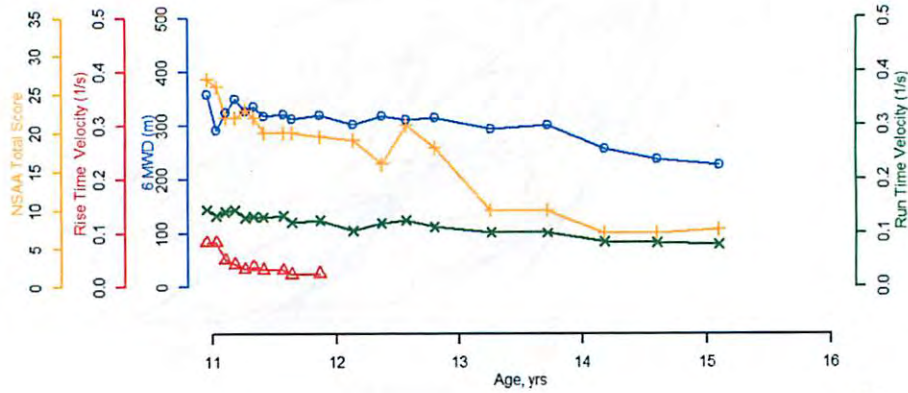
52





Study 202, Patient 12, Progressing Similarly, with <0.4% Dystrophin

012



55

Temple, Robert

From: Dunn, Billy
Sent: Thursday, July 07, 2016 5:47 PM
To: Choy, Fannie (Yuet); Unger, Ellis; Temple, Robert; Bastings, Eric; Farkas, Ronald
Subject: saretpa update for today

All,

After just speaking with Ellis, here are the short-term plans:

Labeling – Sarepta submitted their response today. Ron and Fannie will be circulating edits to that document through Fannie later this evening. Fannie will make sure we are working on the right template. Once circulated, Eric, Bob, and Ellis will review prior to sending the next iteration to the sponsor. Note that Ron has made some changes, the sponsor has made some tweaks, and Lois will need to look over changes to the MOA in 12.1.

Confirmatory study PMR/PMC – Eric’s language was apparently circulated. Whether that went to the sponsor or not is unclear. The sponsor needs to receive and agree to our language for the dose response PMR. Then we need to draft and get language to the sponsor for the PMC. The language for the PMR and PMC needs to be circulated to those on this email. We’ll see what Eric weighs in with overnight in terms of process (email, verbal negotiation, etc.)

Sponsor’s proposal for (b) (4) that came in today – the sponsor will need feedback on that, but I think it will effectively take the form of our PMR/PMC language that we will send them, and their specific proposal will be mooted.

Billy

Temple, Robert

From: Choy, Fannie (Yuet)
Sent: Thursday, July 07, 2016 5:41 PM
To: Farkas, Ronald; Bastings, Eric
Cc: Unger, Ellis; Dunn, Billy; Choy, Fannie (Yuet)
Subject: FW: Update / Sarepta
Attachments: Update: ESSENCE Protocol/Synopsis

Just one more question, Sarepta is also asking for feedback on the ESSENCE study. They sent an email with the updated protocol on 7/5, but did not specifically ask for feedback. I have attached the email/protocol for your reference.

Thanks
Fannie

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Thursday, July 07, 2016 5:25 PM
To: Choy, Fannie (Yuet)
Subject: Update?

Dear Fannie,

Can you please give me an update on when we will get feedback from FDA on the following documents:

1. [REDACTED] (b) (4)
2. ESSENCE study
3. USPI

We really want to get these documents finalized as soon as possible.

Thank you for your help.

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: Thursday, July 07, 2016 9:57 AM
To: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: Draft Eterplirsen Dose Ranging Study

Dear Shamim,

I confirm receipt of the draft protocol. I have shared with the team and will keep you posted.

Regards,
Fannie

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Wednesday, July 06, 2016 11:33 PM
To: Choy, Fannie (Yuet)
Subject: FW: Draft Eteplirsen Dose Ranging Study

Dear Fannie

We understand that the Agency would like Sarepta to explore higher doses of eteplirsen via the PMC/PMR process. Sarepta has

(b) (4) (b) (4)

We request an urgent review and feedback from the Division as we would like to complete the process for accelerated approval by the end of this week.

Thanks for your help.

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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CLINICAL STUDY PROTOCOL

(b) (4)

[A large grey rectangular area covers the majority of the page, indicating that the content has been withheld.]

23 pages have been withheld as b(4) (CCI/TS) immediately after this page

(b) (4)

Confidential

FDACDER0004866

Philips, Howard

From: Temple, Robert
Sent: Thursday, July 07, 2016 12:22 PM
To: Dunn, Billy; Choy, Fannie (Yuet); Farkas, Ronald; Bastings, Eric
Cc: Unger, Ellis
Subject: RE: Draft Eterplirsen [REDACTED] (b) (4)

Totally absurd. If they won't do the study we want, they do not get AA, right?

From: Dunn, Billy
Sent: Thursday, July 07, 2016 7:58 AM
To: Choy, Fannie (Yuet); Farkas, Ronald; Bastings, Eric
Cc: Unger, Ellis; Temple, Robert
Subject: RE: Draft Eterplirsen [REDACTED] (b) (4)

Adding Bob. He has firm opinions on this.

From: Choy, Fannie (Yuet)
Sent: Thursday, July 07, 2016 7:52 AM
To: Farkas, Ronald; Bastings, Eric
Cc: Dunn, Billy; Unger, Ellis; Choy, Fannie (Yuet)
Subject: FW: Draft Eterplirsen [REDACTED] (b) (4)

Morning,

Attached please find Sarpta's proposed [REDACTED] (b) (4)

Thanks
Fannie

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Wednesday, July 06, 2016 11:33 PM
To: Choy, Fannie (Yuet)
Subject: FW: Draft Eterplirsen [REDACTED] (b) (4)

Dear Fannie

We understand that the Agency would like Sarepta to explore higher doses of eteplirsen via the PMC/PMR process. Sarepta has therefore prepared [REDACTED] (b) (4)

We request an urgent review and feedback from the Division as we would like to complete the process for accelerated approval by the end of this week.

Thanks for your help.

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

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Philips, Howard

From: Unger, Ellis
Sent: Sunday, July 10, 2016 3:35 PM
To: Diggs, Felicia; Dunn, Billy; Bastings, Eric
Cc: Choy, Fannie (Yuet); Jenkins, John K; Temple, Robert
Subject: RE: Eteplirsen Information Advisory-Clearance
Attachments: Eteplirsen Information Advisory 6-3-16_ODE-I.doc

This needed quite a bit of work. Dr. Temple made some suggestions, and I made many more. I had some trouble with the formatting of the bullets. I had trouble creating bullets, removing them, and putting them into the correct position. I gave up on this eventually.

Ellis

From: Diggs, Felicia
Sent: Wednesday, July 06, 2016 9:03 AM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Temple, Robert; Jenkins, John K
Cc: Choy, Fannie (Yuet)
Subject: Eteplirsen Information Advisory-Clearance
Importance: High

Good morning,

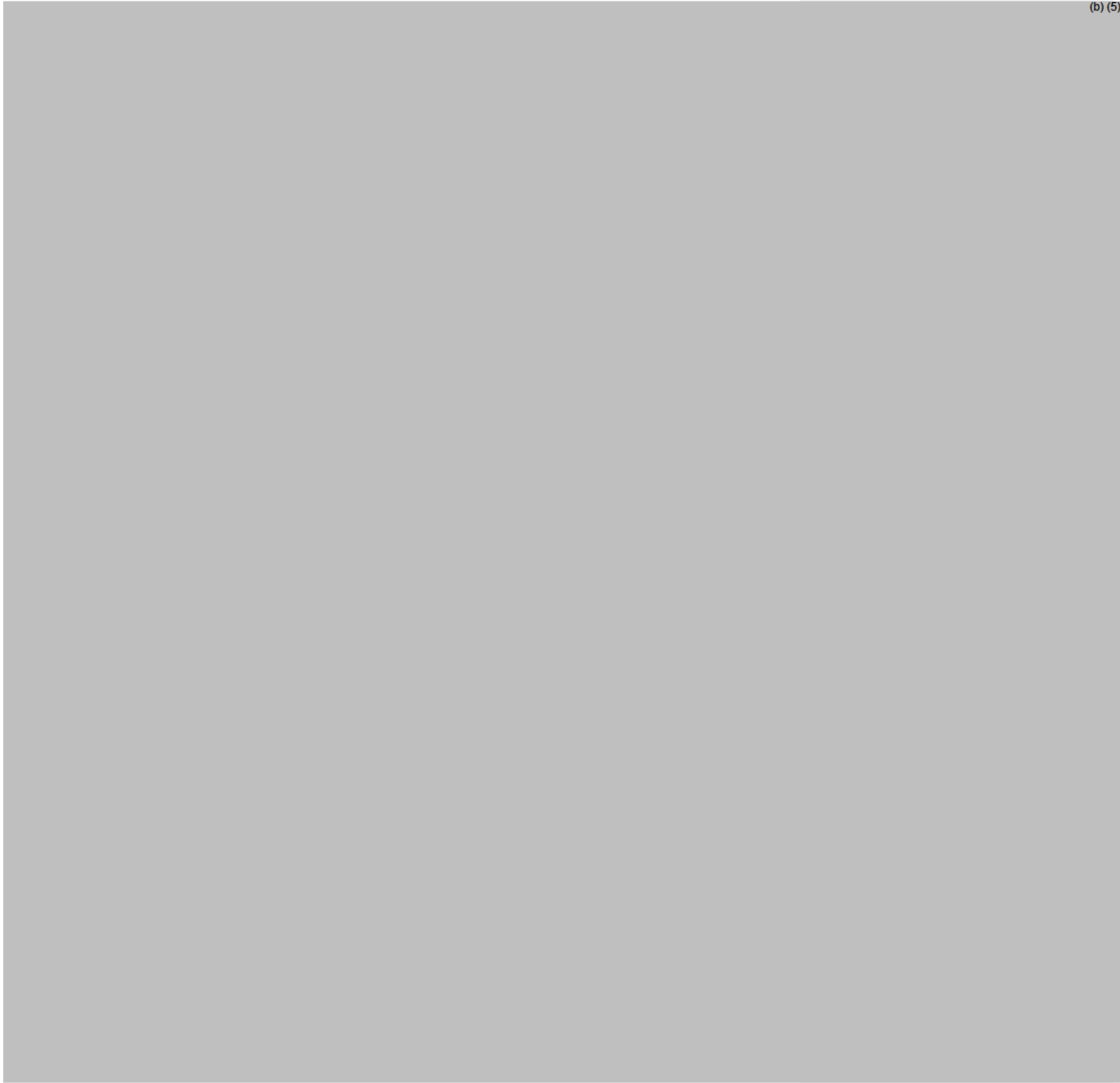
Please see attached a draft IA contingent upon the approval of eteplirsen for your clearance and/or edits. I'm uncertain of the status of the application and therefore am sending this document simultaneously for clearance.

We will need to have the document cleared at least 4 days prior to approval. If you could review and return to me asap (today) I will continue to pass this through the OES clearance process. I received word (from OES by way of OMA I believe) that an approval may occur today.

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







(b) (5)

Temple, Robert

From: Dunn, Billy
Sent: Monday, July 11, 2016 7:21 AM
To: Choy, Fannie (Yuet); Unger, Ellis; Bastings, Eric
Cc: Farkas, Ronald; Freed, Lois M; Temple, Robert; Peters, Tracy
Subject: RE: updated eteplirsen label
Attachments: FDAedits-COMPLETE_Round3_07July16-Eteplirsen PI-RF-tp-eb-lf-ODE-I.DOCX

Regarding Ellis's question below, I think such a disclaimer would be fine.

I have a few points.

Section 1 – (b) (5)
(b) (5) I would be happier with "This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see Clinical Studies (14)]."

Section 8.5 – (b) (5)
(b) (5)

Comment FDA13 – I do not recommend this comment go to the sponsor. I think it is acceptable as written.

Section 12.2 – (b) (5)
(b) (5) I recommend deletion of this sentence.

Comment FR16 part a) – I agree with adding a sentence explaining that PCR does not equate to dystrophin.

Section 12.2 – (b) (5)
(b) (5) This description seems generous given our internal discussions, notwithstanding Table 2.

Section 14 – Something seems off about giving comparable weight to the Study 2 180 week dystrophin values as we do to the Study 3 values. It seems the 0.93% needs some type of context or disclaimer explaining that baseline comparison is not available so to what degree this represents a change is unclear.

Comments A17-A19 – We should strengthen the wording of these comments and state facts, not proposals.

Billy

From: Choy, Fannie (Yuet)
Sent: Monday, July 11, 2016 12:49 AM
To: Unger, Ellis; Bastings, Eric
Cc: Farkas, Ronald; Freed, Lois M; Dunn, Billy; Temple, Robert; Peters, Tracy; Choy, Fannie (Yuet)
Subject: RE: updated eteplirsen label

Eric,

Please use the attached version. It includes your edits (7/8 5:45 a.m.), Lois' edits (7/8 9:31 a.m.) and the 7/10 edits from Drs. Unger and Temple.

Thanks
Fannie

From: Unger, Ellis
Sent: Sunday, July 10, 2016 2:25 PM
To: Choy, Fannie (Yuet); Bastings, Eric
Cc: Farkas, Ronald; Freed, Lois M; Dunn, Billy; Temple, Robert; Peters, Tracy
Subject: RE: updated eteplirsen label

Dr. Temple made a few changes and I made several more. When we show the results of the Western blot in Section 14, what would people think about adding a disclaimer to say that the relationship between dystrophin and clinical outcome is unknown? Food for thought....

From: Choy, Fannie (Yuet)
Sent: Friday, July 08, 2016 12:01 AM
To: Bastings, Eric
Cc: Farkas, Ronald; Freed, Lois M; Dunn, Billy; Unger, Ellis; Temple, Robert; Peters, Tracy; Choy, Fannie (Yuet)
Subject: RE: updated eteplirsen label

Eric,

This is the latest version (last updated 7/7 11:36pm by Tracy) for your review.

Thanks
Fannie

From: Choy, Fannie (Yuet)
Sent: Thursday, July 07, 2016 6:04 PM
To: Farkas, Ronald; Bastings, Eric; Freed, Lois M; Dunn, Billy; Unger, Ellis; Temple, Robert; Peters, Tracy
Cc: Choy, Fannie (Yuet)
Subject: RE: updated eteplirsen label

All,

Just want to make sure we have the proper version control. I have uploaded Ron's version in SP with this link [SharePoint](#).

Eric – I don't think you can access SP. I'll check later tonight to make sure you have the latest version for review.

Please note that Edits/comments by Author = Sarepta's changes and comments.

Thanks
Fannie

From: Farkas, Ronald
Sent: Thursday, July 07, 2016 5:42 PM
To: Bastings, Eric; Freed, Lois M; Dunn, Billy; Unger, Ellis; Temple, Robert; Choy, Fannie (Yuet); Peters, Tracy
Subject: updated eteplirsen label



11 pages of draft labeling have been withheld as b(4) (CCI/TS) immediately following this page

Philips, Howard

From: Woodcock, Janet
Sent: Tuesday, July 12, 2016 7:17 AM
To: Temple, Robert
Subject: draft of sarepta decision
Attachments: Sarepta dct.docx

Here is a draft of my decisional memo. JW

Center Director Decisional Memo DRAFT

(b) (5)



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

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Tuesday, July 12, 2016 6:56 PM
To: Dunn, Billy; Bastings, Eric; Farkas, Ronald
Cc: Unger, Ellis; Temple, Robert; Peters, Tracy; Freed, Lois M; Choy, Fannie (Yuet)
Subject: Eteplirsen Proposed Labeling / Sarepta Response 7/12

Sarepta has responded to our proposed PI sent earlier today. I have uploaded the latest version with Sarepta comments in [SharePoint](#).

The OPDP review is still pending and might have additional comments. We have previously addressed their [preliminary](#) comments (6/29/16).

Thanks
Fannie

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Tuesday, July 12, 2016 2:45 PM
To: Choy, Fannie (Yuet)
Subject: FW: FDAedits-COMLETE_Round4_12July16-Eteplirsen PI_to Sarepta SRPT.docx

Dear Fannie

Please find attached our response to FDA's latest draft USPI. We have [accepted all of FDA's changes](#) and have only made a couple of edits to ensure accuracy as follows:

1. **Section 12.2 : Corrected (b) (5) to Study 2 – to ensure accuracy**
2. **Section 12.2: Corrected a typo from "(b) (5)" to "subjects"**
3. **Section 12.3: Under subheading of "Sex" – changed "(b) (5) to "studied"**

I hope we can now finalize the label.

Regarding the PMCs/PMRs, if you are unable to provide us written feedback by end of day today, I'd like to request a tcon tomorrow morning to discuss any outstanding issues or questions from DNP.

Thanks for your help.

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: Unger, Ellis
Sent: Tuesday, July 12, 2016 6:48 PM
To: Temple, Robert
Subject: Fw: MEMO

Sent from my BlackBerry.

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Sent: Tuesday, July 12, 2016 5:25 PM
To: Woodcock, Janet; Unger, Ellis; Dunn, Billy; Bastings, Eric
Cc: Jenkins, John K
Subject: RE: MEMO

Janet

As we discussed in the hallway, I had some comments on your memo:

1. You said you did not consider data from the first three biopsies, but you do not say why. It was my understanding that the re-read of the first three biopsies for IHC was considered valid and the review team saw no change from baseline from the first biopsy to week 180. This is an important part of their perspective on the amount of dystrophin produced and its significance. They noted that the baseline ICH results from the patients in Study 201 were very different from the "new" baseline data that were conducted in parallel to the week 180 biopsy and that these differences were not explained. So, I think you need to explain why you are not considering the IHC data from the first three biopsies in your review, and instead focusing on the comparison of the "new" controls versus the week 180 IHC results.
2. I am not familiar with the references you added to the memo and cannot comment on your summary of the findings of each paper. Perhaps the review team know those references and can provide their take on the findings. Even taking your summaries at face value as accurate, I did not find the summary of the references to be particularly helpful in determining whether the dystrophin findings for eteplirsen are "reasonably likely" to predict clinical benefit. As you noted, there are issues related both to the quantity of dystrophin produced as well as its quality (functionality) that are hard to tease apart in the small sample of boys treated. It is possible that the "responders" are making functional protein, it is also possible they are making non-functional protein, and I don't think we have the data to sort this out. It still seems to be a judgment on the totality of evidence where reasonable people may disagree.
3. I find the correlation graphs at the end to be problematic since they graph a delta for a clinical endpoint on the y-axis against an absolute endpoint value for dystrophin on the x-axis. While one might assume the baseline dystrophin levels were low and therefore using the absolute endpoint value is a reasonable estimate of the effect of the drug on dystrophin (e.g., a surrogate for the delta); we don't know that and therefore it is hard to know whether the graphics are isolating a drug effect or capturing a prognostic difference that may have been present at baseline. So, I don't find them as convincing as you suggest, but again, that may be a judgment.
4. You focus on the "responders" in the population to support your argument, but we don't know how to identify the responders and therefore will have to approve based on the sponsor's grouping of mutations that are "amenable to exon 51 skipping," which likely include mutations that are not responsive to eteplirsen. This is a frustrating intersection of "targeted" therapies and approval based on a group mean based on characteristics chosen by the sponsor that we cannot validate. This is very analogous to the CF cases that we have been discussing and I think the review teams in both cases are struggling with these issues. It feels like we have to "unlearn" what we think we know from targeting and regress to approving an un-validated grouping of mutations. I know we do this all the time for non-targeted therapies, but it is still discomfoting to face this for targeted therapies. While the drug at the proposed dose has not been shown to be toxic, it will likely require a central line for chronic administration, which is not benign, and families/society will be

burdened with a very expensive drug that may only be working in a small subset of the indicated population. This is an issue we will have to grapple with for many “targeted” therapies for rare diseases.

As we discussed, I am asking the review team members to provide any feedback they have on your memo by COB tomorrow so you can finalize the memo. That step is necessary for the appeal process to be formally triggered and I think we all agree we need to move quickly to resolve this case on way or the other.

John

From: Woodcock, Janet
Sent: Monday, July 11, 2016 7:21 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: MEMO

Here is a draft version of my decisional memo. I welcome comments on it. An appeal can't be done until I finalize this, I am told. Thanks. jw

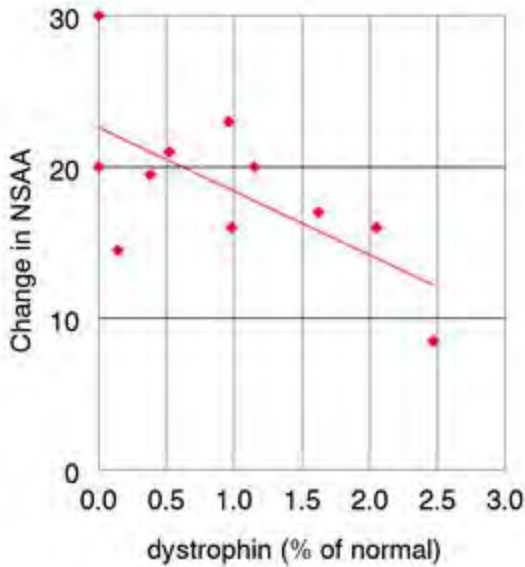
Philips, Howard

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 12:59 AM
To: Temple, Robert
Subject: FW: MEMO

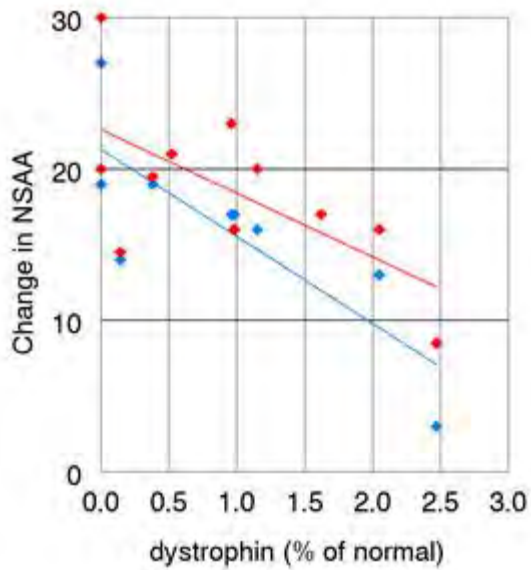
My comments to JW on her memo.

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 12:57 AM
To: Woodcock, Janet
Cc: Jenkins, John K; Dunn, Billy; Bastings, Eric
Subject: RE: MEMO

I just noticed that the y-axis scales for the blue and red plots were different. This was not intentional. Here's the red plot on the same 0 to 30 scale as the blue plot:



And here they are together:



From: Unger, Ellis
Sent: Wednesday, July 13, 2016 12:52 AM
To: Woodcock, Janet
Cc: Jenkins, John K; Dunn, Billy; Bastings, Eric
Subject: RE: MEMO

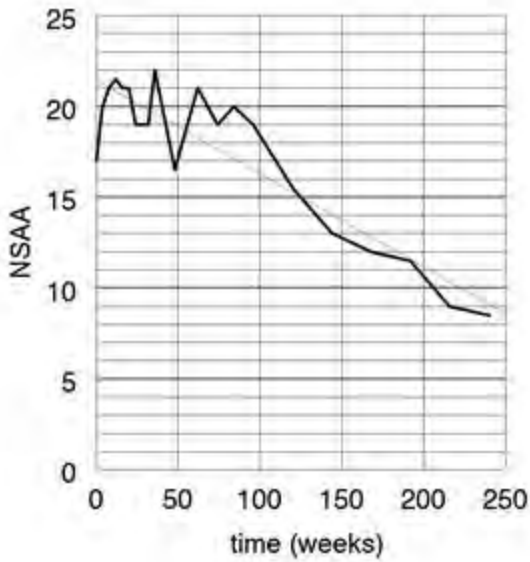
Janet,

I have some concerns with respect to Table 1 and Figure 2. You say that $R^2 = 0.8$. I've plotted the NSAA data in your Table 1, and I was able to reproduce your graph exactly. But I got $R=0.8$, which means that $R^2 = 0.64$. So I think that " $R^2 = 0.8$ " is a typo. If R^2 were actually 0.8, then R would have been 0.9 (0.9 squared = 0.81).

More importantly, I cannot tell how you got the deltas for the NSAA for each patient in Table 1. If you want to include the table and figure as they are now in your draft, I think you might consider citing your source for the table (presumably a Sarepta table or a reviewer's table). If it is your own work, then you might want to explain how you calculated the numbers, i.e., identify the name and location of the original data file you used and explain the methods you used to calculate the deltas.

Looking deeper at your table, I was curious about the data from patient 006. This patient had the highest dystrophin value (2.47%) and an NSAA change of just 3 units, as noted in the table.

Here are the NSAA data on this boy:



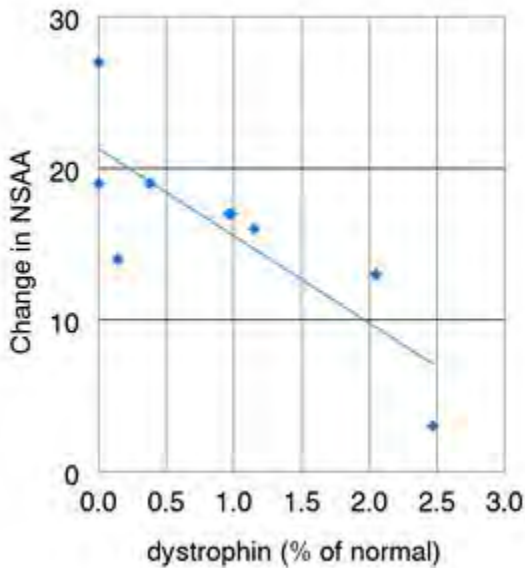
Looking at the data above, I have some difficulty characterizing his change as “3.”

Instead of picking an arbitrary time point as the “final” point, I thought that the most reasonable way of doing this would be to include all of the data that have been collected through Week 240. Because all patients have remained on weekly treatment for 240 weeks, I see no reason to truncate the data at the time the biopsy was obtained. Thus, for each patient I calculated their delta as their Week 240 score minus their baseline score. EXCEPT - for the 4 patients who started on placebo for 24 weeks, I considered Week 24 to be their baseline.

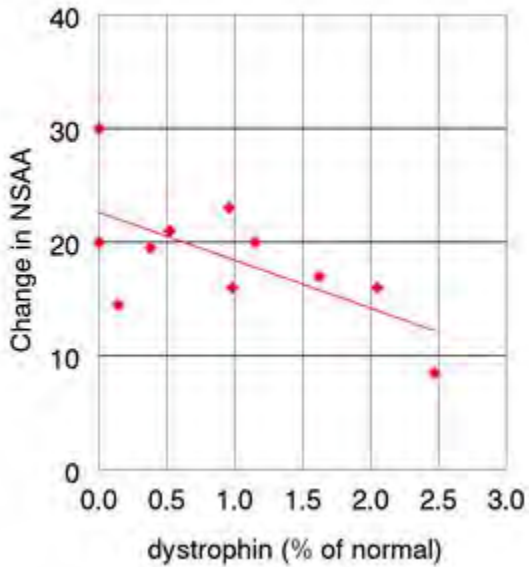
Also, I think we should use the data from all 11 patients with Week 180 biopsies, including the 2 who lost ambulation early, though I understand you might not agree.

Here is what I found...

First, below in blue is my version of your plot of 9 patients. My plot looks the same as yours, but I get $R=0.80$. (At the dystrophin value of 1%, there are two closely overlapping data points.)



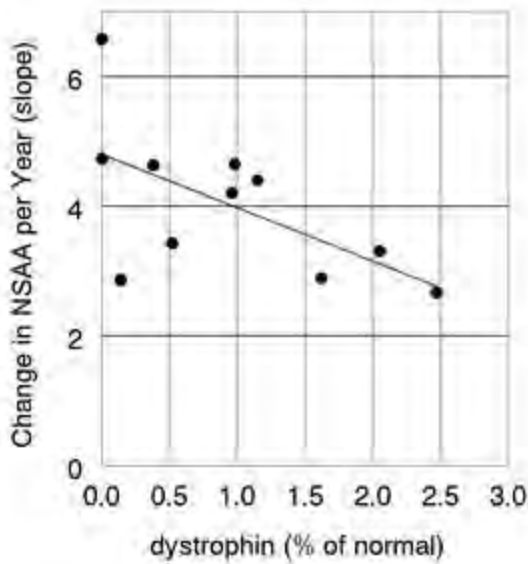
Second, below, my plot of all 11 patients, where I calculate delta as Week 240 minus baseline (for patients who started on placebo, it's Week 240 minus Week 24):



Using all of the data through Week 240, the slope is less steep and the correlation is worse. And knowing that you might not agree with inclusion of the 2 boys who became unable to ambulate, I will tell you that if I include all 11 boys, $R=0.65$. If I leave out the 2 non-ambulatory boys, $R=0.64$. So it makes no difference whether they are included or not. And the slope is essentially the same.

An alternate analysis I've been interested in is one that uses ALL of the aforementioned data for each patient. Rather than using just the first and last data points for each patient, we can calculate a slope for each patient using linear regression. For example, consider patient 006 graphed above. The red line is the linear regression. His slope is -0.051 units per week, or (multiply by 52) -2.7 units per year.

Below is a plot of the slope for each boy vs. dystrophin at Week 180 by Western blot. The slope for each boy is expressed as the change in NSAA per 52 weeks. For this plot, $R=0.60$, which is quite similar to the correlation of simple pre-treatment minus post-treatment (above).



In short, when you consider all of the NSAA data through Week 240, you get essentially the same plot whether you simply subtract pre- from post (red plot), or calculate a slope for each patient (black plot). And in either case, R is in the 0.6-range.

You can feel free to use some or all of these plots. Obviously, you can use your own table/plot, but if you do, I suggest you explain how you got your numbers, as I noted above.

Ellis

From: Jenkins, John K
Sent: Tuesday, July 12, 2016 5:25 PM
To: Woodcock, Janet; Unger, Ellis; Dunn, Billy; Bastings, Eric
Cc: Jenkins, John K
Subject: RE: MEMO

Janet

As we discussed in the hallway, I had some comments on your memo:

1. You said you did not consider data from the first three biopsies, but you do not say why. It was my understanding that the re-read of the first three biopsies for IHC was considered valid and the review team saw no change from baseline from the first biopsy to week 180. This is an important part of their perspective on the amount of dystrophin produced and its significance. They noted that the baseline ICH results from the patients in Study 201 were very different from the “new” baseline data that were conducted in parallel to the week 180 biopsy and that these differences were not explained. So, I think you need to explain why you are not considering the IHC data from the first three biopsies in your review, and instead focusing on the comparison of the “new” controls versus the week 180 IHC results.
2. I am not familiar with the references you added to the memo and cannot comment on your summary of the findings of each paper. Perhaps the review team know those references and can provide their take on the findings. Even taking your summaries at face value as accurate, I did not find the summary of the references to be particularly helpful in determining whether the dystrophin findings for eteplirsen are “reasonably likely” to predict clinical benefit. As you noted, there are issues related both to the quantity of dystrophin produced as well as its quality (functionality) that are hard to tease apart in the small sample of boys treated. It is possible that the “responders” are making functional

protein, it is also possible they are making non-functional protein, and I don't think we have the data to sort this out. It still seems to be a judgment on the totality of evidence where reasonable people may disagree.

3. I find the correlation graphs at the end to be problematic since they graph a delta for a clinical endpoint on the y-axis against an absolute endpoint value for dystrophin on the x-axis. While one might assume the baseline dystrophin levels were low and therefore using the absolute endpoint value is a reasonable estimate of the effect of the drug on dystrophin (e.g., a surrogate for the delta); we don't know that and therefore it is hard to know whether the graphics are isolating a drug effect or capturing a prognostic difference that may have been present at baseline. So, I don't find them as convincing as you suggest, but again, that may be a judgment.
4. You focus on the "responders" in the population to support your argument, but we don't know how to identify the responders and therefore will have to approve based on the sponsor's grouping of mutations that are "amenable to exon 51 skipping," which likely include mutations that are not responsive to eteplirsen. This is a frustrating intersection of "targeted" therapies and approval based on a group mean based on characteristics chosen by the sponsor that we cannot validate. This is very analogous to the CF cases that we have been discussing and I think the review teams in both cases are struggling with these issues. It feels like we have to "unlearn" what we think we know from targeting and regress to approving an un-validated grouping of mutations. I know we do this all the time for non-targeted therapies, but it is still discomfoting to face this for targeted therapies. While the drug at the proposed dose has not been shown to be toxic, it will likely require a central line for chronic administration, which is not benign, and families/society will be burdened with a very expensive drug that may only be working in a small subset of the indicated population. This is an issue we will have to grapple with for many "targeted" therapies for rare diseases.

As we discussed, I am asking the review team members to provide any feedback they have on your memo by COB tomorrow so you can finalize the memo. That step is necessary for the appeal process to be formally triggered and I think we all agree we need to move quickly to resolve this case on way or the other.

John

From: Woodcock, Janet
Sent: Monday, July 11, 2016 7:21 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: MEMO

Here is a draft version of my decisional memo. I welcome comments on it. An appeal can't be done until I finalize this, I am told. Thanks. jw

Philips, Howard

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 3:28 PM
To: Woodcock, Janet
Cc: Jenkins, John K; Dunn, Billy; Bastings, Eric; Temple, Robert; Choy, Fannie (Yuet); Farkas, Ronald; Lowy, Naomi
Subject: Proposed PMR/PMC for Sarepta

Hi Janet,

Please review and comment on our proposed PMR and PMC for eteplirsen:

PMR:

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

Draft Protocol Submission: MM/YY
Final Protocol Submission: MM/YY
Trial Completion: MM/YY
Final Report Submission: MM/YY

PMC:

Conduct a 2-year controlled trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing of the corresponding exon. The (b) (5) should include at least two well-separated doses of each PMO, with the high dose designed to provide the greatest dystrophin response possible, based upon preliminary dose-finding, with an expectation of acceptable tolerability. The primary objective of this study will be to evaluate the effect of the two PMO doses (combined-active group) compared to control on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy. A double-blind, placebo-controlled trial design should be used, if feasible, as this would be most informative. If it is not feasible to include a placebo group, an untreated concurrent control group may be considered, with appropriate care to reduce bias in outcome assessments given the lack of randomization and blinding. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the (b) (5)

Draft Protocol Submission: MM/YY
Final Protocol Submission: MM/YY
Trial Completion: MM/YY
Final Report Submission: MM/YY

Philips, Howard

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 10:19 AM
To: Jenkins, John K
Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy
Subject: RE: eteplirsen PMR/PMC

Let's go with this for the PMC:

Conduct a 2-year controlled trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing of the corresponding exon. The (b) (5) should include (b) (5). The primary objective of this study will be to evaluate the effect of the two PMOs (combined-active group) compared to (b) (5) on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy. (b) (5) a double-blind, placebo-controlled trial design, if feasible, as this would be most informative. If it is not feasible to include a placebo group, (b) (5) an untreated concurrent control group, with appropriate care to reduce bias in outcome assessments given the lack of randomization and blinding.

Draft Protocol Submission:	MM/YY
Final Protocol Submission:	MM/YY
Trial Completion:	MM/YY
Final Report Submission:	MM/YY

From: Jenkins, John K
Sent: Wednesday, July 13, 2016 9:56 AM
To: Unger, Ellis
Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy
Subject: RE: eteplirsen PMR/PMC

You could say a "controlled" trial and recommend placebo if feasible and ethical or a concurrent untreated control with appropriate care to minimize bias in outcome assessments due to lack of blinding of on or off drug.

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 9:31 AM
To: Jenkins, John K
Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy
Subject: RE: eteplirsen PMR/PMC

Not sure if (b) (5) " was intentional or not, but we can remove it and change to "... (b) (5)"

Some people might think that it's ethical to do 2 needle biopsies in boys on placebo; others might disagree. And we know what we think about a port/central line in placebo patients, but reasonably people might reach a different conclusion in other countries.

From: Jenkins, John K
Sent: Wednesday, July 13, 2016 8:28 AM
To: Unger, Ellis

Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy; Jenkins, John K
Subject: RE: eteplirsen PMR/PMC

I'm OK with the wording. I think the "confirmation" in another exon will be helpful to the concept, but not definitive for confirming benefit of eteplirsen, which needs to come from the PMR. In essence the PMC places them on notice that we expect a well-designed development program for products for other exons and that information will be available to the public in the AP letter if eteplirsen is approved. So, it will provide some transparency on our advice, which has been lacking in our interactions with this sponsor. (b) (5)

John

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 1:18 AM
To: Jenkins, John K
Cc: Temple, Robert; Choy, Fannie (Yuet); Bastings, Eric; Dunn, Billy
Subject: eteplirsen PMR/PMC

John,

What do you think of this language? I must tell you that neither I nor DNP think that the PMC will be useful.

PMR:

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

Draft Protocol Submission:	MM/YY
Final Protocol Submission:	MM/YY
Trial Completion:	MM/YY
Final Report Submission:	MM/YY

PMC:

Conduct a 2-year, (b) (5)-controlled, (b) (5) trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing (b) (5). The (b) (5) should include (b) (5). The primary objective of this study will be to evaluate the effect of the two PMOs (combined-active group) compared to (b) (5) on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy.

Draft Protocol Submission:	MM/YY
Final Protocol Submission:	MM/YY
Trial Completion:	MM/YY
Final Report Submission:	MM/YY

Temple, Robert

From: Farkas, Ronald
Sent: Thursday, July 14, 2016 4:45 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: RE: Sarepta Document / Dr. Woodcock's memo

A few more points about possible issues with the examples Dr. Woodcock gives to support that low levels of dystrophin are associated with milder DMD phenotype

- a. From her review Section 5, example h, Bellow et al, 2016. Dr. Woodcock's review states the following:

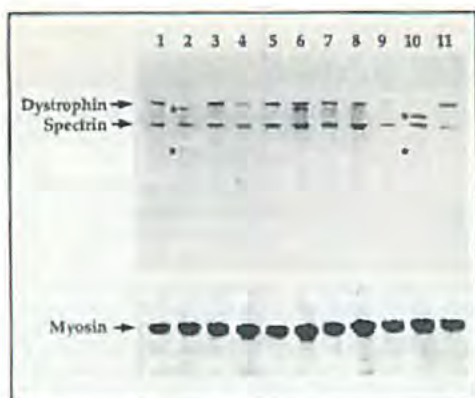
"They found patients with exon 44 amenable mutations to have a two-year delay in loss of ambulation compared to the overall comparison group. This finding had previously been reported by another group (van den Bergen, et al., *J Neuromuscul Dis*, 1, 2014). The mutations studied (primarily single-exon deletion of exon 45) are known to undergo spontaneous skipping with production of some dystrophin. According to the Bello report, of six patients previously tested by IHC, three showed traces of dystrophin production and **0/four (possibly other patients) had dystrophin detectable by Western blot** ^{(b) (5)}. These authors suggest that the observed differences in loss of ambulation (LOA) could be due to small amounts of spontaneously induced dystrophin that slightly ameliorate the ordinary DMD phenotype."

However, it seems important to understand what "previously tested" means. Bello et al state right after they give these numbers that "these findings were from retrospective laboratory reports [emphasis added] and were not performed using some of the quantitation techniques recommended in clinical trials". It's hard to know what that even means, but the type of rough test used in clinical care calls low levels 'undetectable'.

- b. The patients cited in 5a, Hoffman et al 1988, and in 5b, Beggs 1991, are largely the same patients, as stated in the footnote to Beggs 1991:

* Partial information on some patients has been previously published as indicated: 56, Angelini et al. (1990); 3, 5, 12, 15, 16, 19, 20, 21, 23, 26, 29, 34, 35, 36, 37, 40, 41, 42, 44, 57, 58, 64, 67, Arahata et al. (1991); 5, 7, 9, 16, 19, 20, 23, 29, 35, 40, 44, 57, 58, 64, Arahata et al. (1989); 1, Boyce et al. (1991); 61, Hoffman et al. (1988); 4, 11, 13, 17, 22, 25, 27, 30, 31, 33, 38, 45, 47, 49, 50, 51, 55, 56, 60, 61, 62, 66, Hoffman et al. (1989b); 22, 33, 38, Koenig et al. (1989); 15, 26, 34, 36, 37, Sunohara et al. (1990); 32, Sklar et al. (1990).

- c. The precision of dystrophin measurement that Dr. Woodcock cites from Beggs et al. , "20% variability between blots according to the authors" is certainly what the authors said, but the number is absurd on face – the odd numbered lanes below (from the paper that Beggs cites for methods) contains normal samples in the odd numbered lanes. The normal samples appear to differ be several fold from each other. And, of course, there is no dilution series.



Thanks
Ron

From: Farkas, Ronald
Sent: Thursday, July 14, 2016 12:07 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: RE: Sarepta Document / Dr. Woodcock's memo

Here's some text I wrote about this issue, but did not include in my review because I didn't foresee that we'd be trying to base approval on single reports of single patients.

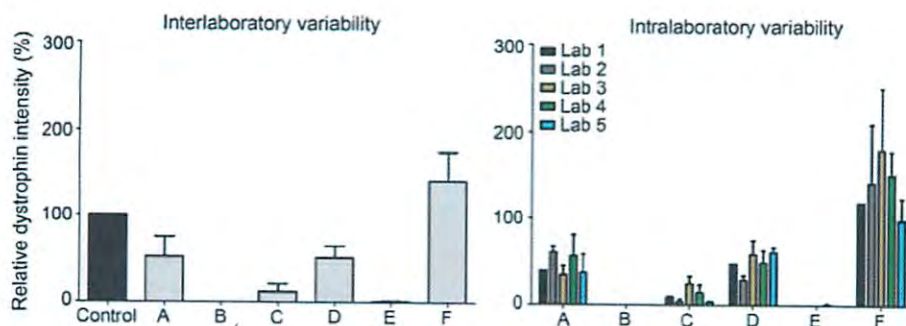
(b) (5)

From: Farkas, Ronald
Sent: Thursday, July 14, 2016 11:47 AM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: RE: Sarepta Document / Dr. Woodcock's memo

A technical note – Dr. Woodcock cites individual patients with a mild course and very low dystrophin levels, but for most, if not all of these patients, there is low confidence in these dystrophin estimate.

There is a large amount of random variability in Western blots, and in most (really all) literature reports it does not appear that multiple Westerns were done for each patient. See patient C below – if multiple Westerns had not been conducted this patient could have been reported as having anything from <3% dystrophin to 25% dystrophin.

Figure 3 Inter- and intralaboratory variability of dystrophin quantification using Western blotting



Sample	Interlaboratory variability			Intralaboratory variability	
	n	Mean ± SD	CV	Lab	Average CV
A	5	51.62 ± 23.17	44.89	1	0.3
B	5	0 ± 0	n/a	2	37.76
C	5	11.41 ± 9.22	80.81	3	118.88
D	5	50.67 ± 13.39	26.43	4	86.86
E	5	0.4 ± 0.89	222.5	5	32.98
F	5	140.85 ± 33.09	23.49	—	—

Five laboratories each quantified the level of dystrophin expression in the same 6 biopsies using a standardized Western blotting protocol. To assess interlaboratory variability, the mean ± SD for each laboratory and biopsy was plotted on a bar chart and the average coefficient of variation (CV) per laboratory calculated. To assess intralaboratory variation, the mean ± SD for each laboratory per sample was calculated as well as the average CV per laboratory. Laboratories are unidentified.

From: Choy, Fannie (Yuet)
Sent: Thursday, July 14, 2016 9:30 AM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert
Cc: Choy, Fannie (Yuet)
Subject: FW: Sarepta Document / Dr. Woodcock's memo
Importance: High

Morning,

Please see attached email.

Thanks
 Fannie

From: Ligon, Sharnell (CDER)
Sent: Thursday, July 14, 2016 9:09 AM
To: Choy, Fannie (Yuet)
Subject: Sarepta Document
Importance: High

Dear Fannie,

Attached, please find Dr. Woodcock's final Sarepta document. Do you mind checking with the Dr. Unger and the division to see if they have any comments before it is entered into DARRTS? Additionally, will you be the one uploading this document into DARRTS so Dr. Woodcock can sign off on it?

Thanks

Temple, Robert

From: Farkas, Ronald
Sent: Thursday, July 14, 2016 12:07 PM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: RE: Sarepta Document / Dr. Woodcock's memo

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(b) (5)

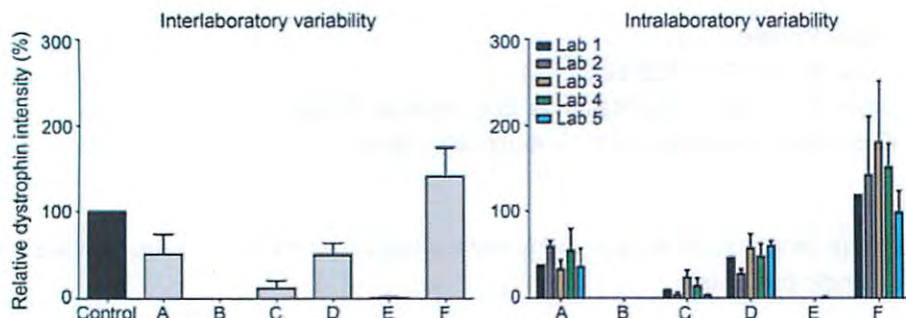


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Sent: Thursday, July 14, 2016 11:47 AM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Temple, Robert
Subject: RE: Sarepta Document / Dr. Woodcock's memo

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From: Choy, Fannie (Yuet)
Sent: Thursday, July 14, 2016 9:30 AM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert
Cc: Choy, Fannie (Yuet)
Subject: FW: Sarepta Document / Dr. Woodcock's memo
Importance: High

Morning,

Please see attached email.

Thanks
 Fannie

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Subject: Sarepta Document
Importance: High

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Thanks

Temple, Robert

From: Unger, Ellis
Sent: Thursday, July 14, 2016 10:58 AM
To: Ligon, Sharnell (CDER)
Cc: Choy, Fannie (Yuet); Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert; Jenkins, John K
Subject: RE: Sarepta Document / Dr. Woodcock's memo

Sharnell,

Here are my comments:

Page 6, line 2, change (b) (5) to "IHC"
Page 8, under f. (b) (5), → "27 patients"
Page 9, under l, (b) (5), □-sarcoglycan"

Page 10, There is an incorrect statement here. The memo states: "There was a positive (inverse) correlation between dystrophin by Western blot and rate of decline in NSAA score, . (Figure 1, (b) (5))

The figure that I sent Dr. Woodcock was my plot of the data that Dr. Woodcock included in Table 1 of her last draft. In other words, these were data that I obtained from Dr. Woodcock, not the other way around. I have no idea where, or how, she obtained those data, and I cannot corroborate them. I hope Dr. Woodcock will remove the statement (b) (5)

Ellis

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Evaluation and Research
US FDA

From: Choy, Fannie (Yuet)
Sent: Thursday, July 14, 2016 9:30 AM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert
Cc: Choy, Fannie (Yuet)
Subject: FW: Sarepta Document / Dr. Woodcock's memo
Importance: High

Morning,

Please see attached email.

Thanks
Fannie

From: Ligon, Sharnell (CDER)
Sent: Thursday, July 14, 2016 9:09 AM

To: Choy, Fannie (Yuet)
Subject: Sarepta Document
Importance: High

Dear Fannie,

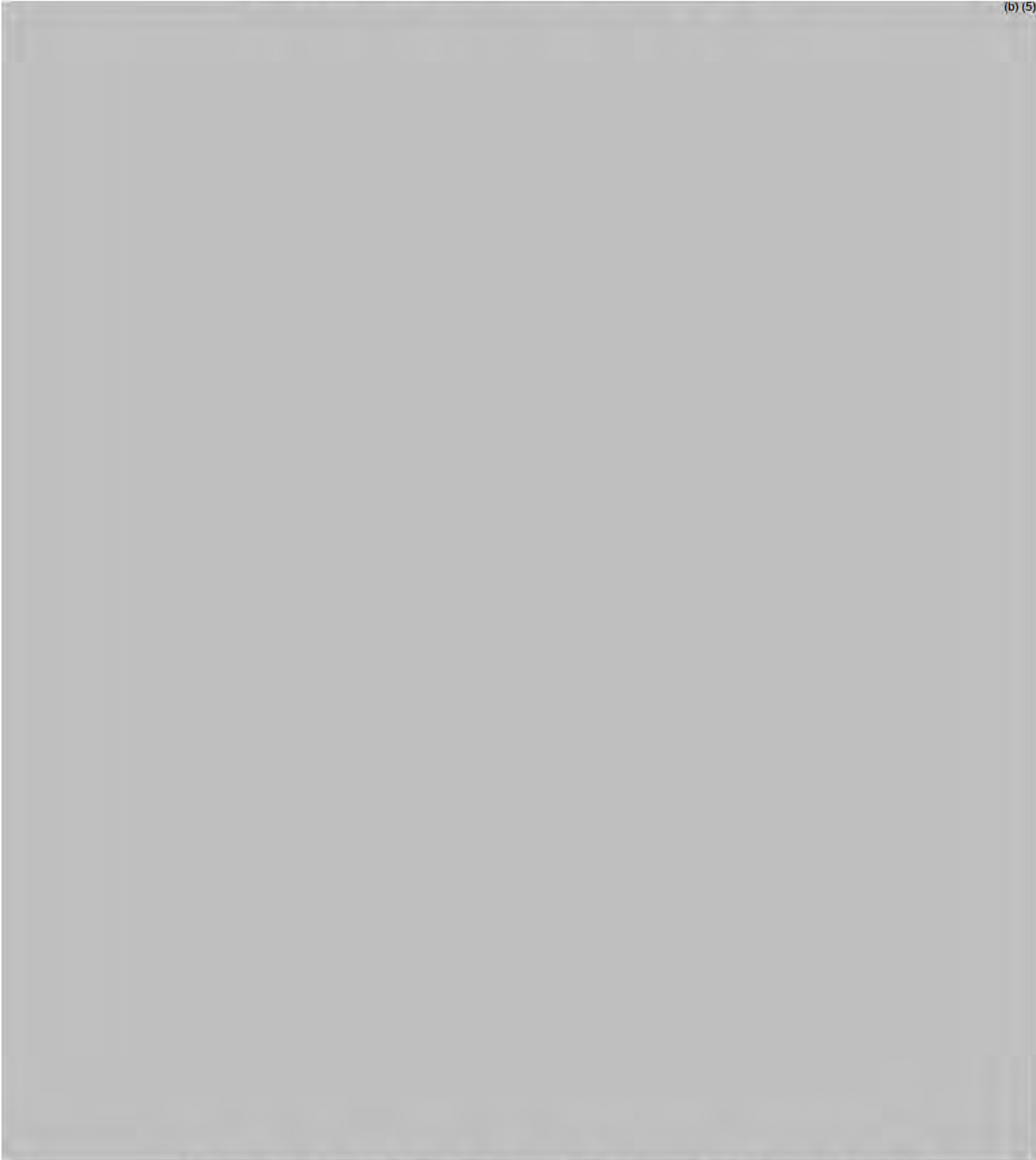
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Thanks

Sharnell

CENTER DIRECTOR DECISIONAL MEMO

(b) (5)



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

Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Thursday, July 14, 2016 9:30 AM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert
Cc: Choy, Fannie (Yuet)
Subject: FW: Sarepta Document / Dr. Woodcock's memo
Attachments: Sareptafinal.docx

Importance: High

Morning,

Please see attached email.

Thanks
Fannie

From: Ligon, Sharnell (CDER)
Sent: Thursday, July 14, 2016 9:09 AM
To: Choy, Fannie (Yuet)
Subject: Sarepta Document
Importance: High

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Thanks

Sharnell

CENTER DIRECTOR DECISIONAL MEMO

NDA# 206488
Drug Name EXONDYS 51 (eteplirsen)
Indication Duchenne Muscular Dystrophy (DMD)
Sponsor Sarepta
Author Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research (CDER),
Food and Drug Administration

(b) (5)

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

Philips, Howard

From: Unger, Ellis
Sent: Friday, July 15, 2016 11:08 AM
To: Farkas, Ronald
Cc: Temple, Robert; Bastings, Eric; Dunn, Billy; Breder, Christopher D; Lowy, Naomi
Subject: RE: eteplirsen memo NDA 206488

Thanks! All incorporated. Also, Billy suggested last night I (b) (5) and I'm doing that.

From: Farkas, Ronald
Sent: Friday, July 15, 2016 7:29 AM
To: Unger, Ellis
Cc: Temple, Robert; Bastings, Eric; Dunn, Billy; Breder, Christopher D; Lowy, Naomi
Subject: RE: eteplirsen memo NDA 206488
Importance: High

Great review. A few suggestions

1. This statement is seemingly true even if it was believed that some patients increased from zero to 2-3%. It appears, therefore, that reproducibility of assays between academic centers has not been established, such that it would not be (b) (5) to compare an increase in Becker-type dystrophin of 0.2 to 0.3% ((b) (5)) with dystrophin values cited in the literature for other mutations/patient populations, assessed at other laboratories.
2. Study 202 did not meet its 1° clinical endpoint, 6MWT, at 48 weeks.
3. This is an important point. The view in the literature has been that 10% dystrophin would be needed for detectable clinical benefit.

Recognizing that the threshold for the effect size needed to be 'reasonably likely' to predict clinical benefit is not known, the view provided in the literature suggests that at least 3% of normal dystrophin is inadequate, (b) (5), and levels perhaps much more, a minimum of 10%, would be necessary for detectable clinical benefit.

Thanks

Ron

From: Unger, Ellis
Sent: Thursday, July 14, 2016 7:14 PM
To: Temple, Robert; Locicero, Colleen L; Farkas, Ronald; Bastings, Eric; Dunn, Billy; Breder, Christopher D; Lowy, Naomi
Cc: Choy, Fannie (Yuet); Mazur, Julia
Subject: eteplirsen memo NDA 206488

All,

Here's my pre-final memo on eteplirsen. The first 16 pages are largely unchanged from before, but there is a lot of new content after that. If you get a chance to look please comment. I'll want to DARRT it sometime tomorrow.

Note that I have to write a separate memo of appeal, which I'll start right after dinner.

Thanks to all for looking,

Ellis

eteplirsen

Agency Scientific Dispute – Appeal

Date: July 18, 2016

To: **G. Matthew Warren**
Director
Office of Scientific Integrity, FDA

From: **Ellis F. Unger, M.D. (initiator)**
Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Research and Evaluation
U.S. Food and Drug Administration

Re: **NDA #** 206488
Drug: eteplirsen (Exondys 51)
Applicant: Sarepta Therapeutics
Indication: Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping

1. Background

The Office of New Drugs within the Center for Drug Evaluation and Research (CDER) oversees regulation of new drugs, and is responsible for making regulatory decisions for approval/non-approval of new molecular entities. Within the Office of New Drugs, there are 6 sub-offices, including the Office of Drug Evaluation-I. The Office of Drug Evaluation-I oversees the Division of Neurology Products, which regulates drugs for the central and peripheral nervous systems, as well as drugs for muscular disorders. Typically, a new drug application (NDA) for a new molecular entity for a neurology indication is reviewed by the Division of Neurology Products in concert with review staff from other offices in CDER.¹ The regulatory decision is typically rendered by Office of Drug Evaluation-I, i.e., the signatory authority.

NDA 206488 for eteplirsen was reviewed by the Division of Neurology Products, and members of the review team reached the unanimous conclusion that the NDA should receive a *complete response* action. This view was shared by the Office of Biometrics, which performed the statistical review, as well as the Office of Clinical Pharmacology, which performed the pharmacology review. Dr. John Jenkins, Director, Office of New Drugs, also supports a *complete response* action for this NDA (verbal communication).

This memo is meant to explain the salient arguments around the scientific disagreement here; additional details are available in my memo recommending a complete response and Dr. Woodcock's memo recommending approval, and the reader is referred to those memoranda.

Disease Background:

¹ Reviews are typically provided by Office of New Drug Quality Assessment, Division of Medication Error Prevention and Analysis, Office of Biometrics, Office of Scientific Investigations, and others.

Duchenne muscular dystrophy is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene. These mutations disrupt the messenger ribonucleic acid (mRNA) reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells. The disorder affects 1 in ~3,600 boys.

Dystrophin protein is thought to maintain the structural integrity of the muscle cell, cushioning it from the stress and strain of repeated contraction and relaxation. Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. With progressive degeneration of skeletal muscle (including breathing muscles) and cardiac muscle, there is loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.

No specific therapies are approved for DMD. Steroids are currently the cornerstone of management, widely believed to delay loss of ambulation and respiratory decline by several years.

Drug Background:

Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. Theoretically, by restoring of the mRNA reading frame, a 'truncated' but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.

Drug Development Background:

Three studies are germane to the issues here. Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study (see below).

The endpoints for these studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.

2. Description of How My Position Differs from the Center's Perspective

Dr. Janet Woodcock, Director, CDER, disagrees with some of the findings of the review team, and has reached the conclusion that the NDA should be approved. She finds that the data meet the standard for accelerated approval under 21 CFR 314. 510, based on the change in a surrogate endpoint of dystrophin protein production – a change she concludes is reasonably likely to predict clinical benefit. The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit. The decision of *approval vs. complete response* hinges on this question.

a. Clinical/Statistical Efficacy

Accelerated Approval:

Dr. Woodcock has reached the conclusion that eteplirsen should receive accelerated approval based on a small effect on the surrogate endpoint of dystrophin production.

The relevant statutory and regulatory framework (section 506(c) of the FD&C Act and 21 CFR part 314, subpart H) states that a drug can receive accelerated approval if 3 factors are satisfied:

1. If the drug treats a serious or life-threatening disease or condition,
2. if FDA takes into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments, and
3. if the drug demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit OR demonstrates an effect on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. As noted in section 506(c)(1)(B) of the FD&C Act, the evidence to support the concept "...that an endpoint is reasonably likely to predict clinical benefit may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

In terms of the prospect for accelerated approval for eteplirsen, DMD is clearly a serious, severe, and rare condition with no approved treatments; therefore, factors 1 and 2, above, are satisfied. There is no disagreement.

The critical issue is whether factor 3 is satisfied, and factor 3 can be subdivided into three parts: 1) whether the surrogate endpoint is appropriate for the disease; 2) whether there is substantial evidence of an effect on the surrogate endpoint; and 3) whether the effect demonstrated meets the test of being "reasonably likely" to predict clinical benefit. Importantly, there is no regulatory definition of "reasonably likely."

For the first part of factor 3, whether the surrogate endpoint is appropriate for the disease, the review team has agreed that the near-lack of dystrophin is the proximal cause of DMD, and that the level of dystrophin in skeletal muscle is an appropriate surrogate endpoint that could predict efficacy. There is no disagreement here.

The second part of factor 3 is whether an effect has been demonstrated; the legal standard is 'substantial evidence' based on adequate and well-controlled clinical investigations. Typically, such evidence would be two studies, both achieving a p -value < 0.05 , but in some situations FDA has the flexibility to interpret data from a single trial, or a single trial with supporting evidence, as substantial evidence of effectiveness.² Dr. Woodcock believes that "...there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells." I agree that there is evidence from a single adequate and well controlled trial, Study 301, that eteplirsen induces dystrophin production in muscle cells, but do not agree that there is reliable quantitative evidence from the other trial, Study 201/202.

The third part of factor 3, the conclusion that the demonstrated effect is "reasonably likely" to predict clinical benefit, is where there is disagreement.

A. Are the Data on Dystrophin Protein Production from One or More Adequate and Well-Controlled Studies?

Dr. Woodcock cites 3 lines of evidence pertinent to the conclusion that eteplirsen increases dystrophin production:

1. Production of an appropriate mRNA transcript
2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot
3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

1. Production of an appropriate mRNA transcript

I agree that the applicant has shown expression of mRNA following treatment with eteplirsen. As noted by Dr. Woodcock, this finding establishes proof of concept, but does not by itself mean that there is increased dystrophin production.

2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot

Western blot is a standard laboratory technique used to quantify proteins in body tissues. In Sarepta's development program, Western blot was used to assess dystrophin protein levels in skeletal muscle in Study 201, in Study 202 (again, these were Study 201 patients who were maintained on treatment), and finally in Study 301.

a. Study 201:

The original Western blot analyses from Study 201 were intended to show that dystrophin levels were greater in eteplirsen-treated patients than in patients in the placebo group, and analyses were planned to compare the effects of the lower vs. higher eteplirsen doses on dystrophin production. The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable.

b. Study 202:

² See: "Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products;" May, 1998.

With FDA's assistance, the applicant improved the assays and performed repeat biopsies on 11 of 12 patients of the Study 201/202 patients at Week 180. These were to be compared to stored baseline (pre-treatment) samples; however, evaluable tissue was available for only 3 of the 11 patients. The baseline samples are germane to the determination of the treatment effect because the Week 180 biopsies showed only a small quantity of dystrophin (mean = 0.93% of normal). Thus, for the purpose of computing the *change* in dystrophin resulting from eteplirsen treatment, even small differences in the baseline level are critical.

As noted by Dr. Woodcock, the review team and I had concerns about these controls, leading us to conclude that Study 201/202 was not adequate and well controlled:

1. The goal was to assess the change in dystrophin with treatment, i.e., pre-treatment vs. post-treatment, but most of the baseline biopsies were obtained from subjects external to Study 201/202, who could differ in unknown ways from subjects in Study 201/202.
2. For all patients, the Week 180 biopsies were obtained from different muscles than the baseline biopsies, and studies of both normal human muscle and non-clinical DMD models have shown that dystrophin levels vary among muscles.
3. The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline, accordingly.

Dr. Woodcock believes that "...these issues increase the uncertainty around the results, but do not necessarily render them an inadequate basis on which to draw a conclusion." She notes that the external control patients were similar in age and mutation site to the patients in Study 201/202. She found little difference between dystrophin results across different muscle groups, and little difference based on storage time, leading her to believe that these factors "...did not result in large differences in the findings."

Although I agree that these factors are not likely to lead to large differences, even small differences would affect the calculation of the *change* in dystrophin at Week 180, because the Week 180 values were quite small (mean only 0.93% of normal). At issue is how much of the dystrophin detected at Week 180 was newly produced, vs present at baseline. For example, a difference in the baseline level of only 0.30%, although minute, is substantial compared to 0.93%.

Dr. Woodcock notes that at Week 180, 2 subjects had dystrophin levels between 2 and 3%, 2 had a level between 1 and 2%, and 2 had a level of ~1%. She notes that 2 of these subjects had both baseline and Week 180 samples, and there were clear increases in dystrophin in these 2 patients. Of note, Dr. Woodcock points out that although some subjects had Week 180 dystrophin levels similar to the baseline (i.e., close to zero), she would expect this because she would not predict that all individuals would respond to a drug intervention.

She explains that the issue "...is whether the dystrophin levels found at 180 weeks were within the variability expected for this assay in such patients and, thus, could have arisen by chance, or whether they could have been caused by differences from the controls or from sample

storage as outlined above, or whether they reflected a drug effect, and, thus, whether these data could be seen as adequate and well-controlled.”

In the end, taking Dr. Woodcock’s arguments into consideration, my view is that the data from Study 202 are *suggestive* of an increase in dystrophin in response to eteplirsen, but the study was not adequate and well controlled. If we accept that there *is* a difference, Study 202 does not reliably speak to the *amount* of dystrophin produced by eteplirsen, given the concerns above. There is only certainty that the largest *possible* amount was 0.93% of normal (on average), and <3% in any individual (if we assume that the quantity was zero at baseline).

Below I will present another concern that leads me to question the veracity of the Western blot data from the Week 180 biopsies from Study 202, based on an issue that Dr. Woodcock did not address in her memo.

c) Study 301:

With the May 26, 2016 goal date approaching, OND and CDER could not reach agreement on the regulatory action for this NDA. In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in an ongoing study (Study 301, PROMOVI). These samples were originally planned to be analyzed at the end of the study; however, we requested an interim analyses of a subset of samples. Western blot analyses were performed on paired biceps samples from 13 of the patients. For each of these patients, samples obtained at baseline (prior to treatment) were compared to those obtained at Week 48, after 48 weekly infusions of eteplirsen 30 mg/kg.

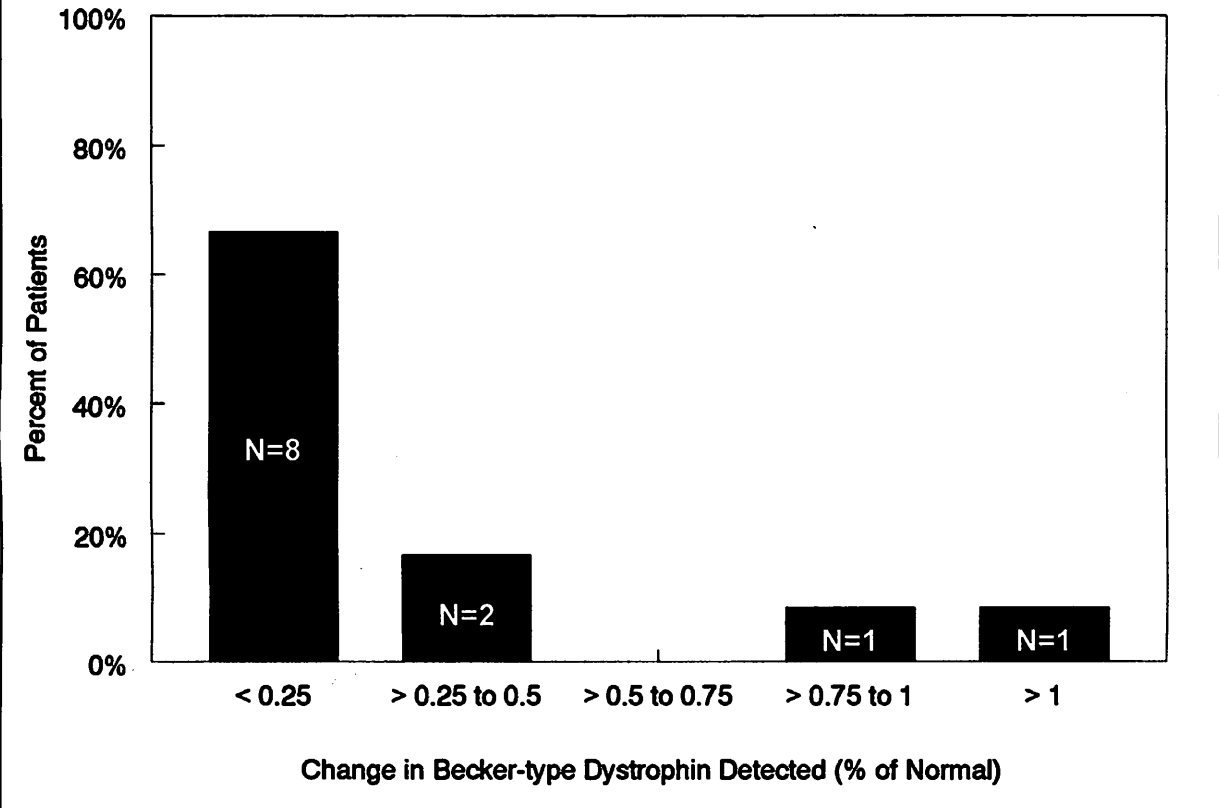
The data are shown in Table 1 and the distribution of these changes is shown graphically in Figure 1. Of these 12 patients, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a change greater than 1%. The applicant used 3 methods to consider the numerous values below the limit of quantification, but irrespective of the method used, the mean treatment effect was similar, ranging from 0.22% to 0.32% of normal, a change of approximately 2 to 3 parts per thousand that was nevertheless statistically significant.

Patient	Time	status	value (%)	mean (%)	delta (%)	Patient	Time	status	value (%)	mean (%)	delta (%)
1	Baseline	pass	0.15	0.13	0.13	8	Baseline	fail	0.08		
		pass	0.11					fail	0.14		
	Week 48	pass	0.22	0.26			fail	0.08			
		pass	0.29					fail	0.05		
2	Baseline	pass	0.35	0.35	0.01	9	Baseline	fail	0.14	0.24	1.33
		fail	0.26					pass	0.24		
	Week 48	pass	0.36	0.36			fail	1.17			
		fail	0.12					pass	1.57		
3	Baseline	pass	0.06	0.06	0.31	10	Baseline	pass	0.11	0.11	0.01
		pass	0.06					fail	0.05		
	Week 48	pass	0.5	0.37			pass	0.12			
		pass	0.24					fail	0.11		
4	Baseline	pass	0.04	0.04	0.06	11	Baseline	pass	0.01	0.05	0.43
		fail	0.06					pass	0.08		
	Week 48	pass	0.1	0.1			pass	0.31			
		fail	0.19					pass	0.63		
5	Baseline	fail	0.1	0.17	0.85	12	Baseline	pass	0.02	0.02	0.07
		pass	0.17					fail	0		
	Week 48	fail	0.92	1.02			pass	0.09			
		pass	1.02					fail	0.01		
6	Baseline	pass	0.37	0.37	-0.07	13	Baseline	fail	0.34	0.18	0.03
		fail	0.46					pass	0.18		
	Week 48	pass	0.3	0.3			fail	0.34			
		fail	0.29					pass	0.21		
7	Baseline	fail	0.04	0.17	0.25						
		pass	0.17								
	Week 48	fail	0.22	0.42							
		pass	0.42								

All parties agree that these data were obtained from an adequate and well controlled study, and that there is a statistically significant effect of eteplirsen. The disagreement is whether or not the dystrophin production is at a meaningful level that is reasonably likely to predict clinical benefit.

To the extent that one can compare results across studies, these changes in dystrophin are even lower than the values obtained from Study 201/202 (the latter represent the quantity detected at Week 180, not the treatment effect). Dr. Woodcock wrote that "Only 2 of 12 patients achieved a level over 1% of normal control." Her characterization refers to the amount of protein detected at Week 48, not the change in protein. In fact, only a single patient out of 12 had a treatment effect that exceeded 1%.

Figure 1: Study 301: Distribution of Changes in Becker-type Dystrophin in 12 Patients



3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

Study 201/202 – Data through Week 48

Dystrophin production was assessed in Study 201 using immunohistochemistry, a standard laboratory procedure used primarily to localize proteins in tissue sections, but also used as a semi-quantitative method to measure dystrophin levels. Muscle samples were analyzed at baseline, and at Weeks 12, 24, and 48.

Dr. Woodcock notes “A finding of increased dystrophin was also seen in several IHC assays performed by the applicant.” She explains that several baseline and other pre-Week 180 assays were performed (from Study 201/202), but the validity of the results was questioned at the FDA inspection because of methodological issues, and so she does not consider these data further.

I do not agree with Dr. Woodcock’s outright rejection of these data. In fact, FDA requested a re-reading of the stored images by 3 masked pathologists under improved viewing conditions. We did not request any changes in immunohistochemistry methods or techniques, other than a different approach for selecting microscopic fields for image capture and analysis. Thus, we stressed that their stored images could provide useful data if properly read. The re-read

I thought it showed zero
~ 12% vs ~ 12%

showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group. (The p -value is nominal because the type-I error rate was not controlled for multiplicity.) Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.

? no data

Study 201/202 – Week 180 Data

The applicant performed immunostaining along with Western blot analyses from the skeletal muscle biopsies obtained at Week 180.

Importantly, prior to performing these analyses, the applicant made changes to the immunohistochemistry protocol with the intent of decreasing non-specific staining. Dr. Woodcock details the technical factors in her memo. Their aim was to determine the treatment effect for each patient, by comparing dystrophin levels at baseline and Week 180. Frozen archived baseline tissue was available for only 3 of the patients, however, and so the applicant supplemented these samples with muscle tissue from 6 untreated external DMD patients, together to be compared to the Week 180 levels. Images were read by the same 3 pathologists, masked to treatment group.

not really

Because external controls were used, the comparison of pre- vs. post-treatment values suffers from the same problems described for the Western blot analyses (i.e., different patients, different muscles, and possible loss of immunoreactive dystrophin with long-term storage).

These concerns notwithstanding, the applicant claimed a remarkable increase in dystrophin immunostaining at Week 180: the 9 baseline samples (from 3 patients in Study 201/202 and 6 external controls) showed $1.1\% \pm 1.3\%$ positive fibers (mean $\pm$ SD), whereas the Week 180 samples (from 11 patients in Study 201/202) showed $17.4\% \pm 10.0\%$ positive fibers. I will note that FDA made no attempt to inspect or oversee these analyses.

but these are totally different from previous 12-13%

Given that the original analysis showed, at baseline, 13% positive fibers for patients in Study 201/202, it is important to understand why the results from a new immunostaining protocol provided results of 1.1%, an order of magnitude lower.

sylo

As noted above, there were 3 patients in Study 201/202 with adequate archived tissue from baseline, which permitted a new immunohistochemistry analysis and a comparison of results between the old and new methods. Figure 2 shows how the two methods compare.

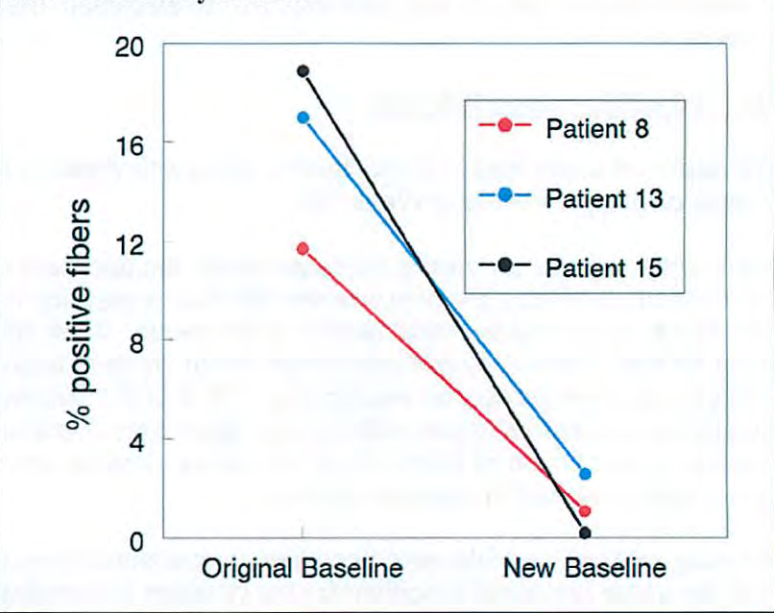
These are essentially replicate analyses of a single tissue sample using the two immunohistochemistry methods. There is an inexplicable difference of more than an order of magnitude between results of the old and new immunohistochemistry protocols. Such marked differences raise concerns with respect to the validity of the applicant's methods, and make interpretation impossible.

yes

The disparity also underscores the difficulty of comparing results of immunohistochemical analyses for dystrophin across laboratories, or, for that matter, within the same laboratory.

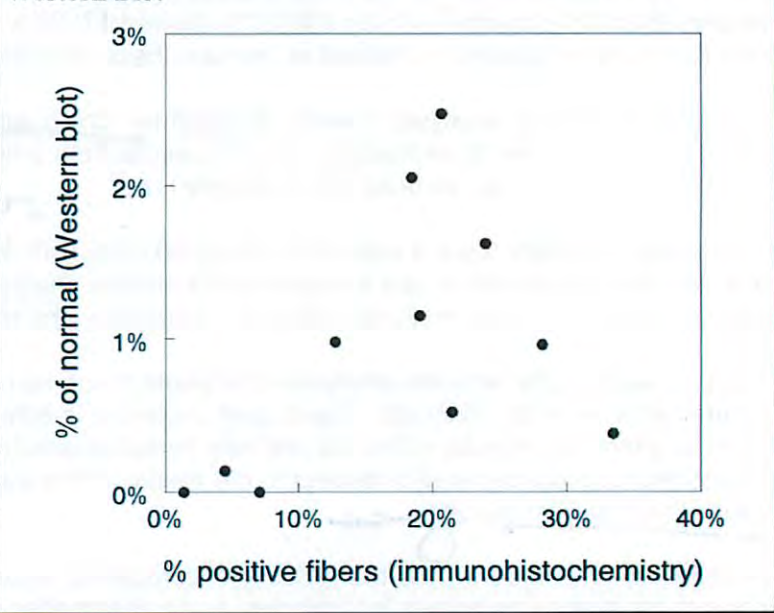
The integrity of the applicant's data is further called into question by lack of agreement between the immunohistochemistry and Western blot methods, i.e., a lack of internal consistency. The applicant claims to have enhanced both the immunohistochemistry methods and the Western blot methods in preparation for processing the Week 180 biopsies. Following these methodological improvements, single tissue blocks were subjected to both analyses – analyses considered to be complementary. Yet the lack of concordance between these two assessments of dystrophin levels is striking (Figure 3).

Figure 2: Comparison of Results from the New and Old Immunohistochemistry Protocols – Lack of Agreement for 3 Patients in Study 201/202



It is simply not possible to determine whether the immunohistochemistry methods are inaccurate, the Western blot methods are inaccurate, or both methods are inaccurate. In light of the discordance between methods, the issues with the control samples, and the order-of-magnitude discrepancy between the old and new immunohistochemistry protocols, these data provide little confidence that the study was designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation” (§314.126).

Figure 3: Study 201/202 Week 180 Dystrophin Assessment – Lack of Agreement between Immunohistochemistry and Western Blot



A critical point is that results of immunohistochemistry analyses are method-dependent, and results from different laboratories are not directly comparable. Here we see a striking difference between results of different methods within a single laboratory.

Dr. Woodcock concluded "Although the IHC assays provide only semi-quantitative assessments of dystrophin content, they do support an effect of eteplirsen on the proposed surrogate endpoint (an increase of dystrophin production as a result of drug exposure)."

Although this statement does not constitute an important part of her argument in favor of dystrophin production, I do not agree that the immunohistochemistry data show an increase in dystrophin as a result of drug exposure. Given that changes in the immunohistochemistry protocol led to remarkably disparate results, and in light of the lack of correlation between dystrophin results as determined by immunohistochemistry and Western blot, I question the accuracy and interpretability of the Week 180 immunohistochemistry data. Moreover, the results from the properly blinded re-reading of the original data through the first 48 weeks of Study 201/202 are negative. I do agree, however, that the immunohistochemistry images appear to show dystrophin in the proper location, which helps support proof-of-concept.

In summary, I agree that there are data on dystrophin production from one adequate and well controlled study, Study 301, by Western blot. The amount of dystrophin produced and the likelihood of a clinical effect are discussed below.

B. Is the Effect on the Surrogate Endpoint "Reasonably Likely to Predict Clinical Benefit?"

As noted by Dr. Woodcock, "The usual way to address this question would be to rigorously evaluate what is known about the correlation between dystrophin levels in muscle and expression of disease."

Without restating the details of Dr. Woodcock's discussion, I generally agree with her basic summary of the many challenges of interpretation (quoted below). Most of her discussion speaks to the *uncertainties* inherent in correlating dystrophin levels with disease severity. I strongly agree that we lack a sound basis upon which to relate dystrophin levels observed in this development program to observations in the literature.

"1. The clinical classification of disease severity (i.e., phenotype) in the literature appears broad, variable, and somewhat subjective."

I agree. And importantly, as Dr. Woodcock notes, "the zone of real interest for this discussion, between DMD and intermediate presentations, is not rigorously categorized."

"2. Much of the prior data reporting the relationship of dystrophin protein levels to phenotype have been from immunohistochemistry studies using a variety of techniques and antibodies."

I will add that the applicant's own data show a striking difference between results of two somewhat different immunohistochemistry protocols conducted at the same laboratory (Figure 2). Thus, it would be treacherous to try to relate various levels of dystrophin, determined by immunohistochemical methods at various laboratories, to a particular clinical course.

“3. Both IHC analyses and WB results are influenced by the anti-dystrophin antibodies used, as well as other experimental conditions”

Agree. Thus, is not feasible to relate levels of dystrophin determined by older Western blot methods, which lacked, for example, appropriate internal controls, to levels of dystrophin reported in these eteplirsen studies.

“4. The phenotype is significantly influenced by dystrophin isoform quality as well as dystrophin quantity.”

Agree. It is difficult to predict a protein's function from its structure; even small changes in dystrophin structure can be important.

“5. The literature contains various findings on the relationship of dystrophin expression to clinical status, including the low levels of dystrophin protein of interest in this case.”

Agree. There is little consensus on the relationship between dystrophin expression and clinical course at the low levels observed in eteplirsen-treated patients.

I also agree with Dr. Woodcock on the following points, and I paraphrase here:

- Dystrophin levels >10% on Western blot are usually associated with a BMD phenotype. Within the BMD phenotype, the relation between disease severity and protein expression is not clear. Protein quality, rather than quantity, may play a key role in determining phenotype in BMD.
- Patients with DMD are usually found to have undetectable levels of dystrophin, or very low levels. Dr. Woodcock notes that she believes the conventional threshold of <10% protein resulting in DMD was based on immunohistochemistry data. She tries to make a conversion between values observed from immunohistochemistry (~10% points higher on immunohistochemistry than Western blot in DMD) and those observed from Western blot, but I caution that immunohistochemistry results, in particular, are highly method-dependent, as noted above.
- Rarely, dystrophin levels in the 3 to 10% range have been associated with Becker Muscular Dystrophy phenotypes. Dr. Woodcock found no evidence of a threshold value for protein content and expression of a DMD phenotype.

Despite the absence of reliable data, Dr. Woodcock concluded that evidence from Western blot and other experiments shows that protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, all other things being equal, i.e., mutation status and non-dystrophin-related factors affecting phenotype.

Because of the lack of reliable evidence, I do not agree that the small increase in dystrophin shown in Study 301 is 'reasonably likely' to predict clinical benefit. This is the central issue in this appeal.

The “reasonably likely” question hinges on whether the protein is functional, and whether the quantity is adequate.

These two uncertainties, protein function and protein quantity, are separate issues that must be considered in series. The function of the Becker-type dystrophin detected in Study 301 cannot be assessed. Nevertheless, the review team has been willing to assume that whatever Becker-type dystrophin is produced would function as well as it does in the Becker form of the disease. Although there can be no certainty on this point, the question of function seems small relative to the uncertainty regarding the adequacy of the quantity of protein, and so function is less germane to the question of "reasonably likely." In short, it is the quantity of Becker-type dystrophin produced that is central to the question of 'reasonably likely,' and central to the approvability of this NDA under accelerated approval.

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At the outset, it must be stated that the minimum quantity of Becker-type dystrophin that is reasonably likely to predict clinical benefit in patients with DMD is unknown.

There are two ways to consider the quantity of dystrophin produced: as a binary responder analysis and as a mean response. The former has the advantage of considering the possibility that some patients may respond to the treatment whereas others do not; the latter does not allow for this type of consideration.

The problem with a responder analysis is that there are no data upon which to define a threshold for a 'response.' Various cut-points could be selected, but their selection would be arbitrary, and the particular threshold chosen would have a major influence on the effect size.

Here I provide 3 lines of reasoning to support my view that there is not an adequate basis to believe that the small increase in dystrophin shown in Study 301 is reasonably likely to predict clinical benefit: 1) the treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications; 2) the effect size is inadequate on its face; and 3) no evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.

- 1) *The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications.*

In order to place these small quantities of Becker-type dystrophin into a clinical perspective, many have considered publications from laboratories that attempt to relate particular levels of Becker-type dystrophin protein to clinical course, e.g., maintenance of physical function, age at loss of ambulation. Ideally, as suggested by Dr. Woodcock, there would be reliable data showing that Becker-type dystrophin levels in excess of a particular level are associated with a more benign clinical course.

Realistically however, the use of such a framework would be contingent on the ability to make interpretable cross-laboratory comparisons of dystrophin levels, which would require standardized methods to measure dystrophin levels in muscle specimens. Unfortunately, the methods have differed greatly, and the methods in the literature have lacked critical internal controls such as dilution-series. As stressed above, comparison of dystrophin values across laboratories seems unreliable.

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With respect to immunohistochemistry analyses, Figure 2 provides ample basis for concern regarding comparability of results using different methods. Results of separate immunohistochemical analyses of skeletal muscle dystrophin, conducted by the same laboratory on single blocks of tissue, differ by more than an order of magnitude. These results underscore the inherent methodological variability of immunohistochemistry assays, and the futility of attempting to compare dystrophin levels across assays/laboratories.

Even with respect to more recent Western blot methods, reproducibility across laboratories is low. As discussed by Dr. Woodcock, Anthony K *et al* (*Neurology* 2014;83;2062) compared results of Western blot analyses from 6 patients (3 with DMD; 3 with Becker Muscular Dystrophy) across 5 experienced laboratories, and found a high degree of variability. Only one of the 5 laboratories had a coefficient of variation (CV = SD/mean X 100) below 0.3%. The authors found that variability was particularly pronounced with low levels of dystrophin – precisely the area of interest here.

During the applicants' presentation at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Dr. Kaye, a pediatric neurologist and interim Chief Executive Officer of Sarepta, could not have been more clear in warning us not to make comparisons between their Western blot results and reported data in the literature:

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation. Furthermore, samples were randomized, blinded and run in duplicate on separate gels. In contrast, the Western blot methods in the majority of historical publications referenced by FDA were performed using older methodology that is semi-quantitative at best. Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: Official transcript of the meeting; underlining for emphasis.)

In summary, the field has not achieved adequate standardization of methods for dystrophin quantification at the very low levels observed in eteplirsen-treated patients; therefore, it is not valid to compare an increase in Becker-type dystrophin of, at best, 2 to 3%, with dystrophin values cited in the literature for other mutations/patient populations, assessed at other laboratories. *If the applicant's results cannot be compared to results in historical publications, then there is simply no way to determine whether the low dystrophin levels in eteplirsen-treated patients are reasonably likely to predict clinical benefit.*

2) *The effect size is inadequate on its face.*

If one were to assume that it is possible to make cross-laboratory comparisons of dystrophin levels, the *largest* change reliably demonstrated in Study 301, 1.3%, is an order of magnitude less than the minimum dystrophin levels cited to be important in affecting the course of patients with Becker muscular dystrophy (at least 10%).

Some of the better data come from Van den Bergen *et al*, who studied the relation between dystrophin levels (quantified by Western blot) and clinical severity in 33 patients with Becker Muscular Dystrophy (*J Neurol Neurosurg Psychiatry* 2014; 85:747). Although the authors did not find a linear relationship between dystrophin levels and disease severity, all 4 of their

good
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patients with dystrophin levels <10% showed poor muscle strength and early symptom onset. As discussed by the review team, DMD experts have proposed that "induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit."

Initially, the applicant reported results from immunohistochemistry analyses purportedly demonstrating that eteplirsen caused 50 to 60% positive staining of muscle fibers for dystrophin. This seemingly unprecedented achievement aroused much excitement in the field of DMD research and in the DMD patient community. Upon proper re-analysis, however, the numbers were far lower, and rigorous statistical analyses showed that the changes weren't statistically significant. The Western blot analysis from Study 201/202 showed a mean dystrophin level of only 0.93% (range 0 to 2.5%), but these values are of questionable reliability. Finally, an adequate and well controlled study (Study 301) showed a mean change of 3-tenths of a percent (range 0 to 1.3%). Given that dystrophin is a structural protein, it seems highly unlikely that such changes would translate to a clinical effect.

Here are Dr. Woodcock's assertions on this topic:

"The broad phenotypic distinctions made in the clinic (e.g., DMD vs IMD vs BMD) are different from the prediction of benefit to an individual patient who has a specific baseline dystrophin level and whose mutation and external factors do not change pre- and post-drug. For example, extending ambulation by six months to a year would not normally move a patient from one to another of these categories, but could be very important to quality of life (e.g., as suggested in the Bello study). This is also true for other functional improvements.

For these reasons, incorporating the analysis of dystrophin content discussed above, I conclude that the biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit."

I agree that broad phenotypic distinctions made in the clinic (e.g., Duchenne vs. Intermediate vs Becker Muscular Dystrophy) are different than trying to predict benefit to an individual patient on the basis of a particular change in dystrophin. And I agree that extending ambulation by 6 months to a year (or similar improvements in other functional areas) would be extraordinarily important.

But Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that "...low-level increases in dystrophin production are reasonably likely to predict clinical benefit." She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit.

3) *No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.*

Dr. Woodcock states:

"Additional support for "reasonably likely" comes from the long-term experience with the drug. The sponsor's comparison of the experience of the treated cohort to natural history data does not reach the level of substantiation required for traditional approval

Insured
201 data
skewed
huge ↑ in
western
blot

based on the clinical data. However, it is highly suggestive of improvement in some parameters, in some patients, over natural history. My conclusion is informed by all the caveats expressed in the reviews about the pitfalls of nonrandomized comparisons. Given that the two exon 52 deletion patients in the study had fairly good long-term results in terms of rate of disease progression, the question arises as to whether exon 52 is a prognostic factor that could have skewed the results.”

The review team analyzed the clinical data in great detail, and could not reach the conclusion that there was any reliable evidence of improvement relative to the expected natural history of the disease. Study 201 did not show a treatment effect on its 1° clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients (see my review memorandum for more details).

The Advisory Committee voted (7 to 3 with 3 abstentions) that the clinical results of Study 201/202 did not provide substantial evidence that eteplirsen is effective for the treatment of DMD, and their vote was in the face of extraordinary pressure from patients and patient advocates to vote for approval. Two of the 3 “yes” votes were from patient representatives.

Correlation between dystrophin production and clinical effect

A correlation between dystrophin production (or with less certainty – dystrophin *detected*) and clinical function could provide some support for a conclusion that dystrophin production is reasonably likely to predict clinical benefit.

The applicant collected data on both dystrophin production and physical performance in Study 201/202. On the basis of the data presented in the NDA, the Division concluded that no patient in Study 201/202 clearly deviated from the natural history of the disease. The Division reasoned, therefore, that whatever the quantity of Becker-type dystrophin detected, it did not predict clinical benefit. Thus the Division opined that the clinical data weaken, and do not strengthen, the “reasonably likely” argument.

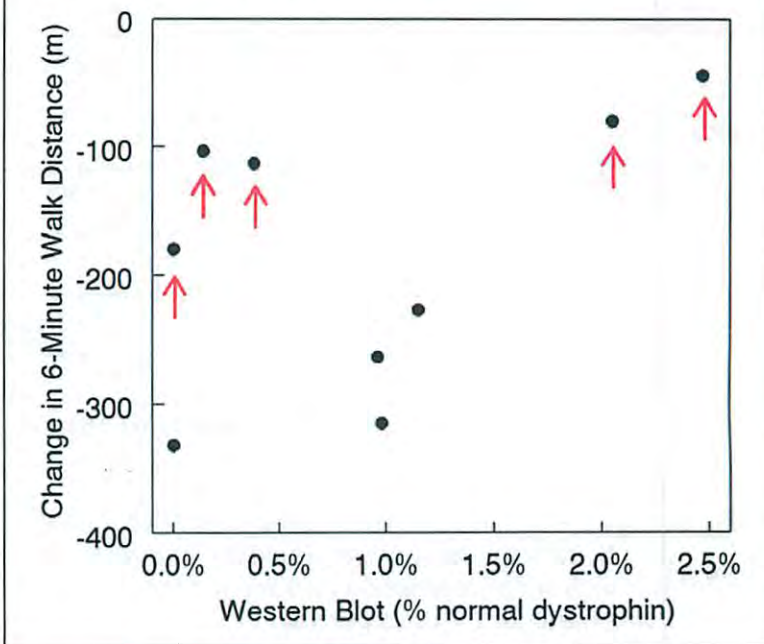
The Division's view notwithstanding, it is worth considering patients on an individual basis to assess the correlation between the quantity of Becker-type dystrophin detected and changes in physical performance.

As noted by Dr. Woodcock, the 6-minute walk test results do not show a strong correlation (Figure 4). For the 9 patients in Study 201/202 who remained ambulatory at Week 180 and agreed to undergo a fourth muscle biopsy, the figure shows little correlation between the quantity of dystrophin detected (x-axis) and preservation of physical function as assessed by the change in 6-minute walk distance from baseline (y-axis) after weekly infusions of eteplirsen for 3 to 3.5 years.

For the 5 patients whose 6-minute walk performance was best preserved (red arrows), 2 had the highest dystrophin levels detected in the study (upper right), but 3 had levels that were near-zero (upper left).

Dr. Woodcock also evaluated the North Star Ambulatory Assessment (NSAA) as a function of dystrophin detected in boys who could still walk and who had a dystrophin result at Week 180. She obtained the data from the applicant's briefing document for the Advisory Committee meeting, and found a correlation between dystrophin detected at Week 180 by Western blot and rate of decline in NSAA score through 180 weeks. Her graph is reproduced below:

Figure 4: Study 201/202 – Lack of Correlation between Quantity of Dystrophin Detected and Preservation of Physical Function (6-Minute Walk Distance)



With respect to the correlation, Dr. Woodcock explained: "This adds additional support to the idea that dystrophin production is "reasonably likely to predict clinical benefit."

Given that the correlation was driven by the patient depicted at the lower right (blue arrow; dystrophin level =

~2.5%; change in NSAA = 3), I considered the NSAA data from that patient (Figure 6). I found that his course was less benign than would be inferred from a change in NSAA of only 3 units. Specifically, using linear regression (red line in Figure 6), his NSAA score has, instead, worsened by a mean of 2.7 units per year.

I reasoned that inclusion of all of the NSAA data for each patient would provide a more reliable representation of their course than calculating the change between single pre-treatment and post-treatment data points, because of the test-to-test variability (e.g., short-term swings of 4 to 5 points for patient 006). Thus, using linear regression, I calculated the slope of the relationship between NSAA and time for each patient (as per the red line in Figure 6) and plotted the slopes as a function of the dystrophin detected at Week 180. (Slopes were calculated as loss of NSAA units per year.)

Using this method, there was no correlation ($R^2 = 0.36$), Figure 7. Importantly, the slight trend apparent here is driven by one or two data points.

Figure 5: Study 201/202: Analysis of Change in NSAA vs. Expression of Becker-type Dystrophin by Western Blot (Analysis by Dr. Woodcock)

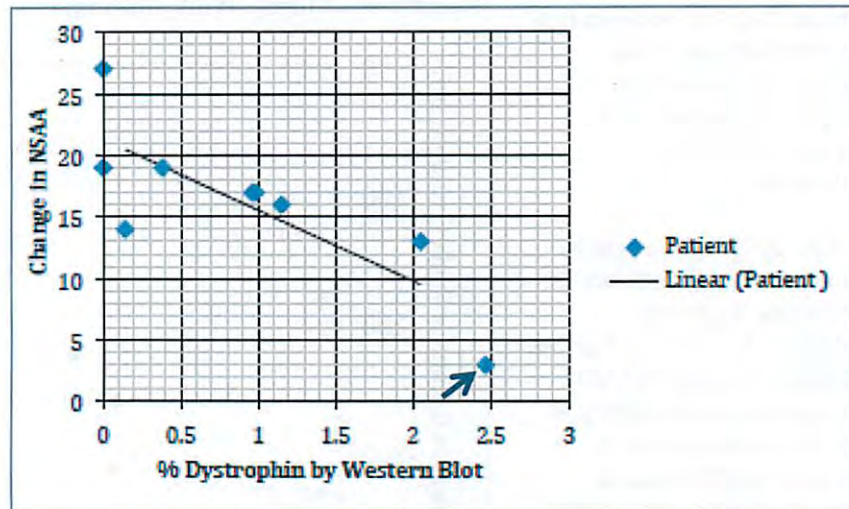
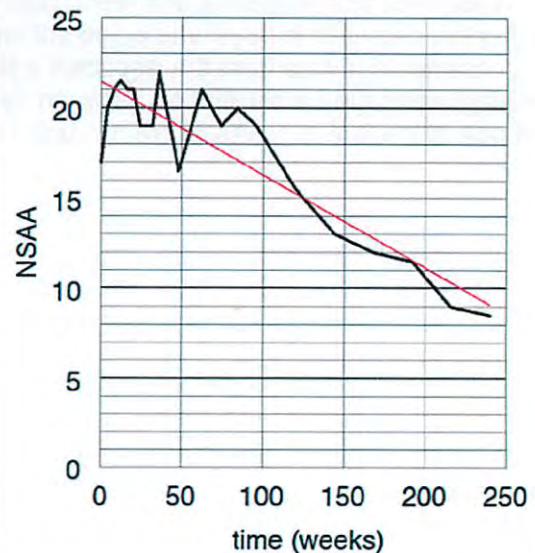


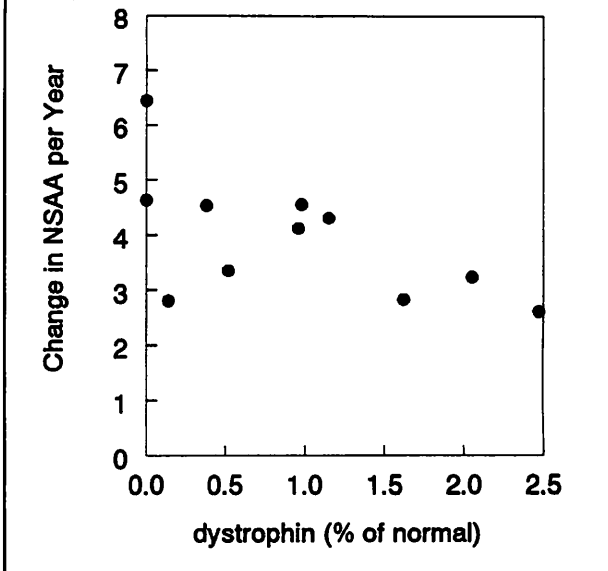
Figure 6: Patient 006: NSAA vs Time



Summary:

In summary, I find no evidence that the increase in dystrophin demonstrated in Study 301 is reasonably likely to predict clinical benefit (mean 0.3%, range 0 to 1.3%). The levels of dystrophin linked to various Becker Muscular Dystrophy phenotypes in publications are largely not comparable to dystrophin levels measured in this development program. The applicant's interim CEO correctly urged us not to compare data from their Western blot analyses to historical approximations from the literature. And extremely low levels of dystrophin, as found here, seem particularly difficult to quantify and compare across laboratories. Nevertheless, to the degree that findings can be compared across studies, dystrophin levels of 10% or more would need to be achieved to impact the clinical course. The finding in Study 301 is an order of magnitude below this level.

Figure 7: Study 201/202: Analysis of Change in NSAA (Linear Regression) vs. Expression of Becker-type Dystrophin by Western Blot (My Analysis)



Based on protein levels in other deficiency diseases, the effect size here appears to be too small to provide benefit. If dystrophin were an enzyme that catalyzed a biochemical reaction in myocytes, one might posit that a very small quantity could produce a substantial proportion of the minimum necessary reaction product, and that the increase over baseline might be important because levels are so low in untreated patients. But given that dystrophin is a structural support protein that helps prevent myocyte injury due to stress and strain, I find it difficult to conceive how a treatment effect of 3 parts per thousand could confer clinical benefit. If there were 10 inches of snow on a sidewalk that needed to be cleared, 3 parts per thousand would amount to 1/32nd of an inch. We must also recognize that a treatment that increases dystrophin by 0.3% would seemingly have far less impact than being born with 0.3% more dystrophin, and even *that* seems unlikely to matter.

I can find no precedent of an accelerated approval for a marketing application where the effect size on the surrogate endpoint is as small as 0.3%.

Dr. Woodcock concludes:

"...my conclusion to rely on the surrogate endpoint described above represents the greatest flexibility possible for FDA while remaining within its statutory framework. In this case, the flexibility is warranted because of several specific factors, including: the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a fatal disease in children. Of note, the therapy has been relatively safe in the clinic, although intravenous administration always carries risk.... Therefore, I find that the

probable benefits outweigh the foreseeable risks and that this application should be approved under 21 CFR 314.510.”

As noted in 506(f)(1), the amendments made by the Food and Drug Administration Safety and Innovation Act (FDASIA) “...are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs.”

Some have interpreted this “flexibility” as a lower standard for demonstration of effectiveness, but this is not true.

Section 506(f)(2) of the FD&C Act specifically notes that drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval, notably the substantial evidence standard of section 505(d) with respect to the drug’s claimed effect on a surrogate or intermediate endpoint. These facts have not been altered by FDASIA.

To be clear, 506(f)(2) states: “Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act or under section 351(a) of the Public Health Service Act. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B).”

I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients *could* benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.

Finally, there was no clinical benefit demonstrated in the development program, and the correlation between dystrophin and clinical effect was poor – not surprising given that the applicant provided analyzable data from only 11 patients.

3. Assessment of Possible Impact to Public Health Should My Position Not be Adopted

The approval of this NDA in its present form would have far reaching negative consequences for the public health.

1. Eteplirsen’s risks are certain, whereas its efficacy is not. Having considered Dr. Woodcock’s line of reasoning and her desire to approve eteplirsen, the position of the review team in the Division of Neurology Products, the Office of Biometrics, the Office of Clinical Pharmacology, the Office of Drug Evaluation-I, and the Office of New Drugs (verbal acknowledgement from Dr. John Jenkins) is that the applicant has not provided evidence that this drug is effective at the dose studied.

Dr. Woodcock notes that "...the therapy has been relatively safe in the clinic."

The reality is that only a few dozen patients have been exposed to the drug, such that the safety profile is not well characterized. A closely related drug being studied under a (b) (4). With additional experience, important toxicity may emerge for eteplirsen. It is known that many patients in these studies are now receiving infusions through indwelling catheters. Maintenance of vascular access in patients on chronic corticosteroids poses a certain risk of infections. Although we are not yet aware of any infection-related adverse reactions, there would definitely be serious infections and possibly deaths if this drug is marketed, yet evidence of efficacy is lacking.

2. By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk. I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs – if not to patients, to society.

The prospect of providing false hope to desperate patients from a promising but ineffective therapy recalls the experience with *transmyocardial laser revascularization* (TMLR). In the 1990s, patients with coronary atherosclerosis and severe angina who were poor candidates for conventional revascularization procedures ("no-option" patients) underwent a thoracotomy (opening of the chest cavity) to enable use of a laser to create channels through the heart muscle. Ostensibly, these channels provided conduits for blood to flow from inside the left ventricle to the myocardium. Conduct of sham-controlled studies was impossible; studies were essentially baseline-controlled or historically-controlled. Large treatment effects were reported by a number of investigators, generally from small studies. There were marked increases in treadmill exercise time and relief of angina, with effects sustained for more than a year in some cases. Although many in the cardiology community raised concerns about expectation bias and were highly skeptical of the results, to some the effects seemed larger and more durable than could possibly be explained by expectation bias, i.e., a placebo effect. Thousands of patients underwent this invasive procedure with the hope of angina relief. Some years later, with improvements in technology, the conduct of sham-controlled studies became feasible, and TMLR was not found to be effective. The false hope was ultimately dispelled with the publication of two Cochrane Reviews.³ These reviews found the appearance of a marked treatment effect, but 30-day mortality was 6.8% in the TMLR group vs. 0.8% in the no-treatment group. They noted "The assessment of subjective outcomes, such as improvement in angina, was affected by a high risk of bias and this may explain the differences found." In this case, the cost of false hope was ~6% mortality in the first 30 days post-op.

I will also note that the primary endpoint of these laser studies was generally exercise capacity – the same type of endpoint used in the eteplirsen DMD development program, also for "no option" patients.

3. The accelerated approval pathway is designed to expedite the availability of promising new therapies to patients with serious conditions, especially when there are no satisfactory

³ Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD003712. DOI: 10.1002/14651858.CD003712.pub3

alternative therapies, while preserving standards for safety and effectiveness. For drugs granted accelerated approval, postmarketing confirmatory trials are required to verify and describe the anticipated clinical benefit, and FDA may withdraw approval of a drug if a trial required for verification of the predicted clinical benefit fails.

In reality, it is difficult to withdraw a drug that is deemed to be effective, or possibly effective, by patients with severe diseases and limited treatment options. FDA has not succeeded in withdrawing the marketing of a single drug for lack of verification of clinical benefit following accelerated approval. The reality is that if eteplirsen is given accelerated approval, it is highly likely to remain on the market indefinitely, irrespective of whether or not efficacy is verified.

Inessa

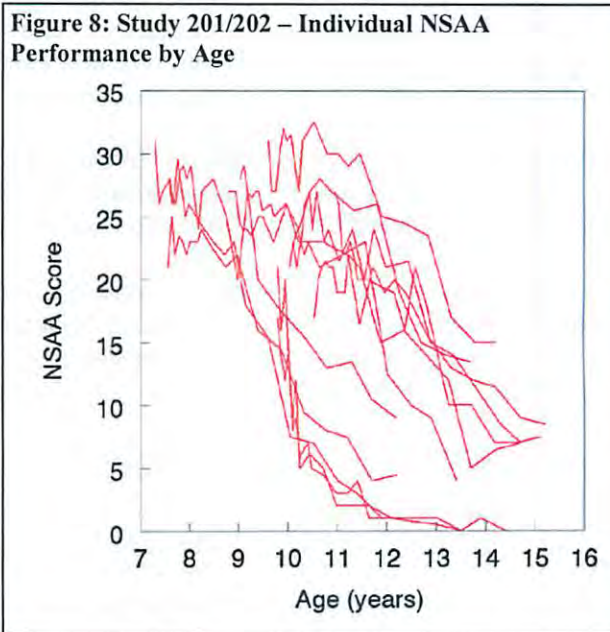
4. With the false perception that eteplirsen is effective, patients who are gaining benefit from steroids but experiencing untoward side effects might be inclined to taper or stop them, which could lead to more rapid disease progression.
5. False scientific conclusions have the potential to mislead the field of medicine, slowing progress in finding and developing therapies that actually *are* effective. For example, consider the scenario of a related drug with far greater potential to promote dystrophin production in patients with DMD. In order for a sponsor to study such a drug, patients would likely have to agree to discontinue eteplirsen, and few patients may be willing to do so. In short, approval of an ineffective therapy has the potential to discourage or inhibit the development of other drugs that *are* effective, and this impact can be significant.
6. Accelerated approval would lower the evidentiary standard for effectiveness to an unprecedented nadir. The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change of 0.3% – a mere 3 parts out of a thousand – is considered adequate to support accelerated approval here, then the question arises as to whether there would be any statistically significant change that would be too small to be considered “reasonably likely” to support accelerated approval. Similarly, if a ‘responder’ had been defined as a patient with an increase in dystrophin of $\geq 1\%$ (and there is no basis to accept such a low threshold), there would have been only a single responder in Study 301. If we were to adopt the concept that, for rare diseases, accelerated approval could be supported by any statistically significant change in an appropriate surrogate, or a response in a single patient, we would enable accelerated approval of a myriad of drugs for rare diseases. No doubt there are some who would applaud this as an advance. But a standard this low would undercut FDA’s ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.
7. With accelerated approval of this NDA, there would be highly detrimental effects on drug development. Traditional drug development for rare diseases might be replaced by a system where small, baseline-controlled, proof-of-concept studies designed to show any change in a surrogate marker would provide a basis for accelerated approval, assuming that the pathogenesis of the disease was well understood and that the surrogate was directly on the causal path. There would be little reason to pursue adequately controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of

Nah
Add on

Yes

failure would provide a disincentive to conduct such trials. For example, a gene therapy designed to produce a missing clotting factor could receive accelerated approval on the basis of a tiny yet inconsequential change in levels of the factor, or a more robust response in a single patient. In short, the precedent set here could lead to the approval of drugs for rare diseases without substantial evidence of effectiveness.

8. Even if the 30 mg/kg/week dose were considered to have a meaningful effect on the surrogate endpoint, we already know this dose is sub-therapeutic. We know this because patients who have been receiving this eteplirsen dose for some 3.5 years have been progressing at a rate that is similar to that expected, based on the natural history of the disease (Figure 8). I question the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic, when the consequence of a sub-therapeutic dose is clinical deterioration and death. The figure shows the unremitting progression in the patients in Study 201/202, based on changes in NSAA.



9. Approval of this NDA would send the signal that political pressure and even intimidation – not science – guides FDA decisions, with extremely negative consequences (See Grainger D., 11/30/15. “DMD Drugs: an existential threat to FDA,” *Forbes*⁴). The public is well aware of this development program: the meager size of the study population, the marginal (at best) effect size, the Division’s dim view of the efficacy data, and the robust activism of some members of the DMD community. Many would be amazed at an approval action, because other DMD drugs, recently turned down for approval, appeared to provide stronger evidence of efficacy.

FDA and Congress were bombarded with correspondence – pleas urging approval of this NDA. More than 50 speakers registered to speak at the April Advisory Committee meeting. I received 2,792 emails urging approval. Here is an example of the body of an email I received last week:

“Dear Dr. califf: How is it that everyone in and around DMD understands this simple Idea and the science geniuses at FDA don't? You stupid f__ _ers are costing each and every DMD kids days of their lives with your Moronic Dystrophin dance. Time to get a

⁴ downloaded 7/18/16 at <http://www.forbes.com/sites/davidgrainger/2015/11/30/dmd-drugs-an-existential-threat-to-the-fda/#5ffc712455f7>

The ramifications here are profound. The public will perceive that it was their unprecedented lobbying efforts that made the difference and earned eteplirsen its accelerated approval. For the future, this will have the effect of strongly encouraging public activism and intimidation as a substitute for data, which is one of the worse possible consequences for communities with rare diseases. This type of activism is not what was envisioned for patient-focused drug development.

4. Detailed Description of the History of the Dispute, Including My Description of the Center SDR Procedures Followed and/or Not Followed, Dates of Meetings, and Decisions Rendered Throughout the Process

The following table shows the dates and main activities for 15 Center Director Briefings associated with the development of this drug: 8 Center Director Briefings took place during the IND phase of development, *prior to submission of the NDA*, and 7 Center Director Briefings took place during review of this NDA.

DATE	MEETING	DETAILS
7/17/2013	Center Director Briefing	Follow up on Action Item from 3/13/13 EOP2 Meeting: Sarepta has submitted a comprehensive discussion of the issues from the EOP2 mtg. To discuss the suitability to file the NDA for Subpart H approval.
10/18/2013	Center Director Briefing	Dr. Unger presented an overview and Dr. Farkas had a slide presentation on drisapersen and eteplirsen data. Discussion: 1. Plan to have a manufacturing facility visit by ONDQA - to observe process and obtain yield calculation. Sponsor is expecting to have 2nd batch in Dec 2013. Determine how much product the sponsor has. 2. OBP: recommended to establish specificity of the antibody and variability of the assay. 3. Next trial - plan to have OSI group to observe the conduct. 4. Need data from the GSK (drisapersen) trial. DNP has previously requested the Phase 3 topline data from GSK, but did not get any response. Dr. Woodcock will initiate an inquiry to the sponsor (raw data). 5. The Agency needs to assist Sarepta (characterize biomarker, CMC facility, observe 6MWT, etc.) 6. 2nd Internal Meeting (Drs. Woodcock, Temple, Jenkins, Unger and Neuro) before the 11/8/13 sponsor meeting. Discuss further what to convey to Sarepta.
10/28/2013	Center Director Briefing (continuation of 10/18/13 meeting)	Suggestions/Recommendations for DNP to Consider: -- We have concluded that we will not ask for biopsy until (we understand the histopathology and are) we're certain what is a quantitative measure and identified the surrogate marker for the study. -- Tell the sponsor that we have changed our view for the quantitative measure of truncated dystrophin as a surrogate PD marker used in their study, because of the recent natural history

		study and failure of the drisapersen trial from GSK. – Dr. Woodcock wants to have a comprehensive literature review to fully understand what's this mean of the deletions, mutations, or duplications in the dystrophin gene, or this exon 51 of dystrophin mRNA ((Office of Translational Science)I believe this task was assigned to a different group). – To ask the Sponsor to provide their production schedule. I believe Dr. Woodcock wants to understand the amount of production and determine if the company can provide the drugs to those DMD patients in the future. – To suggest that the Sponsor consider enrolling patients younger in age (like starting with 5yrs) in their clinical study. – To ask the Sponsor if they could provide drugs for compassionate use to patients (who are very sick or those were in the drisapersen trial previously). – Schedule a T-con with GSK to discuss biomarker data
1/17/2014	Center Director Briefing	Request: Team to present DMD drugs study design to Dr. Woodcock – Path forward for Sarepta (& GSK)
2/6/2014	Center Director Briefing	DMD drugs study design (Discuss Sarepta path forward) Action items: (a) Request biomarker data from the sponsor - done TC on 2/7/14(b) If data interpretable, meet with sponsor for a brainstorming session. Then follow-up with Advice Letter
3/5/2014	Center Director Briefing	Dr. Ash Rao presented biomarker data findings (including Drs. Woodcock, Jenkins, Temple, Unger, Moscicki) Team discussed path forward. Action Item: to invite Sarepta for a brainstorming discussion.
3/19/2014	Sponsor Meeting, with Center Director	brainstorming discussion - study design and path forward Action: Sarepta to submit proposed studies and next steps
4/2/2014	Center Director Briefing	Drs. Woodcock, Moscicki, Temple, Unger Discuss proposal & comments to sponsor ~Advice Letter-include previous meeting discussions ~FDA workshop – biomarker ~Work w/ sponsor on dystrophin biomarker ~Natural history raw data - primary investigators
6/26/2015		SUBMISSION OF NDA
12/9/2015	Center Director Briefing	To brief on the current status of eteplirsen review in advance of the planned Jan 22, 2016 AC meeting. To discuss the application and the plan of action.
1/13/2016	Center Director Briefing	To review the slide presentation and plan of action for eteplirsen, that will be presented during the Advisory Committee Meeting on January 22, 2016 to senior leadership.
2/10/2016	Center Director Briefing	To discuss the ongoing review of the NDA, and what will be presented during the Advisory Committee Meeting in April. 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.
4/15/2016	Center Director Briefing	To discuss the statistical review of the CINRG data. To discuss the review of data on DMD that was conducted by the Cooperative International Neuromuscular Research Group
4/25/2016	Advisory Committee Meeting	
5/4/2016	Center Director Briefing	Discuss the outcome and plan of actions for the application post advisory committee meeting

5/31/2016	Center Director Briefing	Discuss reviews conducted by the review team and leadership along with any additional information obtained from the sponsor. Discussed Dr. Woodcock's memo. Timeline for reviews due to Dr. Woodcock.
7/6/2016	Center Director Briefing	1. The levels of dystrophin observed in 12 DMD patients from the recent interim analysis of an ongoing trial and whether the levels seen can be interpreted to be "reasonably likely to predict clinical benefit" and used as a surrogate endpoint to support accelerated approval. 2. The design of one or more PMR trials to confirm clinical benefit of eteplirsen if it is approved under accelerated approval. 3. Description of the available clinical data in the drug label if approved.

Based on my years of experience in Office of Drug Evaluation-I, the Center Director's direct involvement with this drug, compared to other development programs, has been unprecedented. She also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments.

There is no question that there has been adequate time and place for the discussion of various views. I will note, however, that I found it unfortunate that the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division's final review memorandum or my review memorandum. Prior to reading our reviews, Dr. Woodcock stated that she had already "...reached a different conclusion...." than the review team.

5. Action, Decision or Remedy Sought

Although the above paragraph could be considered grounds for an appeal based on process, I seek instead a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit. I maintain, along with the Division of Neurology Products, Office of Biometrics, Office of Clinical Pharmacology, Office of New Drugs, and the majority of the members of the Peripheral and Central Nervous System Drugs Advisory Committee, that substantial evidence is lacking to support either a conventional or accelerated approval, and that a *complete response* should be issued for this NDA.

The unprecedented finding of an increase in dystrophin protein in response to eteplirsen establishes proof-of-concept and provides great promise that this drug, or other therapies, will eventually be capable of ameliorating the fundamental genetic defect of DMD, but the effect size here is insufficient at the tested doses.

6. Path Forward

Based on the quantity of Becker-type dystrophin produced in Study 301 and the clinical findings in Study 201/202, additional studies at this dose are unlikely to support any type of approval, i.e., the data obtained for eteplirsen at doses of 30 and 50 mg/kg/week are fairly solid, but they do not support efficacy.

I remain comfortable with the concept that substantial evidence of dystrophin production from adequate and well controlled trials could support accelerated approval, but it is clear that higher doses are needed, and greater quantities of dystrophin would need to be produced. The path to a conventional approval would require a double-blind, placebo-controlled (or multi-dose) study, at least one year in duration, using some measure of physical performance as the primary endpoint, again, testing higher doses.

The applicant is continuing to enroll Study 301 (PROMOVI), an open-label, multicenter, 48-week study in patients with DMD amenable to skipping exon 51. All patients are receiving eteplirsen, 30 mg/kg/week as an IV infusion.

My suggestion for a path to approval is to randomize patients in the ongoing Study 301 to:

- 1) either remain on 30 mg/kg/week; or
- 2) have their dose significantly increased. This could be done through use of a higher dose, through more frequent dosing intervals (with dummy infusions), or both. Given that many patients receive eteplirsen through indwelling IV lines and no significant infusion reactions have occurred, perhaps these infusions could be performed at home. For example, the study could compare 30 mg/kg weekly to 30 mg/kg daily. Patients who do not tolerate more frequent dosing could have their doses decreased, as needed. Based on non-clinical findings, monitoring would need to be in place to assess renal toxicity.

Patients and investigators would be blinded to treatment group. For accelerated approval, the primary endpoint would be dystrophin production, comparing the higher and lower doses. For standard approval, the primary endpoint would be a test(s) of physical performance such as NSAA or rise time.

Such a trial would be methodologically sound and ethical. Virtually everyone, patients and physicians alike, would want to know whether higher eteplirsen doses would increase dystrophin production, and would have equipoise for participation. Although there is concern regarding performance of muscle biopsies in patients randomized to placebo, this would not be a concern here with all patients receiving active drug. And I would recommend that the applicant forego immunohistochemistry studies in favor of Western blot analyses, such that needle biopsies with local anesthesia would be sufficient (rather than open biopsies with more intensive anesthesia and greater morbidity).

no problem

I also believe that it would be desirable for the company to provide access to eteplirsen for DMD patients through expanded access programs, with cost recovery, while an adequate dose-finding study is conducted.

FDA is charged with the responsibility of ensuring that drugs are shown to be effective prior to marketing, based on substantial evidence. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients, in essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous.

Philips, Howard

From: Diggs, Felicia
Sent: Friday, July 29, 2016 8:07 AM
To: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis
Subject: Letter to Commissioner-Kyndrisa

Good morning,

Dave Martin of Avidbiotech forwards an opinion letter written by Herbert L. Heynecker PHD to the Commissioner regarding Kyndrisa. Dave states the letter was sent to CDER without appropriate response. It appears that Mr. Heynecker sent his letter to DAC for submission to the PCNS AC however, the AC meeting record was already closed and the letter was referred to the division. I drafted a response based on previously cleared language. Please let me know if you have any additional edits by COB today if possible. The response will come from Tom Kraus (COS).



Due to security concerns, the content of this email and any attachments is redacted. For more information, please contact the sender.

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

Opinion letter on the effectiveness of Kyndrisa for the treatment of DMD

The FDA's rejection of Kyndrisa on January 14, 2016, was clearly a very disappointing outcome and a profoundly emotional loss for the boys affected by Duchenne's Muscular Dystrophy (DMD) and their families. Last week, on April 25, 2016, when an advisory panel for the FDA rejected Eteplirsen, the outcome must have been simply devastating for the affected families. Kyndrisa and Eteplirsen have similar, novel molecular modes of action; each partially reverses the underlying genetic defect in DMD, for which there is no FDA-approved therapy or prophylaxis. In this opinion letter, I wish to opine on the effectiveness of only Kyndrisa because of my involvement with Prosensa as a board member and scientific advisor, well before the Company was acquired by BioMarin.

Seventeen FDA advisory committee panel members voted on BioMarin's Kyndrisa NDA package, and 15 were of the opinion that the lack of statistical significance of positive results in the phase III study weakened the persuasiveness of findings. This lack of statistical significance doesn't surprise me since both the phase II and III studies were short-term studies and short-term studies should not be expected to show effectiveness for an agent which is not expected to reverse the disease and certainly not quickly.

Apparently there is not a clear understanding of Kyndrisa's mode of action, so let me explain: **Kyndrisa does not restore muscle function; it slows down deterioration of muscle fibers and muscle function.** Dystrophin, the genetically absent protein in DMD, is essential for proper muscle function. In the absence of dystrophin, muscle cells slowly atrophy in an **irreversible** process. Kyndrisa is a modified exon-skipping oligonucleotide (nucleic acid), which partially restores RNA to code for the synthesis of a partially functional dystrophin protein in DMD patients with a mutation in exon 51. In younger patients who still have residual muscle function, Kyndrisa will delay the further deterioration of those muscle cells which are still functioning. So, the younger one begins to receive treatment with Kyndrisa, the better the chances are to delay the slow

progression of his disease and maintain sufficient residual muscle function to extend the limited period of ambulation and perhaps of even cardiac function.

In effect, **Kyndrisa is prophylactic and, thus, can only be proven efficacious in a long-term study.** Luckily, BioMarin has the results of such a long-term study, namely the phase I study, DMD114673, which was presented in a poster session at the 19th International Congress of the World Muscle Society, Oct 7 - 11, 2014 in Berlin, Germany. In summary, 12 boys were enrolled in DMD114673, which started in 2008. Two boys dropped out because of lost ambulation during the extension study. They were considered to have severely declined before the start of the study; of all ambulatory subjects, they had the lowest overall baseline 6 minutes walking distance test (6MWD) results (not surprising considering Kyndrisa's mode of action). When progression of the disease in this treated group was compared with extensive historical data from untreated affected boys, the remaining 10 boys were performing significantly better, and the results after 8 years are becoming only more impressive. All 10 boys are still enrolled, which tells me that side-effects of the drug are manageable and tolerable.

(b) (4)

I strongly encourage the FDA to carefully examine these data one more time in light of the full understanding of the drug's mechanism of action on muscle fibers: Kyndrisa, as a prophylactic agent, will not restore muscle function. Kyndrisa delays further the slow muscle deterioration characteristic of the disease., Accordingly, supporting efficacy data can only be obtained from a long-term study. My professional conclusion is that Kyndrisa (and probably Eteplirsen) are effective drugs in delaying the lethal progression of DMD in young, ambulatory boys.

Herbert L. Heyneker, PhD.

May 2, 2016

From: [Russ, Wanda](#)
To: [Diallo, Mame K](#)
Cc: [O'Neill, Jeff](#)
Subject: FW: Opinion letter on Kyndrisa
Date: Monday, July 11, 2016 11:00:51 AM
Importance: High

Hi Mame,

Please log in to Jo for Chief of Staff (Tom Kraus) signature. Include complete email. Jo will work with CDER OEP on preparing a response for Tom's signature.

Thanks,

Wanda

From: Russ, Wanda
Sent: Monday, July 11, 2016 10:59 AM
To: Palmer, Kelly
Cc: O'Neill, Jeff
Subject: RE: Opinion letter on Kyndrisa

Ok. I will assign to Jo Tropea to work with CDER to prepare a response for Tom's signature.

Thank you for the clarification.

Wanda

From: Palmer, Kelly
Sent: Monday, July 11, 2016 10:57 AM
To: Russ, Wanda
Cc: O'Neill, Jeff
Subject: RE: Opinion letter on Kyndrisa

Tom would prefer for the response be sent from him since the gentleman below is complaining about not receiving a substantive response from CDER.

From: Russ, Wanda
Sent: Monday, July 11, 2016 10:16 AM
To: Palmer, Kelly
Cc: O'Neill, Jeff
Subject: RE: Opinion letter on Kyndrisa

If you could confirm whether Tom wants a letter for his signature or the language for him to send through a email that will help on how I log this in and assign. If he wouldn't be the one to sign or send the info via email, then I would assign it to CDER to respond directly to.

Please advise.

Thank you,

Wanda

From: Palmer, Kelly
Sent: Monday, July 11, 2016 10:13 AM
To: Russ, Wanda
Subject: RE: Opinion letter on Kyndrisa

Maybe Tom...but I'm thinking just an email, not a letter. Thanks!

From: Russ, Wanda
Sent: Monday, July 11, 2016 10:07 AM
To: Palmer, Kelly
Subject: RE: Opinion letter on Kyndrisa

I can check with CDER if they have language. Would this be for Tom's signature or Califf's?

From: Palmer, Kelly
Sent: Monday, July 11, 2016 9:56 AM
To: Russ, Wanda
Subject: FW: Opinion letter on Kyndrisa

Hi Wanda,

See note below from Tom. Do we have standard language saying that we can't comment on the substance of an application or can you draft something?

Thanks,
Kelly

From: Kraus, Tom
Sent: Sunday, July 10, 2016 5:27 PM
To: Califf, Robert
Cc: Palmer, Kelly
Subject: Re: Opinion letter on Kyndrisa

Thanks. We can't respond on the substance.

Kelly, is there some boilerplate language we can use to acknowledge receipt and explain that we can't comment on the substance of an application?

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: July 9, 2016 at 11:00:12 AM EDT
To: Kraus, Tom <Tom.Kraus@fda.hhs.gov>
Subject: FW: Opinion letter on Kyndrisa

Robert M Califf MD
Commissioner of Food and Drugs

From: Evans, Dana
Sent: Wednesday, July 06, 2016 2:58 PM
To: Califf, Robert
Subject: FW: Opinion letter on Kyndrisa

Dana Evans, M.P.H.
Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

From: Dave Martin [<mailto:dave@avidbiotics.com>]
Sent: Tuesday, July 05, 2016 6:01 PM
To: Commissioner FDA
Subject: FW: Opinion letter on Kyndrisa

Rob: The “missing” letter is now attached! Dave

From: Dave Martin
Sent: Tuesday, July 5, 2016 11:06 AM
To: 'robert.califf@fda.hhs.gov' <robert.califf@fda.hhs.gov>
Subject: Opinion letter on Kyndrisa

Rob, a delight to see you in D.C. in February, and I also add my enthusiastic congratulations to you.

Undoubtedly you’re aware of the concern, noise, and controversy around the 2 submitted drug candidates for management of Duchenne muscular dystrophy that began before your current role. This is a quick note accompanying an opinion letter from a long time scientific colleague and friend, Herb Heyneker. The letter has been passed through the proper channels at the Agency without substantive response, and in the context of the op ed piece in the WSJ Saturday, I thought it appropriate to draw your attention to the content of Herb’s letter. Herb was the first or second employee at Genentech, well before I was there, having completed his post

doc in Herb Boyer's lab at UCSF. I can strongly vouch for his scientific acumen and depth, and even though I have not seen the Phase I data to which he refers in his letter, I do understand the defect and mechanism of action of the exon skipping oligos. As a one time medical geneticist, I have followed that field for years and have been impressed by the exon skipping approaches. Herb's opinion makes very good sense to me. I recently talked to a senior person in BioMarin's regulatory affairs and learned of some adverse events; however, none were so adverse as the incessant deterioration and demise of these boys.
Best regards, Dave

David W. Martin, Jr., MD
AvidBiotics Corp.
100 Kimball Way
South SF, CA 94080
650-873-1115 office

From: CDER DRUG INFO
<DRUGINFO@fda.hhs.gov>
Date: May 11, 2016 at 3:12:27 PM GMT+2
To: "(b) (7)(A)"
(b) (6)
Subject: RE: Opinion letter on Kyndrisa

Dear Dr. Heyneker,

Thank you for writing to the Division of Drug Information in the FDA's Center for Drug Evaluation and Research.

We appreciate your thoughts and comments regarding this issue, and have forwarded your email to the appropriate CDER Review Division. They will contact you if they have questions or need additional information.

Best regards,
RL
Drug Information Specialist
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration

This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the

views expressed.

[<ATT89150 1.jpg>](#) [<ATT69106 2.jpg>](#)
[<ATT85592 3.jpg>](#) [<ATT56925 4.jpg>](#)
[<ATT27175 5.jpg>](#) [<ATT40320 6.jpg>](#)

From: Herb Heijneker

(b) (6)

:20 AM

To: CDER DRUG INFO

Cc: Dave Martin; PCNS

Subject: Fwd: Opinion letter on Kyndrisa

To whom this may concern, I am forwarding an opinion letter on Kyndrisa which I sent to Ms. Moon Hee V. Choi, who is the Designated Federal Officer, PCNS at the FDA. She was unable to accept my document/comments as the Advisory Committee meeting record is closed since the meeting was adjourned. She suggested that I submit my comments to the FDA Division of Drug Information at druginfo@fda.hhs.gov and that you will be able to direct my correspondence to enter the appropriate process for submitting my comments to the FDA/CDER Division of Neurology Products. Thank you for your help, Sincerely, Herbert Heyneker, PhD.

Begin forwarded message:

From: Herb Heijneker

<[\(b\) \(6\)](#)>

Subject: Opinion letter on Kyndrisa

Date: May 5, 2016 at 8:15:02 PM GMT+2

To: pcns@fda.hhs.gov

Cc: Dave Martin <dave@avidbiotics.com>

Dear Ms. Choi, on November 24, 2015 the PCNS advisory committee concluded that Kyndrisa should not be approved for the treatment of Duchenne's Muscular Dystrophy due to lack of efficacy; especially the phase III data were unconvincing. On January 14, 2016 the FDA followed the recommendations of the advisory committee and rejected Kyndrisa for the treatment of DMD. Respectfully, I would like to ask the advisory committee to read my opinion letter (hereby attached) in which I explain why short-term clinical trials will not

demonstrate clinical benefits. I would greatly appreciate if you could share this letter with the full advisory committee, that voted on the disapproval of Kyndrisa. My professional conclusion is that Kyndrisa (and probably Eteplirsen) are effective drugs in delaying the lethal progression of DMD in young, ambulatory boys. My motivation is purely altruistic: I like to help DMD patients live a longer, more productive life, keeping in mind that there is no treatment currently available for this dreadful disease.

Sincerely,

Herbert L. Heyneker, PhD

(b) (6)

<Opinion letter on Kyndrisa, May 2, 2016.pdf>

Response To David Martin's Forward of Kyndrisa Opinion Letter Written By Herb Heyneker

I understand the opinion letter was forwarded to the Designated Federal Officer of the Peripheral and Central Nervous Advisory Committee (PCNS) for review . Although, the official record for the November 24, 2015, PCNS Advisory Committee meeting was closed and the committee had rendered it's advice, the opinion letter was submitted to the appropriate division for review. We recognize the huge unmet medical need in Duchenne muscular dystrophy, the devastating nature of the disease for patients and their families, and the great urgency to make new treatments available. As a result, we are working diligently with all sponsors on the development and approval of safe and effective drugs for patients who are suffering with this rare and devastating condition. As we continue to review new drug applications, we communicate directly with sponsors and make decisions based on the information received. FDA is prohibited by law to comment on pending applications since these conversations are considered confidential and proprietary to the applicant.

Clearance History:

Draft: FDiggs, DEO, 7/27/16

Edit for Content: JPeterson, DACM, 7/27/16

Edits: FDiggs, DEO, 7/29/16

Temple, Robert

From: Jenkins, John K
Sent: Wednesday, August 10, 2016 8:53 AM
To: Bastings, Eric; Farkas, Ronald
Cc: Dunn, Billy; Unger, Ellis; Temple, Robert; Woodcock, Janet; Califf, Robert; Jenkins, John K
Subject: WSJ Editorial

Eric and Ron

I am sorry that the editorial page of the WSJ (in an anonymous post) has chosen to single you out as targets for scorn related to the eteplirsen NDA review. You have done your job and raised legitimate scientific and regulatory questions about the adequacy of the data to support approval. We honor such work and opinions at FDA. We have regulations that protect the ability of reviewers to state their conclusions and recommendations and we have procedures to allow for appeals in cases of differing scientific opinions. There can be legitimate differences of opinion about how to interpret science and data in making regulatory decisions, it is unfortunate that the media, advocates, politicians, etc., turn such differences of opinion into personal attacks.

Thank you for your work and dedication to FDA and public health.

John

Philips, Howard

From: Diggs, Felicia
Sent: Friday, August 26, 2016 6:49 AM
To: Dunn, Billy; Bastings, Eric
Cc: Temple, Robert; Unger, Ellis
Subject: Letter to Dr. Woodcock-Eteplirsen

Good morning,

Please see attached a draft response to Mr. Flores who asks if FDA can verify that the Agency mixed up the outcomes of two testing techniques (Western Blot & Percent Dystrophin Positive Fibers) for eteplirsen. If you could review, clear, and/or edit by COB Monday, it would be greatly appreciated.



FDAC
The following is a draft response to Mr. Flores who asks if FDA can verify that the Agency mixed up the outcomes of two testing techniques (Western Blot & Percent Dystrophin Positive Fibers) for eteplirsen. If you could review, clear, and/or edit by COB Monday, it would be greatly appreciated.

Have a great day!

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

To: Dr. Janet Woodcock
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dr. Ed Kaye
Sarepta Therapeutics
215 First Street
Cambridge, MA 02142

From: Marcos Flores

Date: August 4, 2016

Re: Sarepta Article

Hello,

Below is an article from the Seeking Alpha website regarding the Eteplirsen Advisory Committee (ADCOM) Meeting held earlier this year. The author suggests that the FDA confused or mixed up the outcomes of two different testing techniques.

I would like to ask the FDA if this is in fact true, and if so, will this be remedied? If this is true, I would like to ask Sarepta what they are doing to help to clarify this with the FDA.

Full disclosure (b) (6) and am therefore biased toward approval. I have no scientific background and have no idea if the author of the article below has a valid point or not.

I would appreciate a response if possible.

Thank you,



Marcos Flores

Sarepta Dystrophin Levels For Duchenne Muscular Dystrophy Drug

Aug. 4, 2016 9:52 AM ET



BosCaptn

Follow @BosCaptn on twitter

Summary

Sarepta Eteplirsen dystrophy testing levels.

Definition of testing methods.

FDA Adcom Faults and Failures and Misrepresentations.

This is a detailed account of how the FDA lied and manipulated the public, the DMD community and the panelists during the Eteplirsen Advisory Committee (ADCOM) Meeting held earlier this year. The final FDA decision continues to be postponed at the cost of boys and their families.

This has been a crowd-sourced effort of independent minds focused on this issue at hand. We are a group of about 18 people that came together using Twitter private group messaging to help fully understand the issue. It is a result of numerous and ongoing discussions to present the true facts of the situation. This article focuses on Dystrophin levels. Additional prepared and yet to be published articles in the series focus on other FDA Adcom faults, failures, and additional laws the FDA ignored.

During the advisory committee meeting for the review of Sarepta's (NASDAQ:SRPT) Duchene Muscular Dystrophy drug Eteplirsen, the FDA made a coordinated effort to accuse Sarepta of misleading the FDA and the DMD community. DMD is caused by an absence of dystrophin, a protein that maintains muscle integrity. The FDA decided to frame the issue regarding dystrophin produced by Eteplirsen to make it look as if Sarepta had greatly overstated the Phase IIb trial results to both the FDA and DMD community.

At the heart of the issue are the two different lab techniques used to measure dystrophin, yielding two very different types of data. The first test, using immunofluorescences, looks for what is known as Percent Dystrophin-Positive Fibers (PDPF). The second test, using Western blots, looks for the total amount of dystrophin protein.

PDPF in simple terms is looking at the tissue at the cellular level and asking the question, 'are there any muscle fibers present, and if so, are they dystrophin positive', it's a yes or no question. Think of **PDPF in terms of a light bulb, is it 'ON' or 'OFF'?**

Western Blot measures the total amount of dystrophin protein present in the muscle tissue. Imagine mashing up all the muscle fibers from a tissue sample together and then quantifying how much total dystrophin is present. Think of total dystrophin protein as measured by WB as **'how bright is the light bulb'?**

These two lab measurements produce very different data and values. Sarepta used PDPF to determine if Eteplirsen was, or was not, having an effect on dystrophin. In Sarepta's October 2012 press release, the company reported an average increase in PDPF of 47% 'of normal'. Sarepta defined 'of normal' as "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." This would be like walking around the house and counting how many light bulbs are 'ON' and dividing by the total amount of light bulbs in the house.

It is important to notice Sarepta included this definition in the Sarepta supplied Briefing Document prior to the FDA reviewers' Briefing Document preparation and full review. The Sarepta BD states:

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 percent of dystrophin-positive fibers.

The FDA focused on the total amount of dystrophin protein as measured by Western blot. The total amount of dystrophin protein in a DMD child, divided by the total amount of dystrophin protein in a healthy child would yield a 'percent of normal'. This method would be like turning 'ON' every light bulb in the house and measuring the total brightness then dividing that number by the maximum output potential of all the bulbs.

As you can see, these two lab methods are vastly different, as to the 'normal' they measure. One method is counting how many light bulbs are "ON"; the other is measuring how bright the light bulbs are.

During the ADCOM meeting, numerous FDA representatives mischaracterized the data presented by Sarepta, specifically, the Phase IIb 48-week data presented by Sarepta in 2012. As you review the way the FDA characterized the data, keep in mind which light bulb measurement is being considered.

FDA Division of Neurology Products, Medical Review Supervisor, Dr. Dunn set the stage when he stated, "it was our understanding that dramatic increases of dystrophin were being observed, as much as 50 percent of normal." (Copied directly from the FDA Adcom Transcript.) It is critical to note that Dr. Dunn doesn't clarify or specify which testing method he is referring to when he mentions the "50 percent of normal." However, he opened the meeting talking about "increased dystrophin expression," and thus implied the number reported was total dystrophin protein, or light bulb brightness, which is incorrect.

FDA Division of Neurology Products Medical Review Lead, Dr. Farkas was next, "instead of the expected 25 to 50 percent normal dystrophin, as was mentioned before, there was only .93 plus or minus .84 percent of normal dystrophin in the treated patients. This was measured by Western blot..." With Dr. Farkas, it is important to note he is now mixing the two completely different testing methods and testing values. Dr. Farkas states that "this was measured by Western blot," directly implying both the "expected 25 to 50 percent normal" and the "only 0.93" were both measured via Western blot, and thus both values refer to light bulb brightness; again this is incorrect.

As the FDA concluded their presentation, FDA Division of Neurology Products Medical Review Officer, Dr. Bastings reinforced, "Great hope was raised... dystrophin numbers were increased to levels as high as 50 percent of normal..." Like Dr. Dunn before, Dr. Bastings does not clarify the method of testing. However, by the time of Dr. Dunn's wrap up session, it was clear that the FDA considered "percent normal" as how bright the light bulb was.

The FDA then claims this misleading information is the reason that additional placebo controlled trials haven't started. Dr. Bastings went on to say, "Few, if any patients, would be willing to participate in a second placebo-controlled trial because they already felt so strongly that Eteplirsen was effective. This was an unfortunate situation."

The FDA was successful in influencing the panel into believing Sarepta had hoodwinked the FDA and the DMD community. During the comment period on why Advisory Committee Panel Member, Dr. Onyike had voted "No," he commented directly to the audience on hand, "I also hope you would consider, as a community, participating fully in controlled trials so that you're not in this position in the future."

During the ADCOM panel's discussion period for the first question, the committee chair Dr. Alexander, clearly shows the effects the FDA had on the panel. He comments, "In the clinical development program, there were estimates that dystrophin levels may have increased as much as 20 to 50 percent, which I think we would all argue or believe or feel would be incredible results relative to, for example, what we're seeing here. Now, I'm referring to the actual quantification with Western blot, and that clearly was a pivotal event that appears to have had a very profound impact on the subsequent decisions that the sponsor and the FDA reached regarding the next steps in the development program."

Dr. Alexander reveals the consequences of the lies told by the FDA. His statement identically mirrors the logic of the FDA. Dr. Alexander clearly confuses the difference between the "20 to 50 percent" as reported by PDPF (how many bulbs are ON) and the 0.93 percent total dystrophin protein as measured by WB (the brightness of the light bulbs). By reinforcing the expectation of a value as high as 50 percent, the actual values become a 'failure' in comparison even though the WB numbers were in fact statistically significant.

So what did Sarepta actually say about the Phase IIb 48-week data? Sarepta released a PR on October 3rd, 2012 regarding the results of the 48-week data. Sarepta reported the data as "Percent Dystrophin-positive Fibers" (how many light bulbs are ON). On October 13th, 2012, the data was presented by the study's lead author, Dr. Mendell, at the World Muscle Society meeting in Perth, Australia. Again, Dr. Mendell presented the data as PDPF. The critical point is both Sarepta and Dr. Mendell reported the data as "percent dystrophin-positive fibers," or PDPF, not total dystrophin production as measured by Western blot.

Is it somehow possible the FDA thought the original 2012 data was in fact a measurement of total dystrophin protein? I believe Dr. Bastings answered that question during the ADCOM when he stated "Just between 2013 and 2015, FDA held 13 formal meetings with the applicant about eteplirsen." The FDA knew exactly what data they had and what data they were looking at.

The FDA had a clear opinion regarding PDPF, as expressed by the clinical team leader Dr. Farkas, "PDPF does not mean a normal amount of dystrophin, a functional amount, or really any specific amount of dystrophin." The FDA obviously knew the 2012 data was presented as PDPF by Sarepta, they obviously disliked PDPF, yet the FDA continued to claim that they were duped by Sarepta via the PDPF data.

It is important to notice Dr. Farkas does in fact know the meaning of PDPF and his understanding was known prior to the Adcom as shown in his statement:

20

First, as discussed by Dr. Rao, percent

21

positive fibers is not a helpful measure of the

22

amount of dystrophin because a positive fiber does

208

1

not mean a normal amount of dystrophin, a

2

functional amount, or really any specific amount of

3

dystrophin. It only means an intensity judged by

In 2012, Sarepta basically said "wow, look we did it, we were able to turn half the lights in the house ON!" (A 50% increase in PDPF). This effect had never been seen before, or since, in any other treatment and shows Eteplirsen does indeed have an effect on dystrophin, the very thing absent in patients with DMD. The FDA claims that they were told, and deceived the Adcom panel to believe, "Originally we were told all the lights in the house are on, at half brightness, when in reality all the lights were only at 1% brightness."

The issue is rather complex, and can be hard to follow, and that's exactly what the FDA wanted. Rather than helping simplify the data, the FDA used the complexity of the data to confuse people and shift the blame. Weaving a story that rather than the FDA dragging their feet for more than three years on the first real treatment for DMD, it was Sarepta that had misled the FDA and the DMD community.

It's appalling, if not criminal, the way the FDA purposefully distorted the facts to the Adcom panelists and the DMD community. Dr. Farkas made it a point both at the start and at the end of his clinical presentation that "it's really important to take a close look at what you're being told." While Dr. Farkas was addressing the DMD community, maybe he should heed his own advice.

Credits and appreciation for this article go to @StunningFeline, @BosCaptn, and many others from the independent group.

Stock Summary

We have attempted to stick to the facts of the FDA faults, failures, and delays. At the same time, it is difficult to even speculate on the reasons behind the FDA decisions. So with that in mind, we leave it up to FDA oversight influence, political figures, and the future to determine the answers.

The FDA has numerous times shown aggravation with the company. In fact, many times over the course of the Adcom in April, FDA reviewers came back to the issue of what was said or what was known in the past instead of only dealing with the safety or efficacy of the drug at hand. If you believe the FDA will continue to stonewall you may want to sit on the sidelines and it is a valid short thesis.

In our view, the stock continues to be a buy with a price target of over \$60. The Adcom created fear and doubt yet the additional delay and request for additional Western Blot data is an indication Eteplirsen will receive FDA approval. The approval is imminent but the timing is unclear. The early quarterly release is also an indicator approval could come in early August. Short Interest, remains extremely high although it is decreasing slowly. On August 2, the confirmatory trial, ESSENSE, changed to "Recruiting" status indicating the trial has initiated.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services

Food and Drug Administration
Silver Spring, MD 20993

August 16, 2017

(b) (5)

(b) (5)

Internal Document

Temple, Robert

From: Unger, Ellis
Sent: Thursday, September 01, 2016 12:07 PM
To: Dunn, Billy
Cc: Temple, Robert; Bastings, Eric
Subject: RE: Draft agreements with Sarepta

Ellis: it was proposed (with known limits) because a pilot controlled trial was thought impossible

Thanks Billy.

I think the exon 45/53, (b) (4) idea came from Janet, John, or Bob. I have always railed against it. Such a study could support the "reasonably likely" proposition for eteplirsen, but if eteplirsen were given accelerated approval, it would serve no purpose whatsoever. And the concept that related PMOs are similar is simply ridiculous. It's like saying that all related DNA is pretty much the same. I was not at all surprised that (b) (4)

Enjoy your weekend. I hope you're far enough inland that you don't see the rain!

Ellis

The D/R is a very good alternative

From: Dunn, Billy
Sent: Thursday, September 01, 2016 11:45 AM
To: Unger, Ellis; Farkas, Ronald; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas
Subject: RE: Draft agreements with Sarepta

The proposal, however, was derided repeatedly and all knew about it and did NOT object

I am checking intermittently.

My only comments:

Ellis wrote below that "I'm hearing that the Division's position is now..." – it is my understanding Ellis, that this was/is your/the Office's position, perhaps even earliest of all, as I think you very quickly questioned the utility of this approach. Regardless, it seems that all are in alignment.

I am not clear that the review team EVER proposed this, but my memory is fuzzy. I think this might have come from supra-Office (ODE1) levels during a Janet briefing.

Anyway, I suggest the following minor adjustments, with affected portions highlighted:



(b) (5)

If this language is sent, then I am not clear if the PMR/PMC document that will be sent should or should not include the PMC to which the above language objects. I am fine with whatever Ellis decides.

Billy

From: Unger, Ellis
Sent: Thursday, September 01, 2016 11:29 AM
To: Farkas, Ronald; Dunn, Billy; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas
Subject: RE: Draft agreements with Sarepta

This text is fine with me – if OK with Billy (I'm not sure Billy is checking email this weekend).

From: Farkas, Ronald
Sent: Wednesday, August 31, 2016 11:49 AM
To: Unger, Ellis; Dunn, Billy; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas
Subject: RE: Draft agreements with Sarepta

Some suggested text below

Thanks
Ron

(b) (5)

From: Unger, Ellis
Sent: Wednesday, August 31, 2016 11:09 AM
To: Dunn, Billy; Farkas, Ronald; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas
Subject: RE: Draft agreements with Sarepta

All,

I'm hearing that the Division's position is now that the study would be non-helpful at best, and counterproductive at worst, for reasons Ron has well explained. If we see no utility in the study with respect to verifying and describing the clinical effect of eteplirsen, then why would we ask an applicant to study a different drug/patient population as a PMC? And as Ron notes, they need advice on the entire development program for the 45/53 drug, not a PMC to run a particular trial.

I suggest that one of you write a sentence or two for Janet, explaining the Division's view. I will agree with it, and we can present it as the agreed ODE-I/DNP view. If Drs. Jenkins or Woodcock would like to add the 45/53 study as a PMC, then they can do that, but they need to hear the DNP/ODEI view and understand our rationale.

Ellis

From: Dunn, Billy
Sent: Wednesday, August 31, 2016 7:23 AM
To: Farkas, Ronald; Unger, Ellis; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas
Subject: RE: Draft agreements with Sarepta

So, what is the status of the "PMC"? Does Sarepta think this is going to be a PMC? Can we just ditch it? What is standing in the way of not including it in the response to Janet?

From: Farkas, Ronald
Sent: Wednesday, August 31, 2016 7:17 AM
To: Dunn, Billy; Unger, Ellis; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas
Subject: RE: Draft agreements with Sarepta

We thought of the exon 45/53 study a long time ago and only more recently realized that the act of writing out the PMC was likely to adversely constrain the development program of what is really a completely separate drug. However, once the ball was rolling for the exon 45/53 study, it seemed hard to stop, particularly given the previous time pressure when we thought eteplirsen would be approved within days.

From: Dunn, Billy
Sent: Wednesday, August 31, 2016 7:09 AM
To: Farkas, Ronald; Unger, Ellis; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas
Subject: RE: Draft agreements with Sarepta

OK, I understand that.

Why is it listed as a PMC then?

From: Farkas, Ronald
Sent: Wednesday, August 31, 2016 7:08 AM
To: Dunn, Billy; Unger, Ellis; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas
Subject: RE: Draft agreements with Sarepta
Importance: High

We should not make the ongoing exon 45/53 study a PMC. The ongoing study is at the 30 mg dose, which was arrived at without necessary dose finding studies. Making it a PMC will stop dose finding efforts for exon 45/53 and probably for all other exons. There might be a way to write out exon 45/53 studies as a PMC, but this should really include phase 1 SAD and MAD, phase 2 dystrophin quantification study, and phase 3 clinical efficacy study.

Thanks

Ron

From: Dunn, Billy There
Sent: Wednesday, August 31, 2016 7:00 AM
To: Unger, Ellis; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas; Farkas, Ronald
Subject: RE: Draft agreements with Sarepta

My only input is that the 45/33 study is listed as a PMC, which by definition does not allow it to serve as the confirmatory study for an accelerated approval. Those are PMRs. The PMC is described in a manner consistent with Eric's email, in which he said it wasn't needed but outlined a description if we did get it. Given that Janet and John both have said they want this study, do we need to disclaim it in this way, since by definition it is not a required confirmatory study?

From: Unger, Ellis
Sent: Tuesday, August 30, 2016 10:43 PM
To: Choy, Fannie (Yuet); Dunn, Billy
Cc: Bastings, Eric; Kozauer, Nicholas; Farkas, Ronald
Subject: RE: Draft agreements with Sarepta

Fanny,

You can send to Dr. Woodcock, but please let her know that (subject to Billy's input):

(b) (5)

But if eteplirsen is given accelerated approval, Sarepta will need to verify the clinical benefit, and a study in patients with other genotype(s) cannot verify the clinical benefit of eteplirsen for exon 51 DMD. Only a positive study that demonstrates clinical benefit of eteplirsen in patients with Exon 51 DMD can verify the benefit.

Thanks,

Ellis

From: Farkas, Ronald
Sent: Tuesday, August 30, 2016 6:47 PM
To: Unger, Ellis; Choy, Fannie (Yuet)
Cc: Bastings, Eric; Kozauer, Nicholas; Dunn, Billy
Subject: RE: Draft agreements with Sarepta

Ellis,
Yes, when we last discussed (e.g. email attached) we all agreed that the exon 45/53 study should not be included, even as a PMC.
Thanks
Ron

From: Unger, Ellis
Sent: Tuesday, August 30, 2016 4:34 PM
To: Choy, Fannie (Yuet); Farkas, Ronald
Cc: Bastings, Eric; Kozauer, Nicholas; Dunn, Billy
Subject: RE: Draft agreements with Sarepta

I'd like to hear Ron's view, but my opinion is that the study in Exon 45 or 53 is not necessary. If it showed correlation between truncated dystrophin production and physical function, it would support the concept that dystrophin is an acceptable surrogate. If such a correlation were shown for even a low level of dystrophin, it would provide even greater support for accelerated approval for eteplirsen. But such a study cannot verify the clinical benefit of eteplirsen for exon 51 DMD. Only a study of eteplirsen that shows clinical benefit in patients with Exon 51 DMD can verify the benefit.

From: Choy, Fannie (Yuet)
Sent: Tuesday, August 30, 2016 4:18 PM
To: Unger, Ellis; Farkas, Ronald
Cc: Bastings, Eric; Kozauer, Nicholas; Dunn, Billy
Subject: RE: Draft agreements with Sarepta

Hi,

Attached is the submission for the clinical PMRs/PMCs with proposed dates. Please let me know when it's ready to forward to Dr. Woodcock.

<\\CDSESUB1\evsprod\nda206488\0044\m1\us>

FYI...there're also 2 CMC-PMCs not included in this submission.

Thanks
Fannie

From: Dunn, Billy
Sent: Tuesday, August 30, 2016 4:09 PM
To: Choy, Fannie (Yuet)
Cc: Unger, Ellis; Farkas, Ronald; Bastings, Eric; Kozauer, Nicholas
Subject: FW: Draft agreements with Sarepta

Fannie,

See below. Can you please send the PMRs to Janet? Please make sure you have any input from Ron and Ellis that they might want to provide prior to sending to Janet. Thanks!

Billy

From: Woodcock, Janet
Sent: Tuesday, August 30, 2016 3:48 PM
To: Dunn, Billy
Subject: Draft agreements with Sarepta

Can someone send me the postmarket requirements with Sarepta and also what they are doing to study their additional drug? I understand the first is a dose comparison trial and the second is a placebo controlled trial. Thanks! jw

Philips, Howard

From: Diggs, Felicia
Sent: Wednesday, September 07, 2016 12:45 PM
To: Dunn, Billy; Farkas, Ronald; Bastings, Eric; Unger, Ellis; Temple, Robert
Cc: Woodcock, Janet
Subject: FYI-Writes to express concerns regarding the delay in the FDA decision regarding potential approval of eteplirsen. CC: Dr. Califf.

Good afternoon,

The attached letter from Dr. Stanley Nelson of UCLA is being forward to you as a FYI. Dr. Nelson writes regarding his concerns on the delayed decision for approval for eteplirsen and also offers his opinion.



Best regards,

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



Janet Woodcock, MD,
Director, Center for Drug Evaluation and Research
Food and Drug Administration

July 28, 2016

Dear Dr. Woodcock and Dunn,

We are writing to express our concern regarding the delay in the FDA decision regarding potential approval of eteplirsen. As you are aware, we have thoroughly reviewed all of the data made public in the FDA Briefing documents in January and April 2016 as well as participate in the April 25, 2016 Advisory Committee. Based on all of this information, our experience working in DMD research and care and our discussions with the DMD expert community, we remain with the clear conclusion that there is sufficient evidence to support accelerated approval based on strong evidence that eteplirsen induces dystrophin production and apparent improvement of the clinical course of treated subjects relative to external controls and comparable natural history groups. Thus, there is sufficient evidence to meet the standard of 'reasonably likely to predict clinical benefit'.

Our opinion is driven by critical review and conclusion that functionally relevant dystrophin induction was observed in systemically treated boys with Duchenne, as quantified by improved quantitative western blot, and immunohistochemistry analysis of biopsy 4, in combination with and bolstered by, the consensus opinion of 3 blinded pathologists analyzing dystrophin induction in biopsies 1-3, as measured by immunofluorescence based immunohistochemistry. In human and animal models very low levels of dystrophin have an impact on disease, and no lower threshold has yet been found. Further, analysis of functional measures including six minute walk test and age at loss of ambulation (LOA) collected over the course of four years of eteplirsen treatment demonstrated that this cohort is deviating from the typical progression of Duchenne. The clinical experience in the 201/202 trials with these subjects strengthens the interpretation that the increase in dystrophin is reasonably likely to predict clinical benefit and validates the use of dystrophin induction as a surrogate biomarker.

Many of these conclusions were apparent from data available prior to the AdComm, and our opinion was provided in a letter to the FDA Neurology Division prior to the April 25, 2016 Advisory Committee and was co-signed by 36 scientists with broad knowledge of Duchenne and dystrophin restoration strategies for Duchenne. We requested that this expert opinion be shared with the AdComm as it reflects an external expert and critical assessment of the available data appropriately evaluating the eteplirsen data package. It remains unclear to what extent this expert opinion was or has been incorporated into FDA or considered by the AdComm.

Further, along with 13 world-renowned scientist/physician, we travelled to the AdComm and spoke in the Open Public Hearing in order to share our collective expertise, provide context, and express our strong opinions. Our goal was to provide a means for the FDA staff and AdComm members to have ready access to this large expertise to clarify any issues or questions that may persist and allow proper interpretation of the data. To us, this was a rather unprecedented opportunity for the AdComm where scientists including institute heads, department chairs, a national academy of science member, and physicians who have cared for over 5,000 DMD patients could be consulted. It was clear that the overwhelming consensus of this group of experts was that eteplirsen induces dystrophin expression, that any level of dystrophin protein production is reasonably likely to lead to clinical gain, and that clinical gain was observed based on comparison to other natural history datasets. This consensus was well founded in decades of scientific and clinical research and patient care.

We were disappointed to see that neither FDA officials nor AdComm members capitalized on the tremendous scientific and clinical expertise present to clarify questions, claims of apparent inconsistencies, or misunderstandings of the basic biology and clinical course of DMD. In fact, despite FDA confusion and controversy revolving around DMD biology and data interpretation, there was no

apparent effort to consult or solicit expert opinion publicly. This is worrisome and reflects poorly on the ability of the Neurology Division to appropriately review, and integrate expert opinion for the consideration of drugs for rare diseases in the context of FDASIA, which imposes the obligation to exercise flexibility in granting accelerated approval. The very nature of rare diseases requires the FDA to establish clear opportunities for introduction of expert opinion, given the likelihood that specialized knowledge of pathology and disease course is not expected to be represented within a standing committee that covers a broad range of disease areas. The lack of sufficient specific expertise in Duchenne muscular dystrophy within the AdComm panel was apparent and made clear that some mechanism for greater expert input will be necessary.

In several instances criticisms of the data could have been easily and completely addressed at the AdComm given that the leading authority on the subject was present and available for comment, but not consulted. Oftentimes, a manuscript was being cited by the Neurology Division, but misinterpreted, yet the author of the manuscript was present in the audience to clarify, but their opinions were not sought. In our opinion, the Neurology Division presentations of the data package and criticism were poorly organized and sometimes inaccurate, leaving the AdComm confused in key areas. Thus, seeking clarification from experts in the room would have been most appropriate and would have allowed the AdComm to more meaningfully contribute a thoughtful and more informed public opinion to the Neurology Division.

One such example is that Dr. Farkas asserted that findings of 25-50% dystrophin positive fibers originally reported by the sponsor in support of dystrophin induction are inconsistent with finding of .93 % of wildtype dystrophin protein expression and uses this argument to disqualify the strong scientific evidence provided in support of dystrophin induction. *"So this is the fourth biopsy results, and it's one of the most important slides that we're going to be looking at today. So instead of the expected 25 to 50 percent normal dystrophin, as was mentioned before, there was only 0.93 plus or minus 0.84 percent of normal dystrophin in the treated patients. This was measured by Western blot, the most accurate method of quantification used by the applicant. It seems concerning that the fourth biopsy result was so inconsistent with earlier results, and this appears to raise additional important questions and to highlight the need for independent confirmation of findings."* This makes little sense and demonstrates a lack of understanding of the core metrics used for quantifying dystrophin in muscle and relevance to the disease process. There is no expectation that the number of dystrophin positive fibers correlate with the overall percentage of dystrophin expressed relative to normal. Immunofluorescence is used to assess distribution of dystrophin across muscle fibers, and western blot to quantitate the overall level of dystrophin distributed within the whole muscle sample. It is entirely plausibly and somewhat expected that relatively low levels of dystrophin would be distributed across a limited subset of the fibers. Indeed, on average .93% of wild type dystrophin was distributed across on average of 15% of the muscle fibers. Similarly, Dr. Farkas argued that the data from the fourth biopsy could not be interpreted due to the lack of matched pre-treatment control samples for all but 2 patients. Pre-treatment biopsies from Promovi were run alongside three pretreatment biopsies from the 202 study. Given that the same three pre-treatment 202 patient samples were present in analysis of biopsies 1-3 and biopsy 4, these samples serve as an internal reference that should enable validation of the PROMOVI study pretreatment biopsies as typical of the original pre-biopsy cohort. The findings are interpretable and provide strong support for dystrophin induction in response to eteplirsen treatment.

In a second example, Dr. Farkas refers to a single recent CINRG publication authored by Dr. Craig McDonald erroneously indicating that it represents the best and most robust data available reflecting typical age at of loss of ambulation; and concluding that loss of ambulation in DMD often occurs at 16-18 years. He persisted in that view despite clarification from Dr. McDonald and others that: the quoted 16-18 yr estimate was based strictly on 3 data points, that multiple available natural histories assessing much larger cohorts were available and are comparable to the clinical course of untreated external control group, with a mean age at loss of ambulation of about 12.5 years with steroid treatment. We note that the additional comparison based on LOA comparison with steroid treated/comparable mutation groups from DuchenneConnect further support that the 12 201/202 study participants are deviating from the expected disease course (independent analysis submitted to Dr. Woodcock in our email dated May 13. Dr. McDonald's data was also used to highlight apparent discrepancies between functional abilities measured by rise from floor data and 6MWT. When the sponsor asked that Dr. McDonald himself be able to explain his view that the FDA interpretation of the his study was not

correct, the request that he clarify aspects of his own data set was denied by Dr. Alexander, leaving stand an erroneous criticism that made the data seem less credible than it actually is.

In response to quantitative comparisons of clinical data, Dr Farkas stated "But as to your question of numerical comparisons, I mean, I think that's an important point that that's not the way we can analyze studies like this. This is just the truth about historically controlled trials. There's not really going to be an answer in the numbers because we have to account for these other sources of differences between the groups." This was a shocking comment. Perhaps this attitude, dismissive of a data-driven approach, is why data presented to contradict the efficacy of eteplirsen were not subjected to standard statistical analysis and rather presented as subjective data that for the reader/viewer to "eyeball". Similarly, these analyses made no attempt to match subjects for potential skewing imposed by the inclusion criterion.

Despite the lack of rigor and ability to incorporate expert opinion, we were pleased to see so many senior FDA officials present at the AdComm. The senior FDA officials clarified potentially confusing criteria for granting accelerated approval and reiterated the acceptability of the use of historical controls in assessing efficacy of non-placebo controlled studies in some circumstances. We are hopeful that they share our concern about the lack of rigorous analysis, unorganized presentation and the inability to incorporate expert opinion presented by the Neurology Division and were able to integrate the clear, concise and unanimous opinions of the DMD expert presentations, both within the Sarepta bullpen and within the open public hearing. It is possible that the appropriate mechanisms are in place and that this expert opinion is being given appropriate consideration within the agency after the OPH. However, with the ever extending timeline, there is growing concern that false controversy over the legitimacy of the sponsors claims and experimental support indicating that eteplirsen induces dystrophin expression, stabilizes walk times and pushes back expected time to loss of ambulation persists. Our consistent opinion is that data quantitating 6MWT, LOA and induced dystrophin expression each provide sufficient data for accelerated approval and that together they are more than sufficient to reasonably predict clinical gain.

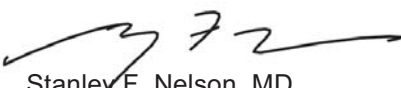
Though unnecessary, in our opinion, requested analysis of pre and post treatment biopsies from the PROMOVI study for dystrophin expression by western blotting should be straightforward and interpretation should be swift once the agency receives the data. Should findings confirm that eteplirsen treatment resulted in induction of any level of dystrophin in a subset of treated patients, interpretation should be straightforward. There should be no criteria for threshold levels or uniformity between samples; simply clear induction of even low levels of dystrophin protein in at least a significant subset of the post treatment biopsies should suffice. While we applaud the FDA's presumed rigor in taking care to properly interpret findings, we urge you to remember that delays in approval have a tangible and significant cost to families affected by Duchenne. Boys, men and even some girls with mutations amenable to correction with eteplirsen who are not included in ongoing trials continue to decline each day.

Sincerely,



M. Carrie Miceli, Ph.D.

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Stanley F. Nelson, MD
Professor of Human Genetics and Pathology and Laboratory Medicine
Co-Director, UCLA Clinical Genomics Center
Co-Director, Center for Duchenne Muscular Dystrophy
David Geffen School of Medicine at UCLA

From: [Russ, Wanda](#)
To: [Diallo, Mame K](#)
Subject: FW: Sarepta / Eteplirsen: Please read
Date: Wednesday, September 07, 2016 8:02:15 AM
Attachments: [Woodcock Eteplirsen_072816.pdf](#)
Importance: High

Log in to CDER/OEP as FYI, it is a cc to Dr. Califf

From: Evans, Dana
Sent: Wednesday, September 07, 2016 8:00 AM
To: Russ, Wanda
Subject: FW: Sarepta / Eteplirsen: Please read

Dana Evans, M.P.H.

Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

From: Louis Sterling [REDACTED] (b) (6)]
Sent: Tuesday, September 06, 2016 7:26 PM
To: Commissioner FDA
Subject: Sarepta / Eteplirsen: Please read

Hi Commissioner Califf,

Please see the attached.

Regards,
Louis

Unger, Ellis

From: Unger, Ellis
Sent: Wednesday, September 14, 2016 6:52 PM
To: Califf, Robert
Cc: Woodcock, Janet; Jenkins, John K; Borio, Luciana
Subject: RE: memo
Attachments: 2016_Sept_012_R2_Eteplirsen_CLEAN_unger.doc

Follow Up Flag: Follow up
Flag Status: Flagged

Rob,

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

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

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

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

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

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

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

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

Importantly, this discrepancy, raising important doubts about all of the immunohistochemistry data, was not known to Dr. Woodcock at the time she filed her approval memo on 7/14/16. (I had not performed these analyses until the evening of 7/15/16.) Her issuance of a decisional memorandum prior to careful consideration of my final review

represents a critical deviation from protocol. As pointed out in the SDR memo (page 10): “Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014,” and page 20: “...at the conclusion of the review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level.”

It follows, therefore, that:

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

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

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

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

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

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

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

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

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

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

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

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

I thank you for your consideration in all of this.

Ellis

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

Dear Colleagues,

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

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

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

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

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

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

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

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

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

Robert M. Califf, MD

Commissioner, Food and Drugs

Temple, Robert

From: CDER Center Director
Sent: Monday, September 19, 2016 10:01 AM
To: FDA-CDER-wide
Subject: Approval of first drug for Duchenne muscular dystrophy

CDER Staff:

Today, FDA approved the first drug to treat patients with Duchenne muscular dystrophy (DMD), a rare genetic disorder that causes progressive muscle deterioration and weakness in young children. The drug, Exondys 51 (eteplirsen) injection, is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, who constitute approximately 13 percent of the population with DMD.

Exondys 51 was approved under the accelerated approval program, reserved for drugs to treat serious or life-threatening diseases, and where there is a lack of available therapy. Accelerated approval is based on data that shows the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. Based on the data submitted by the applicant, the Agency has concluded that there is a statistically significant increase in dystrophin production in indicated patients who are exposed to the drug that meets this requirement.

While accelerated approval provides earlier patient access to promising new drugs, under its provisions FDA requires the sponsor to conduct clinical trials to verify the predicted clinical benefit of the drug. FDA is requiring Sarepta Therapeutics to conduct a clinical trial to show that the drug preserves motor function.

The approval of Exondys 51 reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases – while remaining within our statutory framework. In this case, flexibility is warranted because of the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a life-limiting disease of children. These factors, combined with the dystrophin production data – and the drug's low risk profile – led the Agency to approve the drug under the accelerated approval pathway.

In June 2015, FDA issued a [draft guidance](#) for industry on developing drugs for the treatment of DMD and related dystrophinopathies – one year following our receipt of a proposed draft guidance for consideration from the advocacy group, Parent Project Muscular Dystrophy (PPMD). This effort highlights how collaboration between engaged stakeholders and FDA can contribute to drug development. We appreciate PPMD's tireless efforts, and value their and the DMD community's input.

FDA held an [advisory committee meeting](#) on April 25, 2016 to discuss the marketing application for this drug. The advisory committee recommended that there was not substantial evidence that the drug is effective in providing clinical benefit, which is the standard for traditional approval. The AC also voted 7-6 against accelerated approval, because of uncertainties about the dystrophin data presented by the sponsor. Subsequently, the sponsor submitted additional data showing substantial evidence of dystrophin production, although the amount of dystrophin produced was only a small fraction of the normal level.

I would like to acknowledge the work done by the review team. The effort spent to evaluate the application data and scientific discussions are much appreciated.

We will continue to work with sponsors to facilitate the development and approval of effective treatments for DMD and other rare diseases.

For more information about DMD, and today's approval, visit [the press release](#).

Janet Woodcock

Philips, Howard

From: Walsh, Sandy
Sent: Monday, September 19, 2016 10:35 AM
To: Unger, Ellis; Dunn, Billy
Cc: Choy, Fannie (Yuet); Bastings, Eric; Temple, Robert
Subject: eteplirsen approval press release and documents

Here are the decisional documents that have been posted.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf

Press release: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM521263>

Sandy Walsh

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669
Sandy.Walsh@fda.hhs.gov



Philips, Howard

From: Unger, Ellis
Sent: Monday, September 19, 2016 10:22 AM
To: Dunn, Billy; Bastings, Eric; Ware, Jacqueline H; Freed, Lois M; Kozauer, Nicholas; Breder, Christopher D; Hawver, David; Choy, Fannie (Yuet); Peters, Tracy; Lowy, Naomi
Cc: Temple, Robert; Locicero, Colleen L
Subject: Eteplirsen SDR Board's Memo, Commissioner's Memo



SDR
Eteplirsen
Eteplirsen SDR Board's Memo, Commissioner's Memo



Date: August 8, 2016

To: Robert Califf, M.D.
Commissioner of Food and Drugs

From: Luciana Borio, M.D.
Acting Chief Scientist

Luciana Borio -
A

Digitally signed by Luciana Borio -
DN: cn=US, o=US Government, ou=HHS,
ou=FDA, ou=People, cn=Luciana Borio -
A, email=borio@fda.hhs.gov,
date=2016.08.08.20:00:37 -0400

Subject: Scientific Dispute Resolution Appeal regarding Eteplirsen

This matter is before the Office of the Commissioner on an appeal submitted by Ellis Unger, M.D., Director of the Office of Drug Evaluation I (ODE-I) (the initiator), under Staff Manual Guide 9010.1, “Scientific Dispute Resolution at FDA” (the SDR-SMG). In his scientific dispute resolution (SDR) appeal, dated July 18, 2016, Dr. Unger challenges the basis for a decisional memorandum issued by Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research (CDER). Dr. Woodcock’s decisional memorandum concludes that a new drug application (NDA) submitted by Sarepta Therapeutics Inc. (Sarepta) for eteplirsen, a drug intended to treat Duchenne muscular dystrophy (DMD), meets the standard for accelerated approval under 21 CFR § 314.510. Specifically, Dr. Woodcock’s memorandum states that the data submitted in support of the NDA establishes “increased dystrophin protein production, a surrogate endpoint [for DMD] that [she] conclude[s] is reasonably likely to predict clinical benefit.”¹ Dr. Unger states that he disagrees with Dr. Woodcock’s decisional memorandum because he does not believe “the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit.”²

Upon receipt of the appeal from Dr. Unger, in accordance with the SDR-SMG, the Office of the Chief Scientist convened the Agency Scientific Dispute Process Review Board (the SDR Board), a standing committee, which I chair, whose role in evaluating the appeal is to conduct a review of the processes used in the Center to render a decision on the scientific dispute at issue.³ Under the SDR-SMG, “The goal of this review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.”⁴ My role in the process, as Chair of the SDR Board, is to provide a recommendation to you, as Commissioner of Food and Drugs, with respect to “whether a Center failed to follow its processes and/or did not provide an adequate opportunity to the initiator to express his or concerns; [whether] all relevant evidence bearing on the scientific question at issue has been considered; and[] whether the dispute should be remanded to the Center Director.”⁵ The written

¹ Woodcock Decisional Memorandum at 1.

² Appeal at 3.

³ SDR-SMG at 3. (“The Agency Scientific Dispute Process Review Board (hereafter Board) is a standing committee comprised of representatives of the Office of Accountability and Integrity, Ombudsmen from all Centers and the agency (or officials so designated) and representative(s) from the Office of the Chief Scientist. The Board is chaired by the Chief Scientist.”).

⁴ *Id.* at 12.

⁵ *Id.* at 5.

recommendation must reflect the SDR Board’s underlying rationale, along with minority views among the members, for those findings.⁶

In conducting its evaluation, the SDR Board reviewed pertinent aspects of the Center’s administrative file for the eteplirsen NDA and interviewed Dr. Unger, Dr. Woodcock, one member of the review team for the NDA, who requested anonymity, and Virginia Behr, the Ombudsman for CDER. Based on its review, the SDR Board has determined that the processes followed by CDER provided Dr. Unger with an adequate opportunity to present his scientific views and that CDER considered all relevant evidence. As Chair of the SDR Board, I therefore recommend that you do not remand this matter to the Center Director for further action.⁷ However, there are additional considerations meriting your attention, which I describe below. Furthermore, the SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit.

BACKGROUND

1. *Eteplirsen and DMD*

Dr. Unger provides an overview of eteplirsen and DMD in his appeal.⁸ In short, DMD is a genetic disorder with catastrophic effects on its sufferers:

[DMD] is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene[,] . . . [which] disrupt the messenger ribonucleic acid (mRNA) reading frame [and] lead[] to the absence or near-absence of dystrophin protein in muscle cells. . . . Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. . . [and a concomitant] loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.⁹

There are no FDA-approved therapies for DMD.¹⁰ Sarepta has designed eteplirsen to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded from the resulting mRNA:¹¹

[B]y restoring [] the mRNA reading frame, a ‘truncated’ but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug

⁶ *Id.* at 13.

⁷ *See id.* (“The Commissioner will review the [SDR Board’s] recommendation and render a final decision on . . . whether the dispute should be remanded to the Center Director for corrective action” and “work with the Center Director to determine what corrective actions must be taken, if any.”).

⁸ Unless otherwise indicated, Drs. Unger and Woodcock appear to agree as to the background provided in this section.

⁹ Appeal at 2.

¹⁰ *Id.*

¹¹ The charity, Muscular Dystrophy UK, has a nice description of the technology underpinning eteplirsen, which can be accessed at: <http://www.muscular dystrophyuk.org/progress-in-research/background-information/what-is-exon-skipping-and-how-does-it-work/>.

would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.¹²

In attempting to establish that eteplirsen is safe and effective for the treatment of DMD, and thus meets one of the standards for approval in the Federal Food, Drug, and Cosmetic Act (FD&C Act), Sarepta has submitted data from three clinical studies:

Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study.¹³

Dr. Unger further explains:

The endpoints for [the three] studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.¹⁴

Immunohistochemistry (IHC) analysis looks at thin slices of muscle biopsies to see if dystrophin is present or absent. Each muscle fiber that shows any amount of dystrophin is counted as positive, regardless of the actual quantity of dystrophin present. Western blot analysis assesses how much dystrophin is present.

For Study 201/202, Sarepta submitted Western blot and IHC analysis evaluating proteins in muscle samples obtained from the twelve patients before the study and then again at twelve, 24, and 48 weeks.¹⁵ “The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable.”¹⁶ Because CDER also determined that the conditions under which the original IHC analysis was performed were inadequate, including that the reader was not masked to sequence and time, the Center requested a re-reading of the stored images by three masked pathologists under different conditions.¹⁷ The IHC results from the reread were not nearly as favorable, as compared to the initial IHC results reported by Sarepta.

¹² Appeal at 2.

¹³ *Id.*

¹⁴ *Id.*

¹⁵ *Id.* at 4, 8.

¹⁶ *Id.* at 4.

¹⁷ Unger Decisional Memorandum at 12-13.

The re-read showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group[] (. . . [T]he type-I error rate was not controlled for multiplicity.)¹⁸ Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.¹⁹

For Study 201/202, CDER also worked with Sarepta to improve the Western blot assays, and researchers performed repeat biopsies on eleven of twelve patients at Week 180.²⁰ Only three of the eleven patients had stored baseline samples that were adequate for evaluation, and so baseline samples were obtained from six additional patients external to Study 201/202.²¹ Dr. Unger also notes that all baseline samples were obtained from a different muscle group than the samples obtained at Week 180.²² Based on its own analysis of the IHC data, Sarepta claimed a remarkable increase of dystrophin immunostaining at Week 180: from 1.1% $\pm$ 1.3% positive muscle fibers at baseline to 17.4% $\pm$ 10.0% positive fibers at Week 180.²³ The Western blot analysis resulted in Week 180 dystrophin levels that were small, with a mean increase of only 0.93% of normal dystrophin levels in the muscle fibers.²⁴ Dr. Unger remarked that the lack of concordance between the IHC and the Western Blot results is “striking” and also noted that FDA did not verify the integrity of the IHC results.²⁵ As previously noted, each muscle fiber that shows any amount of dystrophin is counted as positive in IHC, regardless of the actual quantity of dystrophin present.

As noted above, Study 301 is an ongoing study. For purposes of its review of the NDA, CDER requested that Sarepta perform Western blot analysis on samples obtained from 13 patients enrolled in the study.²⁶ The analysis compared paired biceps samples: baseline samples and samples obtained at 48 weeks, after 48 weeks of treatment with 30 mg/kg of eteplirsen infusion.²⁷ Dr. Woodcock told the SDR Board that representatives from CDER were present in the laboratory for the Western blot analysis and oversaw the procedures and controls. The Western blot analysis showed a statistically significant increase in dystrophin, ranging in an increase from 0.22% to 0.32% of normal.²⁸ It should be noted, however, that a statistically significant increase in dystrophin, the surrogate endpoint, of an exceptionally small magnitude does not imply clinical benefit, which is the issue at the core of Drs. Unger and Woodcock’s scientific disagreement.

¹⁸ That is, with respect to time points of assessment and the 2 doses tested.

¹⁹ Appeal at 8-9. Of note, in her decisional memorandum, Dr. Woodcock rejected the findings in both the original and second evaluation of the images: “Much of the controversy over the adequacy of these assessments relates to the fact that rigorously validated assays were not used to evaluate the initial 3 muscle biopsies, apparently resulting in overestimation of the various readouts and some irreproducibility of IHC and Western blot dystrophin assays. For these reasons, I do not discuss or rely upon the results of these earlier assays, or on re-reads of them.” (Woodcock Decisional Memorandum at 2). She explained to the SDR Board that, after consultation with others in CDER, she does not view IHC results standing alone as a valid method to evaluate dystrophin levels.

²⁰ Appeal at 5.

²¹ *Id.* at 5, 9.

²² *Id.* at 5. Dr. Unger clarifies in his decisional memorandum that the baseline biopsies were from the biceps muscle, the Week 180 biopsies from the deltoid muscle. (Unger Decisional Memorandum at 17).

²³ Appeal at 9. As discussed below, however, Dr. Unger does not believe that those results are reliable.

²⁴ *Id.* at 5.

²⁵ *Id.* at 9-10.

²⁶ *Id.* at 6. Dr. Unger states that the biopsies were obtained from 13 patients but only reports the data as to 12 patients. “There was one patient for whom none of the values met the acceptance criteria [for the Western blot assay].” (Unger Decisional Memorandum at 21).

²⁷ Appeal at 6.

²⁸ *Id.*

2. Legal Standard for Accelerated Approval and Patient Perspectives

On December 11, 1992, on the basis of its broad statutory authority to approve drugs under the FD&C Act, FDA issued regulations providing for accelerated approval of drugs.²⁹ Under 21 CFR § 314.510, FDA may grant accelerated approval for a drug based on a surrogate endpoint under certain circumstances:

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** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.³⁰

The preamble to the proposed rule defines “surrogate endpoint” as follows:

A surrogate endpoint, or “marker,” is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy. For example, elevated cholesterol and hypertension, two surrogate endpoints, are important because they are risk factors for coronary and cerebral artery disease; but it is the impact of the diseases (e.g., angina, congestive heart failure after a heart attack, paralysis after a stroke, or sudden death) that is important to the patient.³¹

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA). Section 901 of FDASIA amended the FD&C Act to provide FDA with specific authority to grant accelerated approval to drugs for serious conditions.³² Section 506(c) of the FD&C Act now largely tracks language in the regulations issued by FDA in 1992. Section 901 of FDASIA also added current section 506(e) to the FD&C Act, which clarifies that the amendments were “intended to encourage [FDA] to utilize innovative and flexible approaches to the assessment of products under accelerated approval” but that “[n]othing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d) of [the FD&C Act].”³³

Section 901 of FDASIA also directed FDA to issue guidance to industry on the development of

²⁹ 57 Fed. Reg. 58942 (Dec. 11, 1992).

³⁰ Emphasis added.

³¹ 57 Fed. Reg. 13234, 13235 (Apr. 15, 1992).

³² FDASIA, PL 112-144, July 9, 2012, 126 Stat. 993.

³³ *Id.*

drugs for accelerated approval and required consideration of the following:

In developing the guidance . . . [FDA] shall consider how to incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence in such guidance, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical.³⁴

Section 1137 of FDASIA further directs FDA to:

develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions, including by—(1) fostering participation of a patient representative who may serve as a special government employee in appropriate agency meetings with medical product sponsors and investigators; and (2) exploring means to provide for identification of patient representatives who do not have any, or have minimal, financial interests in the medical products industry.³⁵

In May 2014, FDA finalized a guidance on “Expedited Programs for Serious Conditions — Drugs and Biologics.” The Guidance provides general information on the evidence that the agency considers in determining whether to grant accelerated approval.³⁶ The Guidance clarifies that assessing a surrogate endpoint hinges on understanding both the disease process and the relationship between the drug’s effect and the disease process.³⁷ With respect to the latter, the Guidance states:

The extent to which a drug’s effect on the surrogate endpoint is known to predict an effect on the disease either because the effect is on the causal pathway or correlates with clinical outcomes is critical. Sometimes this relationship can be assessed epidemiologically[,] but it is most persuasively established by knowing that a drug that affects the surrogate endpoint also affects a clinical outcome.³⁸

The Guidance also provides some insight on how the agency exercises its judgment in evaluating surrogate endpoints when little is known about how an effect on a surrogate endpoint might affect clinical endpoints:

Particularly in rare diseases, there may be limited information in the literature, lack of in-depth epidemiological or historical data, and little or no experience with other drugs to inform the interpretation of surrogate endpoints or intermediate clinical endpoints. FDA may consult with external experts on surrogate endpoints and intermediate clinical endpoints where there is a lack of historical data for a given disease.³⁹

³⁴ *Id.*

³⁵ *Id.*

³⁶ Expedited Programs Guidance at 19-22.

³⁷ *Id.* at 20-22.

³⁸ *Id.* at 21.

³⁹ *Id.* at 21-22.

FDA obtains patient perspectives through a variety of avenues, “such as open public hearings on specific diseases or drug development issues, and as speakers at FDA-sponsored conferences and workshops.”⁴⁰

3. *SDR-SMG and CDER’s SDR-SOPs*

The Office of the Commissioner issued the SDR-SMG on January 13, 2009. Its stated purpose is “to improve the process of internal scientific dispute resolution[] and to encourage open communication throughout the agency.”⁴¹ The SMG “encourages the resolution of scientific disputes at the working level in the organization, starting with the frontline employees and their immediate supervisors or team leaders” and cautions that the “agency’s appeals process for scientific disputes is not a replacement for robust and fair Center-level processes.”⁴² As noted above, the SDR-SMG provides for submission of SDR appeals to the Office of the Commissioner and outlines the process and standards for evaluating such appeals. Under the SDR-SMG, the SDR Board evaluates whether “the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.”⁴³ As Chair of the SDR Board, the Chief Scientist then provides a written recommendation on those issues to the Commissioner, who renders a final decision on whether the scientific dispute should be remanded to the Center for further action.⁴⁴

In addition to outlining the process for elevating scientific disputes to the Office of the Commissioner, the SDR-SMG details the agency’s “requirements for the minimum standards for scientific dispute resolution processes in the Centers” and provides a collection of non-mandatory “best practice[s]” for such dispute resolution.⁴⁵ The SDR-SMG’s requirements for resolving scientific disputes at the Center-level begin with an obligation on the part of Center management to ensure open scientific debate on controversial issues:

Center management shall create an atmosphere in which consultation and open discussion on controversial issues are encouraged. When disagreements occur, it is necessary to follow appropriate procedures for resolving them. Informal methods, using good management practices for resolving conflict, should be employed prior to instituting the more formal procedures described here. Notwithstanding informal good management practices used to try to resolve the conflict, timely written reviews of the scientific matter in dispute should be completed by all members of a review group, including initiator and supervisors, to enable as open and complete a discussion of the issues as possible at the working level of the organization.⁴⁶

The SDR-SMG then goes on to require the Centers to have in place written standard operating procedures for formally resolving scientific disputes (SDR-SOPs) in the event that such informal attempts at resolution are unsuccessful.⁴⁷ In contrast to the procedural review contemplated by

⁴⁰ 79 Fed. Reg. 65410, 65411 (Nov. 4, 2014).

⁴¹ SDR-SMG at 1.

⁴² *Id.* at 2.

⁴³ *Id.* at 12.

⁴⁴ *Id.* at 12-13.

⁴⁵ *Id.* at 2-3.

⁴⁶ *Id.* at 6.

⁴⁷ *Id.*

the SDR-SMG, Center-level SDR-SOPs should provide for substantive review of the scientific disputes at issue within the Center.⁴⁸

At CDER, there are three interrelated chapters of the Center’s Manual of Policies and Procedures (MAPPs) that serve to implement the SDR-SMG’s requirements. The first, MAPP 4151.8, “Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions,” sets forth CDER’s principles for resolving scientific disputes informally and requires “a collaborative environment for decision-making.”⁴⁹ According to the MAPP, “[s]uch an environment requires open communication and exchange of ideas in a mutually respectful professional environment[] and the full and open participation of all relevant disciplines and organizational components in the decision-making process.”⁵⁰ MAPP 4151.8 states that “[e]ach individual who contributes to the decision-making process” must “be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component” and that “[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made.”⁵¹

The second and third MAPPs at issue directly relate to CDER’s formal SDR process. MAPP 4151.1, “Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain,” provides for raising a scientific issue to the “Next Highest Management Official” (NHMO) if alignment on an issue cannot be reached by the staff on a team or through discussions with a team leader or first-level supervisor. The individual who disagrees with the decision (the disputant) “. . . may initiate a dispute resolution process by writing a statement (called a dispute statement) describing the position, concept, opinion, or recommendations with which the disputant disagrees . . . as well as the proposed changes and rationale for the changes in recommendations and/or conclusions.”⁵²

The disputant submits the statement to the NHMO, i.e., “the management official one level above the management official who made the decision being disputed.”⁵³ The NHMO then issues a written decision on the issue, and any disputant may then appeal the written decision up the chain of command all the way to the Center Director through use of the same process.⁵⁴ MAPP 4151.2, “Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director,” provides for further formal review under certain circumstances if alignment cannot be reached under the process in MAPP 4151.1.⁵⁵ A CDER employee may initiate the process by submitting a written package, which must include “[a]n assessment of the possible significant negative consequences to the public health” at issue in the dispute, to the CDER Ombudsman.⁵⁶ The CDER Ombudsman and the Center Director then “determine whether the consequences of the decision in question are potentially serious enough to warrant” additional review.⁵⁷ If so, the Center Director appoints a chairperson to lead an *Ad Hoc* review panel for purposes of evaluating the scientific dispute and providing a recommendation to the Center

⁴⁸ See *id.*; see also footnote 136.

⁴⁹ MAPP 4151.8 at 2.

⁵⁰ *Id.*

⁵¹ *Id.* at 2-3.

⁵² MAPP 4151.1 at 3.

⁵³ *Id.*

⁵⁴ *Id.* at 4.

⁵⁵ *Id.* at 5; MAPP 4151.2 at 1-2.

⁵⁶ MAPP 4151.2 at 5.

⁵⁷ *Id.*; see also *id.* (“In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted . . .”).

Director, who renders the final decision.⁵⁸ The *Ad Hoc* panel typically includes one member with relevant technical expertise, one member chosen from a list provided by the person requesting review, and, if possible, one member with relevant expertise who is external to the agency.⁵⁹

4. *Procedural History of the Dispute in CDER*

Sarepta submitted its NDA for eteplirsen (#206488) on June 26, 2015.⁶⁰ CDER assigned it for review to the Division of Neurology Products (DNP) within ODE-I, the office for which Dr. Unger serves as Director.⁶¹ Even before submission of the NDA, however, representatives from the Office of New Drugs (OND), DNP and ODE-I (the review team) regularly briefed Dr. Woodcock on issues related to the ongoing study of eteplirsen pursuant to an investigational new drug application (IND) and the anticipated NDA.⁶² The discussions at these briefings included among their topics: the suitability of eteplirsen for accelerated approval, an overview and background for eteplirsen, study design, a clinical site inspection report for Sarepta, general brainstorming, and planned communications.⁶³ Dr. Unger told the SDR Board both that there were far more briefings of the Center Director than is typical and that the scope of those briefings included an unusual level of detailed discussion.

During the SDR Board's separate interviews of Dr. Unger and the review team member (RTM), the SDR Board learned that, at Dr. Woodcock's direction, the review team also joined her in meetings with patient advocacy groups for DMD on multiple occasions—anywhere from six to twelve times—from very early on in the review process. The RTM described the meetings with the patient advocacy groups, which frequently included boys with DMD and their parents, as “intense,” “personal,” and “intimidating.” Dr. Unger and the RTM both thought that Dr. Woodcock's early interest and involvement in DNP's approach to guiding the development of eteplirsen was based in part on the enthusiasm in the DMD community in relation to an article published about the initial findings for Study 201/202, which Drs. Unger and Woodcock now agree are misleading and unreliable. Indeed, Dr. Woodcock told the SDR Board that she became involved because of the broader public interest the article generated, along with encouragement from the Commissioner of Food and Drugs at the time and her long-held belief that OND has been very conservative in evaluating drugs for accelerated approval. In his decisional memorandum, Dr. Unger explains the excitement surrounding eteplirsen at the time as follows:

[The initial findings for Study 201/202] were substantially reported in a 2013 publication, which claimed that eteplirsen markedly increased functional dystrophin production: “...*the percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients (p≤0.002). Even greater increases occurred at week 48 (52% and 43%*

⁵⁸ *Id.* at 6-7.

⁵⁹ *Id.* at 6.

⁶⁰ Unger Decisional Memorandum at 1.

⁶¹ *Id.* at 2.

⁶² Appeal at 24-25; Chronology prepared by Virginia Behr and submitted to the SDR Board (Behr Chronology) at 1-2. In his appeal, Dr. Unger consistently refers to the representatives from OND, OND-I and DNP who were involved in the review of the eteplirsen NDA as the “review team” or as “the division,” even though he appears to be referring to senior management within OND on occasion. Dr. Woodcock has also used the same terminology on occasion, though not as consistently. For the sake of efficiency, this memorandum refers to everyone at CDER who was involved in the review of the eteplirsen NDA, besides Dr. Woodcock herself, as the review team. Nonetheless, the SDR Board notes that, within FDA, “review team” is often used to reflect the core team of individuals within a division who are directly engaged in the review of the science underlying a regulatory submission.

⁶³ Appeal at 24-25; Behr Chronology at 1-2.

in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma.” The publication also stated that dystrophin expression was confirmed by Western blot, with a figure showing what were termed “representative” results.

Publication of this paper was followed by a Sarepta press release, which also claimed a remarkable treatment effect from eteplirsen and raised wildly unrealistic expectations in the DMD community.⁶⁴

In their interviews with the SDR Board, Dr. Unger and Dr. Woodcock stated that FDA also received significant correspondence from the public and Congress, much of which urged approval of eteplirsen.⁶⁵ Some of the correspondence used vulgar language and was abusive to the review staff.⁶⁶

The briefings of Dr. Woodcock began again five to six months after submission of the NDA for eteplirsen.⁶⁷ The focus of these briefings was on preparation for a planned meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (AC meeting) to provide advice on the review of the eteplirsen NDA, which meeting was initially scheduled for January 2016 but then rescheduled for April 25, 2016.⁶⁸ The preparation involved discussions of the ongoing review of the data, including 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.”⁶⁹ During their respective interviews with the SDR Board, both Dr. Unger and the RTM conveyed their belief that Dr. Woodcock was inclined to grant approval from very early on in the process. But the RTM stated that Dr. Woodcock’s views were not always clear during discussions throughout the review of the science—sometimes she seemed to agree with external constituents, sometimes not. The RTM told the SDR Board that, in his or her view, the review team was never sure whether they were discussing science, policies, or politics. According to both Dr. Unger and the RTM, Dr. Woodcock frequently conveyed that she thought the review team was being unreasonable and encouraged DNP to find a way to approve the eteplirsen NDA. Both Dr. Unger and the RTM told the SDR Board that Dr. Woodcock seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of overarching policy (e.g., the need to be more flexible for ultra-rare diseases). The RTM highlighted to the SDR Board that at least two members of the review team were leaving FDA or had left the agency in the wake of both the decision-making process within CDER and the pressures exerted by outside forces.

Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014. She said that her goal throughout the discussions

⁶⁴ Unger Decisional Memorandum at 11 (emphasis in original), citing Mendell JR, *et al*: Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013;74:637-47 and Sarepta press release, dated 8/8/13 (<http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irolnewsArticle&ID=1846052>). Dr. Unger also notes, “It was these perceptions and expectations that led the applicant to declare that a placebo-controlled study was no longer feasible.” Unger Decisional Memorandum at 11.

⁶⁵ See also Appeal at 23.

⁶⁶ See, e.g., *id.* at 23-24.

⁶⁷ *Id.* at 25; Behr Chronology at 2-3.

⁶⁸ Appeal at 25; Behr Chronology at 2-3.

⁶⁹ Appeal at 25.

with the review team was to convince them to come around to her more flexible way of thinking about the data. According to Dr. Woodcock, she recognized that there were serious and significant flaws in the study design for Study 201/202 and the data it generated but that she did not “want to hold” those flaws “against the patients.” She conceded that the results produced by Studies 201/202 and 301 were always less than anyone in CDER had hoped.

In their respective interviews with the SDR Board, both Dr. Unger and the RTM focused to some extent on Dr. Woodcock’s involvement in the planning stages for the AC meeting. They expressed some surprise at the extent of her involvement. Dr. Unger indicated in his interview with the SDR Board that Dr. Woodcock even advocated, unsuccessfully, for changing the order of the questions to be posed to the committee and wanted the question on conventional approval to come before the one on accelerated approval.

The RTM told the SDR Board: (1) that Dr. Woodcock made it clear in one or more of the meetings leading up to the AC meeting that she intended to speak at the meeting but (2) that the substance and purpose of her participation were never communicated. Although the RTM affirmatively stated that the review team was free to develop its own presentation to the committee, uncertainty with respect to Dr. Woodcock’s role made doing so more difficult. The RTM also noted that Dr. Woodcock requested a longer than is typical Open Public Hearing portion of the AC meeting that, as a result, the review team thought there would insufficient time for them to make their presentations during a one-day meeting. The RTM stated that the review team asked to extend the advisory committee to two days but that they were overruled.

On April 25, 2016, CDER held the AC meeting. The meeting focused on the data from Study 201/202.⁷⁰ Dr. Woodcock spoke at the meeting several times. At the meeting she made a presentation that was intended to “provide a framework within which to consider [the] data [underlying the eteplirsen NDA] based on [her] 30 years of experience at FDA and really extensive experience in implementation of the legal standards for drug approval.”⁷¹ She highlighted many of the difficulties in interpreting the data.⁷²

At the AC meeting, Dr. Woodcock also described the standards for both conventional and accelerated approval of drugs but mentioned that the agency had not “articulated an evidentiary standard for determining if a surrogate endpoint is reasonably likely to predict clinical benefit.”⁷³ She concluded her presentation with the following remarks:

I would note that 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 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 borne by patients who traditionally [] have little say in how the standards are implemented.

The accelerated approval program includes a requirement for confirmatory studies for efficacy, so as you've heard from the sponsor, you have to do further studies to explore and confirm effectiveness. An inherent

⁷⁰ Sarepta had not yet submitted the data from Study 301.

⁷¹ Advisory Committee Transcript at 151.

⁷² *Id.* at 151-155.

⁷³ *Id.* at 155-156.

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.⁷⁴

During the questions to the committee members, Dr. Woodcock restated the standard for accelerated approval and emphasized that, with regard to the surrogate endpoint of dystrophin, there has never been a “threshold established [to show a reasonable likelihood of predicting clinical benefit] because there’s never been a drug to do this.”⁷⁵ When later asked for clarification of the extent to which the committee members were to incorporate the testimony of the boys and their families into their evaluation of clinical outcomes for Study 201/202, Dr. Woodcock stated:

Well, we are instructed, as people said, to take the use of the patient community into account, more on the benefit and the risk. * * * So the statutory standard is more or less as described there, but there is flexibility, and that’s where we should take the views of the community into account.⁷⁶

During his SDR Board interview, the RTM stated that, notwithstanding Dr. Woodcock’s emphasis on accelerated approval and the standard of “reasonably likely to predict clinical benefit,” “[s]urrogacy was not discussed in any genuine scientific way” during the AC meeting because it had not been framed that way by Sarepta through its presentation to the committee. The RTM specifically stated that there was no discussion of “substantial evidence” in the context of accelerated approval, nor what might constitute “interpretable evidence.” The RTM believed that, by the end of an emotional AC meeting, the framework for evaluating the data under the appropriate regulatory standards, as provided by the review team toward the start of the meeting, had been forgotten by the committee members.

Dr. Woodcock explained to the SDR Board that she thought both that the review team did a poor job framing the issues during their presentations and that the questions were confusing and poorly worded. Indeed, during her interview with the SDR Board, Dr. Woodcock opined that the review team “did not put its best foot forward.” She speculated that the confounding factor was the number of interested persons attending both in person and by webcast. She stated that she did not interfere with either aspect of the AC meeting because she knew she disagreed with the review team and Dr. Unger had already signaled that he would file an SDR appeal if she decided to grant accelerated approval to eteplirsen. She thought that the review team’s presentation of the IHC data, in particular, was confusing. She further opined that the review team’s failure to highlight the clinical data made the questions on conventional approval and accelerated approval difficult for the committee members to understand. Dr. Woodcock also criticized the review team for how it downplayed and undercut the views of the patient advocates.

At the conclusion of the AC meeting, the committee voted against accelerated approval by a margin of 7-6.⁷⁷ Three of the members who voted in favor of accelerated approval were the consumer representative and the two patient representatives.⁷⁸

⁷⁴ *Id.* at 158-59.

⁷⁵ *Id.* at 484.

⁷⁶ *Id.* at 548-549.

⁷⁷ *Id.* at 486-95.

⁷⁸ *Id.* at 2-7, 486-88.

On May 4, 2016, Dr. Woodcock met with the review team to discuss the AC meeting and plan of actions for the NDA.⁷⁹ In his appeal, Dr. Unger contends that Dr. Woodcock “made clear her intent to approve the drug” at this meeting, even though she had not yet reviewed drafts of DNP’s final review memorandum or his review memorandum.⁸⁰ According to Dr. Unger, Dr. Woodcock explained that she had already “reached a different conclusion” than the review team.⁸¹ Dr. Woodcock explained to the SDR Board that the memoranda were discussed during the Center Director briefings and that she felt she understood the views of the review team and did not see the point of an “exchange of reviews.”

On May 24, 2016, Dr. Unger met privately with Dr. Woodcock to discuss the eteplirsen decision.⁸² On May 31, 2016, Dr. Woodcock met with representatives from the review team to discuss their reviews and her initial draft of a decisional memorandum based primarily on the data from Study 201/202.⁸³ Dr. Woodcock received comments back from the review team at the same meeting.⁸⁴ Dr. Unger told the SDR Board that he and members of the review team—including Dr. Robert Temple, Deputy Center Director for Clinical Science and Dr. John Jenkins, Director of OND—discouraged Dr. Woodcock from finalizing the decisional memorandum and granting accelerated approval for eteplirsen until the additional data from Study 301 could be obtained.

On June 3, 2016, in response to an email from Sarepta, a letter signed by Dr. Woodcock issued to the sponsor.⁸⁵ The letter requested the additional data from Study 301, which was to include comparisons of any biopsy samples obtained at Week 48 to the respective baseline samples for those patients.⁸⁶ The letter stated,

If you are successful in showing, to FDA’s satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).⁸⁷

Dr. Woodcock explained that Dr. Unger and the review team essentially agreed to the timeframe of four business days, though they pushed instead for six. She felt that there was general agreement that data from only twelve patients could be reviewed quickly, especially given that representatives from CDER would be overseeing the Western blot analysis and ensuring that it was done properly.

On June 27, 2016, Sarepta submitted the requested data.⁸⁸ Dr. Woodcock explained that accelerated approval was not granted within four business days of that date precisely because the results of the analysis were disappointing in that they provided evidence of only a minimal increase in dystrophin at 48 weeks. Dr. Unger sent an email to Dr. Woodcock that read:

⁷⁹ Appeal at 25; Behr Chronology at 2.

⁸⁰ Appeal at 26.

⁸¹ *Id.*

⁸² Behr Chronology at 2.

⁸³ Appeal at 26; Behr Chronology at 2.

⁸⁴ Behr Chronology at 2.

⁸⁵ June 3, 2016, General Advice letter.

⁸⁶ *Id.* at 1.

⁸⁷ *Id.* at 1-2.

⁸⁸ Unger email to the SDR Board, dated July 22, 2016.

I don't have to tell you how difficult the eteplirsen decision has been for many of us in ODE-I. As you know, we have reached different scientific conclusions on the strength of the data, and in particular, the likelihood that the small increase observed in Becker-type dystrophin is reasonably likely to predict clinical benefit. This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed "reasonably likely to predict clinical benefit." Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.

I know that Dr. Jenkins has mentioned the possibility of involving Dr. Califf in the eteplirsen decision on at least one occasion, and I would like to request a formal appeal to the Commissioner on this matter.

I'm aware that the Commissioner's official role is to consider the administrative aspects of review decisions and not the science. But given the potential for setting a precedent here, I think he should be aware of the various points of view and consider the potential ramifications of the matter at hand.

I'm also aware that you advised Sarepta that we would be prepared to grant accelerated approval of their NDA within 4 business days of receiving their new data, but there was a provision in the letter that the increase in dystrophin had to be meaningful, and we do not have agreement on this point. Thus, it is my hope that a Commissioner Briefing can be held before an action is taken.

I have discussed the above with Dr. Jenkins, and he supports this course of action.

I propose that we reserve a few minutes at the briefing tomorrow to discuss this matter.⁸⁹

On July 6, 2016, Dr. Woodcock met with the review team one final time.⁹⁰ During the meeting, Dr. Woodcock "indicated to the review team that [she] had read their memoranda that had been updated to reflect the new [Western blot] data, and that [she] maintained [her] position that the application should receive accelerated approval based on dystrophin production."⁹¹ She discussed her rationale, which—based on her notes—appears to have tracked the rationale in her final decisional memorandum.⁹²

On July 8, 2016, in light of Dr. Unger's stated intention of filing an appeal with the Office of the Commissioner, Virginia Behr, CDER Ombudsman, began working with him and Dr. Woodcock to determine whether the institution of any formal appeals under CDER's SDR-SOPs was warranted.⁹³ Ms. Behr had determined that the procedure outlined in MAPP 4151.1,

⁸⁹ Unger email dated July 5, 2016.

⁹⁰ Appeal at 26; Behr Chronology at 3.

⁹¹ Woodcock's handwritten notes, dated July 6, 2016, at 1.

⁹² *Id.* at 2. Also of note, on July 7, 2016, Dr. Unger briefed you on his rationale for disagreeing with Dr. Woodcock's underlying scientific reasoning for granting accelerated approval for eteplirsen (Behr Chronology at 3).

⁹³ See "Agreement to utilize FDA Staff Manual Guide 9010.1 for internal appeal related to NDA 206488, eteplirsen injection" (SDR-SOPs Agreement).

“Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain” did not apply because the disagreement was between the Center Director and a subordinate two levels below her.⁹⁴ She also questioned the utility of using MAPP 4151.2, “Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director.”⁹⁵ She reasoned that “the CDER Director ha[d] already fully evaluated the issues and [was] one of the parties involved in the dispute” and that “utilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days.”⁹⁶ She nonetheless consulted with both Drs. Unger and Woodcock, who both agreed to bypass the *Ad Hoc* panel process in favor of the process outlined in the SDR-SMG.⁹⁷ During his presentation to the SDR Board, Dr. Unger also indicated that he thinks referring the matter to an *Ad Hoc* panel would have been pointless because Dr. Woodcock had already made up her mind and a new process would not have changed the outcome.

On July 11, 2016, Dr. Woodcock provided a draft of her final decisional memorandum to the review team.⁹⁸ She received comments back from Dr. Unger; Dr. Jenkins, the Director of OND; and Dr. Ashutosh Rao, of the Office of Biotechnology Products, who was also on the review team.⁹⁹ The comments from Drs. Unger and Rao do not debate the action proposed in Dr. Woodcock’s draft decisional memorandum or its underlying scientific conclusions.¹⁰⁰ Instead, they focus on clarifying certain facts asserted in the memorandum, and Dr. Unger provided information regarding the clinical course of 11 patients enrolled in Study 201/202 to 240 weeks.¹⁰¹ Dr. Jenkins provided more detailed analysis on and critique of some of Dr. Woodcock’s findings and he expressed concern about her conclusions. However, he made no attempt in his written comments to dissuade her from her ultimate conclusion regarding accelerated approval.¹⁰² By email on the afternoon of July 13, Dr. Unger stated, “I’ve canvassed the Division, and we have no additional comments.”¹⁰³ Dr. Unger told the SDR Board that he and the review team understood that Dr. Woodcock had already made up her mind and that thus they did not see a point in criticizing Dr. Woodcock’s draft decisional memorandum.

Furthermore, the RTM told the SDR Board that some of the positions taken by Dr. Woodcock in the draft decisional memorandum were brand new to him but that he did not feel any feedback he could provide would receive due consideration by Dr. Woodcock. The RTM expressed concern that Dr. Woodcock’s analysis for “reasonably likely to predict clinical benefit” raised new issues and information that should have been presented at the beginning of the review and that had not been addressed by the review team or, perhaps more importantly, presented by the sponsor in support of the NDA. The RTM specifically discussed with the SDR Board the section of the finalized version of the memorandum addressing whether the data for eteplirsen is adequate to show a reasonable likelihood of predicting clinical benefit.¹⁰⁴ As an example of his concerns, the RTM pointed to section (B)(5) of the decisional memorandum, which details the findings in the

⁹⁴ *Id.* at 1. It is also clear from the record before the SDR Board that the supervisor between Drs. Unger and Woodcock, Dr. John Jenkins, agreed with Dr. Unger.

⁹⁵ *Id.*

⁹⁶ *Id.* at 2.

⁹⁷ *Id.*

⁹⁸ Behr Chronology at 3.

⁹⁹ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); Jenkins email dated July 12, 2016; and emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰⁰ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰¹ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰² Jenkins email dated July 12, 2016.

¹⁰³ Unger email dated July 13, 2016 and sent at 3:19 PM.

¹⁰⁴ Woodcock Decisional Memorandum at 5-10.

scientific literature regarding “the relationship of dystrophin expression to clinical status.”¹⁰⁵

The RTM indicated that he or she knows the scientific literature at issue very well and that he or she could have provided significant input into the evaluation of the literature and the underlying data and analysis. The RTM conveyed that he did not do so because he felt Dr. Woodcock had already made her decision.

On July 14, 2016, Dr. Woodcock finalized her decisional memorandum. She explained to the SDR Board that her conclusion regarding whether the increase in dystrophin production identified by Studies 202 and 301 was reasonably likely to predict clinical benefit was based on her own “medical/scientific judgment.” She emphasized that she has thirty years of experience at FDA and that she has far more experience in assessing this type of evidence for an “ultra-rare rare” disease than the review team. She thought that the review team was unreasonable in its position on a threshold for predicting clinical benefit in this case. Her stated goal for the decisional process was to move the review team toward what she viewed as a more reasonable approach. She acknowledged that there were clear weaknesses in the data but that accelerated approval should not be limited to “sure bet” drugs and that confirmatory trials are required for a reason. Dr. Woodcock emphasized her view that the agency needs to accept more uncertainty when granting accelerated approval. She also criticized OND for not issuing clear guidance on what constitutes a sufficient drug effect to be “reasonably likely to predict clinical benefit,” as she had suggested for an extended period of time. She also thought that the review team’s views on balancing the mean results of a clinical study with a targeted evaluation of responsive patients were misplaced, particularly in a DMD population, where additional genetic mutations or deficiencies could have a profound effect on the outcome.

In her presentation to the SDR Board, Dr. Woodcock suggested that, in making the decision, she was looking at the broader picture for the development of these types of drugs for very limited patient populations in the United States (between 600 and 1300) and that there needed to be some path forward for such innovative products. She opined that Sarepta in particular “needed to be capitalized.” She noted that the sponsor’s stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would “lapse into a position of” self-treatment.

On July 16, 2016, Dr. Unger finalized his own decisional memorandum. In her own decisional memorandum, dated July 14, 2016, Dr. Woodcock indicated that she had read Dr. Unger’s decisional memorandum,¹⁰⁶ although she could not have done so given the timing of the two memoranda. She explained to the SDR Board that she did not feel she needed to see a finalized version of Dr. Unger’s decisional memorandum because she was already familiar with his views on the data and the decision. She also stated that there was nothing in Dr. Unger’s appeal, which is based largely on his finalized decisional memorandum, that would have changed her mind on her decision or the underlying rationale. She stated, “He is entitled to his own opinion.”

5. Dr. Unger’s SDR Appeal

In his appeal, Dr. Unger focuses his arguments almost exclusively on the substance of his scientific disagreement with Dr. Woodcock. Indeed, Dr. Unger makes clear in his appeal that he

¹⁰⁵ *Id.* at 7-10.

¹⁰⁶ *Id.* at 1.

seeks “a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit.”¹⁰⁷ Insofar as he explicitly addresses potential procedural issues under the review process contemplated by the SDR-SMG, he does so in two paragraphs toward the end of the appeal.¹⁰⁸ He first states that Dr. Woodcock’s “direct involvement with this drug, compared to other development programs, has been unprecedented.”¹⁰⁹ He states further that “[s]he also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments.”¹¹⁰ After conceding that “[t]here is no question that there has been adequate time and place for the discussion of various views,” Dr. Unger notes that he found it unfortunate that “the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division’s final review memorandum or my review memorandum.”¹¹¹ As noted above, Dr. Unger indicates that Dr. Woodcock conveyed that she had “already ‘. . . reached a different conclusion . . .’ than the review team.”¹¹²

In his presentation to the SDR Board, Dr. Unger highlighted that Dr. Woodcock had never seen the charts on page 10 of his appeal. Those charts show: (1) a comparison of the *original* IHC results for baseline samples in the three patients whose biopsies were available at 180 weeks to the IHC results for those same samples when they were re-evaluated after 180 weeks and (2) a comparison of the IHC and the Western blot results at 180 weeks.¹¹³ Dr. Unger stated, however, that those charts were consistent with his earlier positions and would likely not affect Dr. Woodcock’s analysis or decision. In a follow-up email to the SDR Board, Dr. Unger also contended that Dr. Woodcock diverted from protocol when she finalized her decisional memorandum on July 14, 2016, two days before his.

In his appeal, Dr. Unger frames his scientific disagreement with Dr. Woodcock as follows: “The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit.”¹¹⁴ Nonetheless, Dr. Unger explains his disagreement with Dr. Woodcock through multiple challenges to the reliability of the underlying data and specific issues he has with her rationale or the evidentiary basis for such rationale. Of note, he makes the following scientific arguments:

- As noted above, Study 201 showed only “a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group...”;¹¹⁵
- Study 201/202 was fundamentally flawed in several respects:
 - “[T]he baseline biopsies were obtained from [external controls] . . . who could differ in unknown ways from the subjects in Study 201/202”;¹¹⁶
 - “[T]he Week 180 biopsies were obtained from different muscles than the baseline biopsies”;¹¹⁷ and

¹⁰⁷ Appeal at 26.

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ *Id.*

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.* at 10.

¹¹⁴ *Id.* at 3.

¹¹⁵ *Id.* at 9.

¹¹⁶ *Id.* at 5.

¹¹⁷ *Id.*

- “The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline....”¹¹⁸
- Although the available data generated by Study 301 were the product of an adequate and well-controlled study and showed a statistically significant increase of dystrophin, the drug effect (i.e., an increase from 0.22% to 0.32% of normal) is not reasonably likely to predict clinical benefit.¹¹⁹
 - “The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications”;¹²⁰
 - “Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that ‘...low-level increases in dystrophin production are reasonably likely to predict clinical benefit.’ She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit”;¹²¹ and
 - “No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.”¹²²

He also makes several overarching policy and legal arguments that call into question the appropriateness of Dr. Woodcock’s decisional memorandum. His key arguments focus on the effects that Dr. Woodcock’s decision would have on the pathway for accelerated approval and the standard for “reasonably likely to predict clinical benefit.”¹²³ He also highlights the negative effects that accelerated approval would have on the patients themselves, including false hope, abandonment of other therapies, and a decline in drug development for DMD.¹²⁴ He further questions “the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic[] when the consequence of a sub-therapeutic dose is clinical deterioration and death.”¹²⁵ Finally he worries that approving eteplirsen based on the data submitted by the sponsor “would send the signal that political pressure and even intimidation—not science—guide[] FDA decisions.”¹²⁶

ANALYSIS

1. *Whether CDER followed its own processes.*

The first issue for the SDR Board to consider is whether CDER followed its own processes in addressing Dr. Unger’s scientific dispute. Dr. Unger does not contend that there were any issues with respect to how CDER chose to address and implement its own formal appeals process under the SDR-SOPs in this case. In his appeal, Dr. Unger points instead to four deviations from typical Center process: (1) Dr. Woodcock’s involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation

¹¹⁸ *Id.*

¹¹⁹ *Id.* at 7.

¹²⁰ *Id.* at 13.

¹²¹ *Id.* at 15.

¹²² *Id.*

¹²³ *Id.* at 21-22.

¹²⁴ *Id.*

¹²⁵ *Id.* at 23; *see also* Unger Review Memorandum at 4, 5.

¹²⁶ *Id.*

in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-I. In its review of the administrative file and the surrounding circumstances, the SDR Board has also identified below other potential deviations from process at the Center level.

The agency-wide SDR-SMG directs the SDR Board to focus on the Center’s SDR-SOPs in evaluating whether the Center followed its own processes in evaluating a scientific dispute. In this case, however, both Drs. Unger and Woodcock have agreed that the only applicable SDR-SOP, MAPP 4151.2, provides for a review by the Center Director in consultation with an *Ad Hoc* panel and that going through such a process at this stage would be futile. The SDR Board has determined that, absent the second aspect of that agreement regarding futility and the underlying unusual circumstance of this scientific dispute, there would be reason to refer the matter back to the Center for further review by an *Ad Hoc* panel.

The interplay between MAPP 4151.1 and 4151.2, the former of which provides for supervisory review of scientific disputes all the way to the Center Director, suggests that MAPP 4151.2 actually calls for additional review of a scientific dispute by the Center Director under certain circumstances even if she has already made a decision on the dispute. Although MAPP 4151.2 provides for bypassing review of the scientific dispute up the chain of command under MAPP 4151.1 if such exhaustion would impede the timely resolution of a serious public health issue, MAPP 4151.2 also emphasizes that it should not be used before other means of resolution have been attempted.¹²⁷ However, the key consideration for obtaining review by an *Ad Hoc* panel under MAPP 4151.2 is “whether the consequences of the decision in question are potentially serious enough to warrant [additional review],” not whether the resort to the process would be futile.¹²⁸ It appears that Dr. Woodcock has never made a determination regarding the seriousness of the decision in question, but it would be surprising if she determined that the dispute in this case did not meet the standard, as reflected in the statement she signed.¹²⁹

In this case, however, it is clear from the record before the SDR Board that Dr. Woodcock was so involved in the underlying scientific dispute—including direct and extensive personal review of the data and analyses offered in support of the NDA—that we agree with the conclusion in the agreements signed by Drs. Unger and Woodcock that “the CDER Director has already fully evaluated the issues.”¹³⁰ Indeed, she has already received advice from an advisory committee and had substantial conversations with her staff over an extended period of time with respect to the dispute in question. There is no reason to believe that receiving additional advice from an *Ad Hoc* panel would alter Dr. Woodcock’s views of the scientific issues. As the agreement between her and Dr. Unger reflects, the process would be time-consuming and delay an important

¹²⁷ MAPP 4151.2 at 5. (“In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted before a [request for review under 4151.2] is filed. However, in some cases, an individual may believe that his or her professional opinion will not be considered by his or her supervisors or that there is not time to exhaust other options for dispute resolution without seriously endangering the public health. In this case, the submitter should include . . . a written request to bypass these other mechanisms. . . .”).

¹²⁸ *Id.*

¹²⁹ SDR-SOPs Agreement at 2 (“The difference of opinion between Drs. Unger and Woodcock could be considered to meet the criteria for filing an appeal under MAPP 4151.2 because the drug indication sought is one for a serious and life-threatening disease that has limited treatment options.”).

¹³⁰ *Id.*

regulatory decision unnecessarily.¹³¹ Dr. Unger also told the SDR Board that he thought going through the *Ad Hoc* panel process would have been pointless for the aforementioned reasons.

The difficulty for the SDR Board is that the agency-wide SDR-SMG is predicated on some level of formal scientific dispute resolution within the Center, particularly a decision by the Center Director regarding the formalized scientific dispute.¹³² For that reason, the focus of the SDR-SMG with respect to the process followed is on whether the Center followed its own SDR-SOPs in resolving the scientific dispute.¹³³ Yet, the SDR-SMG also directs the Centers to adopt “[i]nformal methods” for resolving scientific disputes, “to create an atmosphere in which consultation and open discussion on controversial issues are encouraged,” to use “good management practices for resolving conflict,” and “to enable as open and complete a discussion of the issues as possible at the working level of the organization.”¹³⁴ As a result, the SDR Board has determined that reviewing the processes used by a Center to resolve a scientific disagreement is appropriate under the SDR-SMG even when, as here, the initiator has not availed himself of the Center’s formal process for resolving scientific disputes and the Center Director has explicitly agreed to that approach.

Whether the Center followed its own processes for resolving a scientific disagreement cannot be viewed in a vacuum, however. Indeed, the SDR-SMG itself—at its most concise and in its clearest voice—states, “The goal of [the SDR Board’s] review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.”¹³⁵ Particularly in the context of a scientific dispute that did not go through a formal SDR process at the Center but nonetheless received extensive review by the Center Director, focusing on deviations from process without any regard to whether they affected the initiator’s opportunity to present his views of the science (and to some extent whether those views and the evidence were considered) would seem to miss the point of that review. Accordingly, the SDR Board finds that it is more appropriate to address Dr. Unger’s arguments regarding the Center’s deviations from appropriate process under the second prong of its analysis: whether the Center provided Dr. Unger an adequate opportunity present his scientific concerns.

The SDR Board’s one caveat is that, as noted above, the SDR-SMG does appear to assume that there has been both at least some use of the formal dispute resolution within the Center and, accordingly, a *formal* substantive review of the initiator’s scientific concerns before reaching the Office of the Commissioner.¹³⁶ The limited scope of the SDR Board’s review under the SDR-SMG—i.e., an evaluation of the Center’s decision-making process—means that Dr. Unger will also not receive a substantive review of his scientific concerns under the SDR-SMG. In fact, at the conclusion of the SDR Board’s review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level. Particularly in light of

¹³¹ *Id.* (“[U]tilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days.”).

¹³² *See* SDR-SMG at 6 (requiring as a mandatory process for formal scientific dispute resolution a written opinion by the Center Director and stating that such a written opinion as a step in the process is a “central criterion for advancement to the agency-level appeals process.”).

¹³³ *See, e.g., id.* at 12 (requiring the SDR Board to “obtain the full administrative record of the Center’s processes for the dispute and review the Center’s published SOP(s)” and to “review that information to determine whether written Center processes were followed.”).

¹³⁴ *Id.* at 6.

¹³⁵ *Id.* at 12.

¹³⁶ *See id.* at 6 (referring to SOPs for resolution of Center-level scientific disputes without limiting them to procedural reviews and contemplating the Center SOPs as a continuation of the informal SDR process).

Dr. Unger’s explicit request for scientific review of the matter within the Office of the Commissioner, therefore, the SDR Board recommends additional substantive review at this level, as is discussed below.

2. *Whether CDER provided an adequate opportunity to Dr. Unger to present his scientific concerns.*

In his appeal, Dr. Unger admits, “There is no question that there has been adequate time and place for the discussion of various views.”¹³⁷ In so doing, he appears to concede away most of his arguments with respect to whether he had an adequate opportunity to present his scientific concerns, notwithstanding the procedural deviations he identifies. The SDR Board, however, has not taken Dr. Unger’s concession at face value and has instead looked beyond it to evaluate the administrative file and the surrounding circumstances to identify additional procedural issues. We conclude nonetheless that Dr. Unger had an adequate opportunity to present his scientific concerns to Dr. Woodcock before she issued her decisional memorandum.

As noted above, Dr. Unger identified four deviations from Center’s typical decision-making process for the eteplirsen NDA: (1) Dr. Woodcock’s involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-I. In reviewing this matter, the SDR Board—which includes among its members Ombudsmen from other Centers that oversee reviews of medical products—also considered other departures from the typical processes used by Centers in reviewing applications for pre-market approval or clearance.¹³⁸

The SDR Board agrees with Dr. Unger that it was unusual for a Center Director to be so involved in the early stages of reviewing an NDA, but the consensus on the SDR Board was that Dr. Woodcock went several steps further than mere involvement and thereby departed from typical practice among the Centers. By her own admission, Dr. Woodcock had a direct hand in reviewing the data submitted in support of the NDA, even before the review team had written their draft review memoranda, and actively encouraged the review team—including Dr. Unger—to come around to her way of thinking in their own reviews. Specifically, she wanted the review team to agree with her that the limited increase in dystrophin production established by the data in Studies 201/202 was sufficient to show a reasonable likelihood of predicting clinical benefit. At several points during the decision-making process for what is clearly a critical scientific issue for the agency, Dr. Woodcock also provided a very limited amount of time for Dr. Unger and the review team to provide feedback on additional data or her own scientific conclusions—most notably when Sarepta submitted the data from Study 301 and when she provided two separate draft versions of her decisional memorandum to the review team.

Notwithstanding the foregoing procedural shortcomings, the SDR Board finds that Dr. Unger had an adequate opportunity to present his scientific views. Not only does he admit in his appeal that he had an opportunity, but the record before the SDR Board demonstrates that he did. He and the rest of the review team met with Dr. Woodcock on multiple occasions both before and after the AC meeting. Drs. Unger and Woodcock both told the SDR Board that those meetings involved substantive and detailed discussions of the data and science and the appropriate

¹³⁷ Appeal at 26.

¹³⁸ See SDR-SMG at 3 (defining the SDR Board to include Ombudsmen from all of the Centers).

conclusions to be drawn from them. Although Dr. Unger complains that Dr. Woodcock was involved in aspects of the NDA that went far beyond the norm for a Center Director at CDER, including her role in the AC meeting, and that she reached or finalized decisions before reviewing review or decisional memoranda, he does not maintain that those procedural deficiencies compromised his ability to present his views. In fact, his own final decisional memorandum—which Dr. Woodcock apparently saw in draft form before she finalized her own—discloses that he felt empowered to push back on both Dr. Woodcock’s scientific conclusions and their basis, despite the fact that he believed his efforts would be futile. Indeed, he conceded to the SDR Board that nothing in his decisional memorandum or appeal submission would have affected Dr. Woodcock’s decision on the scientific issue in question (including the charts that he created for the first time in preparing his appeal submission under the agency-wide SDR-SMG). He further conceded as much when he agreed not to pursue further review through the *Ad Hoc* panel process under CDER’s SDR-SOPs. In short, through his own perseverance, confidence in his own scientific expertise, and perhaps dint of personality, Dr. Unger ensured that he himself had an adequate opportunity to present his scientific views despite the procedural irregularities in the decision-making process within CDER.

The SDR Board nonetheless remains concerned about Dr. Woodcock’s extensive involvement in the review of the eteplirsen NDA, including her degree of participation at the AC meeting, and the limited timeframe she provided for feedback on the data from Study 301 and her own scientific conclusions on that data. We fear that those actions could have chilled scientific debate within CDER and reduced the level of participation by the review team during the final stages of the decision-making process. By all accounts, Dr. Woodcock made clear her views that CDER should lean toward finding that eteplirsen met the standards underlying accelerated approval nearly from the outset of her involvement. By May 4, 2016, she had orally communicated her intention to grant accelerated approval for eteplirsen, even though she had not yet seen even the draft review memoranda from the review team or a decisional memorandum from Dr. Unger. Then, when she requested data from Study 301 from Sarepta, she communicated to the sponsor a compressed timeframe for CDER’s review. Although she later expanded the timeframe for review when the data proved to be disappointing, she apparently analyzed the data on her own, conducted her own additional search of the scientific literature, and took only six or seven business days to orally communicate to the review team her decision to grant approval.

To complicate matters further, Dr. Woodcock subsequently circulated a draft decisional memorandum but provided only a limited amount of time for comments, even though the draft decisional memorandum was the first time some on the review team had apparently seen key elements for the basis of her decision on “reasonably likely to predict clinical benefit.” The response from the review team is telling. As noted above, only Drs. Jenkins and Unger and another reviewer outside of DNP provided comments. Except for Dr. Jenkins, no one made any effort to make substantive comments beyond tips on how to make factual clarifications or to supplement her analysis with additional data. It appears that, because the review team knew Dr. Woodcock’s views by then, they saw no point in providing any additional substantive review or meaningful feedback on any new issues raised by Dr. Woodcock’s memorandum. Indeed, Dr. Unger and the RTM conveyed as much to the SDR Board.

There is no doubt that a Center Director should have wide latitude in leading the direction of the Center in a manner consistent with her priorities and vision. The SDR Board also believes that Center Directors have a role to play not only with respect to the resolution of scientific disputes at issue in individual applications for pre-market-authorization by FDA, as evidenced by both the SDR-SMG and CDER’s own SDR-SOPs, but also with respect to the ultimate decision on

scientific issues that are not the subject of a dispute. It is also clear from Dr. Woodcock’s presentation to the SDR Board that she firmly believes in the correctness of her scientific decision in this case and that her involvement in the review of the eteplirsen NDA was always motivated by the best of intentions. However, the SDR Board finds Dr. Woodcock’s extensive, early involvement in the review process troubling. Indeed, her involvement here appears to have upended the typical review and decision-making process.

Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages. As a consequence, the regulatory reviews did not start at the staff level with scientific reviews and then proceed through the chain of command for concurrence or non-concurrence at all appropriate levels within the management structure, as would be the typical course of decision-making for a regulatory decision grounded in science. Indeed, before the reviewers had even completed their draft scientific reviews, Dr. Woodcock had told them—on May 4, 2016—that she intended to grant accelerated approval. This sort of top-down review does not, in the SDR Board’s view, “create an atmosphere in which consultation and open discussion on controversial issues are encouraged,” as reflected in the SDR-SMG’s requirements for resolution of scientific disagreements by the Center.¹³⁹ By the time Dr. Woodcock issued her draft decisional memorandum on what she herself acknowledged was a difficult scientific issue of incredible magnitude for the agency—i.e., whether the evidence regarding dystrophin production was reasonably likely to predict clinical benefit—the review team had decided it was pointless to challenge her ultimate conclusion or its basis.¹⁴⁰ Review teams should have the opportunity to conduct their reviews without preemption by the Center Director. As noted above, the SDR Board believes that Center Directors should have a role in shaping policy, expressing concerns, and resolving issues once they are ripe for their review, but we caution that care should be taken to avoid the appearance of interfering with the integrity of scientific reviews at the lower levels of a Center.

3. Whether the Center Director considered all relevant evidence bearing on the scientific question at issue.

The third issue for the SDR Board is whether CDER, including Dr. Woodcock, fully considered all relevant evidence in resolving the scientific dispute at issue, i.e., whether the evidence of eteplirsen’s effect on dystrophin production is reasonably likely to predict clinical benefit. In this case, both Drs. Unger and Woodcock appear to agree that she *considered* all relevant evidence. As noted above, Dr. Unger does not believe that any additional data or evidence available to him could persuade Dr. Woodcock that she has reached the wrong scientific conclusion. For her part, Dr. Woodcock does not feel that she has disregarded any relevant evidence. Moreover, in her interview with the SDR Board, she demonstrated an awareness and command of all of the evidence weighing against the scientific decision she has made, including the arguments and analysis of the evidence presented in Dr. Unger’s appeal.

Whether Dr. Woodcock has *addressed* all of the relevant evidence in her decisional memorandum is a more difficult question. In concluding that the minimal increase in dystrophin

¹³⁹ *Id.* at 6.

¹⁴⁰ In this regard, it is also worth noting again the language quoted above in the background section: “Each individual who contributes to the decision-making process” must “be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component” and that “[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made.” (MAPP 4151.8 at 2-3).

production seen in the data is reasonably likely to predict clinical benefit, Dr. Woodcock has provided a very limited rationale.

At the risk of oversimplification, Dr. Woodcock found, in essence, that the studies attempting to correlate levels of dystrophin with clinical benefit, as have been reported in the scientific literature, are unreliable in this context for variety of reasons, including: (1) the subjectivity of the clinical evaluation, (2) the difficulty in correlating IHC results with Western blot results, (3) the influence of anti-dystrophin antibodies, (4) the lack of information on dystrophin quality (as opposed to quantity) in the different studies, (5) deficiencies in Western blot techniques from earlier studies, and (6) the wide range of findings with respect to the correlation of dystrophin levels with clinical benefit.¹⁴¹ She concluded, therefore, that “protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, all other things being equal, i.e. mutation status and non-dystrophin-related factors affecting phenotype,” and that the “biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit.”¹⁴² She then attempted to bolster that conclusion with a theory regarding the effect of exon 52 deletion and her reanalysis of the intermediate clinical outcomes for a subset of subjects in Study 201/202.¹⁴³ She further explained to the SDR Board that she was exercising her “medical/scientific judgment” in reaching the scientific conclusion that she did.

It is easy for the SDR Board to understand why Dr. Unger’s appeal expressed such frustration with this explanation of Dr. Woodcock’s rationale. He states:

I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients could benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.¹⁴⁴

Of course, *considering* the relevant evidence and *addressing* the relevant evidence in a manner satisfactory to Dr. Unger or the SDR Board are two different propositions. The SDR Board finds, based on the record before us, that Dr. Woodcock has considered all relevant evidence in reaching her scientific conclusion. Based on her own medical judgment, she simply has a difference of opinion with Dr. Unger—both with respect to the scientific conclusion and the sufficiency of the underlying rationale.

4. Whether the dispute should be remanded to the Center Director.

Inasmuch as the SDR Board has concluded that Dr. Unger had an adequate opportunity to present his scientific concerns during the decision-making process at CDER and that Dr. Woodcock considered all relevant evidence in making her decision, the SDR Board does not recommend returning this matter to the Center Director for corrective action. We also believe that, for reasons discussed above, remanding this matter to the Center Director would be futile.

¹⁴¹ Woodcock Decisional Memorandum at 5-9.

¹⁴² *Id.* at 9.

¹⁴³ *Id.* at 10.

¹⁴⁴ Appeal at 20 (emphasis in original).

CONSIDERATIONS FROM THE ACTING CHIEF SCIENTIST

In my capacity as Acting Chief Scientist, I feel the responsibility to convey some comments regarding the underlying science for the decision being challenged by Dr. Unger in his appeal. I cannot begin to understand the depth of pain and suffering that patients with DMD and their families endure. As an experienced physician, I struggle to identify any other diseases associated with this degree of suffering, not only to patients but to their families. Nevertheless, my assessment is that the data presented by the sponsor to date are not adequate to support accelerated approval of eteplirsen

Studies in animals showing that eteplirsen leads to “exon 51 skipping” are an important first step in assessing whether eteplirsen might work for a subset of patients with DMD because skipping exon 51 is necessary for the production of dystrophin in these patients.¹⁴⁵ The next step is to assess whether eteplirsen actually leads to the production of dystrophin in patients with DMD and, if so, whether such an increase in dystrophin confers clinical benefit. Despite the promising animal studies demonstrating exon 51 skipping, both Drs. Woodcock and Unger, as well as the review team in CDER, agree that the amount of dystrophin produced in the clinical studies conducted at doses of up to 50mg/kg per week is very low. Animal data suggest that the doses studied in humans is too low; in animals, exon 51 skipping was detected in a nonlinear, dose-dependent manner (that is, higher doses led to significantly more exon 51 skipping). Specifically, with a 1-log increase in dose (from 5 to 40 mg/kg), there was little change in exon 51 skipping. With a second log increase in dose (from 40 to 320 mg/kg), however, there was more than a log increase in response. These dose-dependent responses are important because it is wholly conceivable that higher doses would lead to a much greater amount of dystrophin production, which could be important for clinical benefit. Because the drug appears to be safe, the review team recommended evaluation of much higher doses of eteplirsen, of at least 200mg/kg per week. Approving a drug at a dose that does not show a meaningful increase in dystrophin (when the drug could theoretically achieve one at higher doses) is concerning.

As for accelerated approval, the regulatory standard at issue requires a sponsor to show that the drug under review leads to an effect on the surrogate endpoint (in this case, the production of dystrophin) and that the effect is reasonably likely to predict clinical benefit (in this case, improving, or slowing down decline in, muscle function). The term “reasonably likely to predict” acknowledges the potential for doubt in the outcome of interest. Indeed, nobody knows the minimum level of dystrophin that is likely to confer clinical benefit in patients with DMD. The critical scientific and regulatory issue at stake in CDER’s decision here is whether such minute amounts of dystrophin are reasonably likely to predict clinical benefit at the dosage of the drug subject to approval. In this case, both Drs. Woodcock and Unger have attempted to provide a rationale, based on scientific and professional judgment, for whether or not such small levels of dystrophin are reasonably likely to predict the clinical effect of interest. By any meaningful objective standard, however, the overall evidence derived from eteplirsen’s limited clinical development program does not support that the levels of dystrophin produced by eteplirsen at the doses studied are reasonably likely to provide clinical benefit. As pointed out in Dr. Unger’s appeal, “Study 201 did not show a treatment effect on its 1^o clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients.”¹⁴⁶

¹⁴⁵ Eteplirsen targets a subset of patients with DMD who are amenable to exon 51 skipping.

¹⁴⁶ Appeal at 16.

Some may argue that it would be reasonable to proceed with accelerated approval based on eteplirsén's safety profile, even where there are significant doubts about the drug's effectiveness. That argument does not take into account the risks of treatment with indwelling catheters to maintain vascular access in young patients, who would otherwise not need one and who often receive adjunct chronic corticosteroids, or, even more importantly, the detrimental impact on their quality of life.

I would be remiss if I did not note that the sponsor has exhibited serious irresponsibility by playing a role in publishing and promoting selective data during the development of this product. Not only was there a misleading published article with respect to the results of Study 201/202¹⁴⁷—which has never been retracted—but Sarepta also issued a press release relying on the misleading article and its findings. As determined by the review team, and as acknowledged by Dr. Woodcock, the article's scientific findings—with respect to the demonstrated effect of eteplirsén on both surrogate and clinical endpoints—do not withstand proper and objective analyses of the data. Sarepta's misleading communications led to unrealistic expectations and hope for DMD patients and their families. It is very disappointing that the findings did not hold up to careful review.

FDA must remain steadfast in its commitment to alleviating pain and suffering, approach the most challenging problems with absolute determination, and apply maximum flexibility to facilitate the development and availability of effective treatments. The agency's value centers on its ability to do all of the above while maintaining objectivity, even in the face of political pressure. FDA should never mislead patients by granting even accelerated approval to products that are not shown to offer the prospect of meaningful benefit to patients under the appropriate regulatory and scientific standard.

I acknowledge that there are currently no specific drugs available to treat patients with DMD and that issuance of a complete response letter would cast uncertainty on whether eteplirsén would continue to be developed, based on business and financial decisions that are external to FDA. However, approving products based on hope, on subjective clinical judgment, or on theoretical constructs that are not anchored in data leads to irreparable damage to patients. Approval at this time could deter others from pursuing the development of truly effective treatments, both for DMD and other serious, life-threatening conditions. Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies—both by discouraging others from developing effective therapies for DMD and by encouraging other developers to seek approval for serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit.

I remain deep in my conviction that, through science and a flexible, sound regulatory approach, good therapies will emerge to provide meaningful clinical benefit to patients with DMD and other rare serious diseases.

THE SDR BOARD'S ADDITIONAL RECOMMENDATION

Although the SDR Board acknowledges that the scope of our review, as prescribed by the SDR-SMG, is limited to procedural questions, we nonetheless feel duty-bound to make one additional recommendation. As noted above, Dr. Unger seeks from the Office of the Commissioner a substantive, scientific review of Dr. Woodcock's decision to grant accelerated approval to

¹⁴⁷ See Mendell JR, et al. *Ann Neurol* 2013;74:637-47.

eteplirsen. The SDR-SMG presumes that an initiator such as Dr. Unger has received some substantive review of the scientific dispute at issue as part of a formal appeals process in the Center. Dr. Unger has never received any such formal review of his scientific arguments or the underlying evidence. To the extent he has ever received any substantive review of his scientific disagreement with Dr. Woodcock, Dr. Woodcock herself was the one who conducted that review and resolved the conflict in her own favor. Neither the SDR-SMG nor CDER's SDR-SOPs contemplate a scientific disagreement that arises between a Center Director and another manager in that same Center—partly because no one has ever anticipated the unique circumstance of this case. Especially given the SDR Board's concerns regarding the decision-making process at CDER, we think additional review within the Office of the Commissioner is appropriate.

The SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit. If you choose the latter, in light of the public and political pressure evident during the entire review process at CDER, as detailed in this recommendation, we believe that delegating this critical evaluation to a panel of experts would help ensure that the agency makes the most appropriate decision from the perspective of protecting patients and the public health, especially for DMD patients. Knowing as we do that you value cross-Center collaboration with respect to medical product development, we recommend that you include on the panel experts from other Centers devoted to the regulation of medical products. Doing so would not only help ensure diverse expertise on the panel but also provide insights on the effects that any proposed regulatory decision on eteplirsen might have on products regulated by those other Centers. We further recommend that you consider whether to include experts from other components within the Department of Health and Human Services and whether, consistent with applicable laws and the appropriate timeframe for a decision, you should also include outside experts on the panel.



TO: Janet Woodcock, M.D., Director, CDER
Ellis Unger, M.D., Director, Office of Drug Evaluation I, CDER
Luciana Borio, M.D., Chair, Agency Scientific Dispute Process Review Board

FROM: Robert M. Califf, M.D., Commissioner of Food and Drugs

RE: Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488) – **Commissioner's Decision**

DATE: September 16, 2016

Overview

The Chair of the Agency Scientific Dispute Process Review Board (SDR Board), Dr. Luciana Borio, has forwarded to me the Board's recommendation regarding the appeal by Dr. Ellis F. Unger, the Director of the Office of Drug Evaluation I, of Dr. Janet Woodcock's decision; namely, that Sarepta Therapeutics' drug eteplirsen (AVI-4658) meets the standard for accelerated approval for treatment of Duchenne muscular dystrophy (Duchenne or DMD) in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13 percent of the population with DMD. Duchenne is a rare genetic disorder characterized by progressive muscle deterioration and weakness and is often fatal. Dr. Unger disagrees with Dr. Woodcock's view and would decline to approve eteplirsen at this juncture.¹

The SDR Board's memorandum of August 8, 2016 concludes that under the standard for review set out in FDA's Staff Manual Guide for formal appeals of internal FDA scientific disputes, Dr. Unger had an adequate opportunity to present his scientific concerns within the Center for Drug Evaluation and Research (CDER), and that Dr. Woodcock considered all relevant evidence in making her decision.² In her capacity as Acting Chief Scientist, Dr. Borio also conveyed her own views on the dispute, stating among other things that she does not believe the available data and information support accelerated approval of eteplirsen.³ As the SDR Board's role was to conduct a procedural review, the SDR Board further recommended that I either conduct a substantive scientific review of the dispute or convene a panel of experts to conduct a scientific review and

¹ Appeal at 1.

² SDR Board Recommendation at 2.

³ *Id.* at 2, 25-26.

advise the Agency on whether the available evidence for eteplirsen meets the standard for accelerated approval.⁴

I note that, in my understanding, it is highly unusual for a Center Director's decision regarding a product application to be appealed to the Commissioner's office. Decisions on medical product approvals and clearances are delegated under provisions of Staff Manual Guide 1410 to the appropriate Center Directors and Center staff.⁵

I have read the documents pertinent to Dr. Unger's appeal, Dr. Woodcock's final Center decision, and the review and recommendation of the SDR Board. I have performed a thorough review of the basic and clinical science, a review that also comprised a briefing with the review team, including Dr. Unger, and discussions with Drs. Woodcock and Jenkins. Although under the standard for review set forth in Staff Manual Guide 9010.1, I was not required to review the science, I did so in order to properly evaluate the positions of Dr. Woodcock and Unger. **My decision following this review is to defer to Dr. Woodcock's judgment and authority to make the decision to approve eteplirsen under the accelerated approval pathway, in her capacity as Director of the Center for Drug Evaluation and Research.**

My reasoning and detailed considerations for my decision are given below.

Examination of the Scientific Dispute

Key Points of Agreement

There is agreement that Dr. Unger's views and those of the review team were heard in great detail in an environment of open discussion and dissent on multiple occasions. I agree with the SDR Board that there is no basis for overturning Dr. Woodcock's decision on procedural grounds and Dr. Unger also agrees with this conclusion.

In addition, the science is not in dispute beyond the usual types of disagreement that occur when experts review clinical evidence from different perspectives. As discussed in detail below, the evidence evaluation is complicated by the unusual circumstance of the development program, which involved a small subset of children with a rare disease and was characterized by major

⁴ *Id.* at 2, 27.

⁵ Although, as described in Staff Manual Guide 1410.21.1.A., the Commissioner retains authority to make decisions on medical product applications, those decisions are most appropriately vested in the Centers and only the most unusual circumstances would warrant overturning the decision of a Center—including that of a Center Director—on a medical product application. As is set out in the Staff Manual Guide 9010.1 applicable to this matter, FDA has adopted a formal scientific dispute resolution process that emphasizes 1) establishing and maintaining robust dispute resolution processes within the Centers to ensure candid and comprehensive discussion of scientific issues, and 2) a Commissioner's Office review that focuses on the adequacy of the internal Center scientific dispute process (i.e., whether the Center's processes were followed, whether the Center considered all relevant evidence bearing on the scientific question at issue, and whether the initiator of the appeal was provided an opportunity to express concerns at all appropriate levels, prior to and including the Center Director). This established dispute resolution process does not contemplate a substantive decision on the disputed issue by the Commissioner.

flaws in the clinical study design, making the judgment on science difficult. The points of agreement include the following:

- DMD is a rare, progressive disease characterized by the virtual absence of functional dystrophin.⁶
- There is no approved therapy for DMD.⁷
- The principal question in this dispute is not whether dystrophin level is an appropriate surrogate endpoint for the purpose of accelerated approval, but whether the quantity of dystrophin produced by eteplirsen is an effect that is reasonably likely to predict clinical benefit, as required under section 506(c)(1)(A) of the Federal Food, Drug, and Cosmetic Act and FDA regulations at 21 CFR 314.510.⁸
- Available preclinical work supports the clinical development of eteplirsen, most notably clear documentation of production of the transcript and the protein in a dose-dependent manner in primates, without measurable toxicity.⁹
- Major flaws in both the design and conduct of the clinical trials using eteplirsen have made it impossible to use much of the resulting trial data as reliable evidence in regulatory decision-making, including for reasonable extrapolation to clinical care.¹⁰
- Despite the flaws in the clinical development program noted above, both Dr. Woodcock and Dr. Unger, as well as the review team, agree that eteplirsen produces measurable increases in dystrophin compared with control.¹¹ All agree that the amount of dystrophin produced is small compared with expectations at the outset of trials in humans.¹² Although the gap between expectations and measured increase is not directly relevant to the final decision, the log-order difference has added further uncertainty. If the levels of dystrophin had reached those measured in the setting of Becker muscular dystrophy, there would be much less concern.
- Although there is some disagreement about whether the data support the expression of dystrophin in one study (201/202), there is agreement that the other (study 301) demonstrates clear evidence for dystrophin production. Dr. Unger concludes that there is

⁶ Appeal at 2; SDR Board Recommendation at 2.

⁷ Appeal at 2. I note that there is a modest body of evidence suggesting that treatment with corticosteroids yields relatively short-term improvements in function and muscle strength (see Matthews E, et al. *Cochrane Database Syst Rev.* 2016;(5):CD003725. doi: 10.1002/14651858.CD003725.pub4), but there is no evidence from adequate and well-controlled trials that this therapy has a major effect on the course of the disease.

⁸ Appeal at 3; SDR Board Recommendation at 4, 17.

⁹ ODEI Decisional Memo, July 2016.

¹⁰ Woodcock Decisional Memorandum at 2-3, 11; Appeal at 4-5, 8-9.

¹¹ Woodcock Decisional Memorandum at 3; Appeal at 6.

¹² Woodcock Decisional Memorandum at 11.

evidence from one adequate and well-controlled trial, while Dr. Woodcock concludes there is evidence from two adequate and well-controlled trials.¹³

Key Points of Disagreement

There is disagreement about whether the amount of dystrophin protein produced is sufficient to be “reasonably likely” to predict a clinical benefit. The basis for the judgment about “reasonably likely” is subjective and is not explicitly defined in statute or regulations. FDA’s Guidance on Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014) states at page 19 (internal citation omitted):

Determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect and the empirical evidence to support that relationship. The empirical evidence may include “. . . epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.”

I conclude that Dr. Unger and Dr. Woodcock have each exercised reasonable scientific judgment in reaching differing conclusions on whether the effect on dystrophin production seen in the studies in Sarepta’s application reasonably predicts clinical benefit for the relevant subpopulation of Duchenne patients. There is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence, including the detailed views of Dr. Unger and the review team; yet she came to a different conclusion. These differing conclusions are detailed immediately below:

- Dr. Unger, the review team, and Dr. Borio have concluded that the demonstrated levels of dystrophin are not “reasonably likely” to predict clinical benefit based on a chain of logic that is well-described in Dr. Unger’s appeal and in Dr. Borio’s summary.¹⁴ In essence, based on the belief that Becker muscular dystrophy provides a model for Duchenne because the dystrophin is similar to that produced with eteplirsen, Dr. Unger concludes that functional protein in the range of 10% of normal levels would be needed to provide evidence that would make it “reasonably likely” that changes in the surrogate would predict clinical benefit.¹⁵ The use of Becker muscular dystrophy as a model for DMD is an extrapolation, but a rational one in the absence of validation of dystrophin as a surrogate.
- Dr. Unger also finds that the results of the eteplirsen clinical trials to be inadequate for supporting the conclusion that there is any relationship between measured levels of dystrophin and improvement in function within the trial data sets. Making certain

¹³ Woodcock Decisional Memorandum at 2-5; Appeal at 4-6.

¹⁴ Appeal at 4, 11-20; SDR Board Recommendation at 25.

¹⁵ Appeal at 12-15.

assumptions, he provides plots and calculations that he interprets as showing that higher dystrophin levels are not associated with improved function in the eteplirsen trials.¹⁶

- Dr. Borio fundamentally agrees with Dr. Unger’s conclusion, and Dr. Jenkins concurs with Dr. Unger.¹⁷
- Dr. Woodcock finds that using “...the greatest flexibility possible for FDA while remaining within its statutory framework,” eteplirsen is “...reasonably likely to predict clinical benefit.”¹⁸ Her conclusion is based on a view that the data from both Study 201/202 and Study 301 are from adequate and well-controlled trials and that, although imperfect, they adequately meet criteria to include as affirmation of a drug effect that is reasonably likely to predict clinical benefit. She points out the many uncertainties about extrapolating from a particular level of a surrogate to clinical benefit when that surrogate is not yet proven, including complexities of assay validation, determining whether protein is functional, and also the extraordinary difficulty of knowing how the amount of protein might affect functional outcome over time and within the context of the multidimensional nature of protein interactions in complex cellular and subcellular functions. She finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is “reasonably likely” to predict clinical benefit.¹⁹ Furthermore, she provides some post-hoc calculations from the eteplirsen clinical trials that she regards as supportive, though not definitive, evidence that higher levels of dystrophin are associated with greater function.

She is clearly employing and interpreting the full range of appropriate information, comprising a “totality of evidence” approach in determining that the clinical trials demonstrated an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Because of the uncertainties in this situation with a surrogate that has not been validated, it is clear that Dr. Woodcock’s decision also utilized the flexibility afforded under the relevant statutory provisions, including consideration of the life-threatening nature of the disease and the lack of alternative treatments.

Conclusions Regarding the Scientific Dispute

I conclude that qualified experts with extensive experience in FDA decision-making and stellar track records can assimilate the same scientific evidence and disagree about the extrapolation to whether the evidence supports a conclusion that the treatment has an effect that is “reasonably likely” to predict clinical benefit. Both Dr. Unger and Dr. Woodcock have drawn upon a deep level of knowledge and practical experience in deriving their conclusions, and their documents reflect strong convictions and profound concern both for the

¹⁶ *Id.* at 15-18.

¹⁷ SDR Board Recommendation at 15, footnote 94.

¹⁸ Woodcock Decisional Memorandum at 12.

¹⁹ *Id.* at 9.

well-being of the patients and families with DMD and for the preservation of the FDA's mission to protect and promote public health. That said, the history of the FDA includes a consistent precedent of final decision-making about medical products at the Center level. Overruling the Center Director is exceedingly rare and, in my view, would be appropriate only if the Center Director's decision could not be supported by the available data and information. In the present case, the scientific uncertainties lead to a situation in which the decision is a matter of reasoned expert opinion and judgment.

Given that I do not have technical expertise beyond those already involved in this decision and the record contains adequate evidence to support her conclusion, I defer to the judgment of the Center Director to approve eteplirsen under accelerated approval with the stipulations delineated in her Decisional Memo.

Additional Concerns

The SDR Board expresses concerns based on Dr. Unger's appeal and on interviews the Board conducted in its procedural review about the level of involvement of the Center Director in the review of the New Drug Application for eteplirsen. The following four points of concern were raised by Dr. Unger and cited by the SDR Board:

1. Intense involvement of the Center Director in early stages of review;
2. Extensive involvement in planning and participating in the Advisory Committee meeting to consider eteplirsen, held on April 25, 2016;
3. Initial decision by Dr. Woodcock on May 4, 2016 to approve before the review team had finalized its process for decision-making; and
4. Final decisional memorandum by Dr. Woodcock completed before Dr. Unger finalized his own decisional memo.

The SDR Board expresses concern about Dr. Woodcock's "extensive, early involvement in the review process" and states that "her involvement here appears to have upended the typical review and decision-making process."²⁰ Furthermore, the Board cautions that "...care should be taken to avoid the appearance of interfering with the integrity of scientific reviews at the lower levels of a Center."²¹ The SDR Board concludes that "Dr. Woodcock herself was the one who conducted that review and resolved the conflict in her own favor."²²

²⁰ SDR Board Recommendation at 23.

²¹ *Id.*

²² *Id.* at 27.

The concerns raised by Dr. Unger and by the SDR Board require that I evaluate the role of the Center Director. While there are many aspects of this situation that are unusual, leading to a rare formal dispute between a review team and a Center Director, I note the following points:

- Dr. Woodcock's management style has been "hands on" during her entire career at the FDA. She is well-known for interacting with staff at all levels and expressing her opinions. Indeed, complex and difficult cases often lead to early interactions with leaders, and as described below, frequent meetings and discussions along the way are common in CDER. This development program may represent a point of particular focus for Dr. Woodcock with the result that her involvement was more intensive than usual and correspondingly had an effect upon the review team, but such a focus does fit within a longstanding management approach.
- At the same time, under Dr. Woodcock's leadership and in conjunction with the leadership of Dr. John Jenkins in the Office of New Drugs, multiple mechanisms have been established for ongoing and interim discussions of evolving drug development programs and decision-making. These sessions, such as the Medical Policy Council, weekly senior staff meetings, the use of frequent Center Director briefings (in this case at least 14), and external advisory committee meetings are known for their exchange of ideas and welcoming of differences of opinion. Within this context it is also understandable that when so much is at stake with this degree of uncertainty, passionate debate can occur.
- An additional factor in this situation is the emergence of patient-centered drug development and the extensive interactions with the patient community as part of the overall environment for development and decision-making. While the appropriate methods for patient-centered drug development are evolving, the fact that DMD involves vulnerable children with a life-threatening illness and understandably concerned parents produces significant pressure on all involved. This dynamic is well reflected in Dr. Unger and Dr. Woodcock's documents. With a significant history dating back to the development of drugs for HIV/AIDS, patient-focused drug development is not an entirely new component of FDA's regulatory process, and it remains an explicit CDER priority in the current era.
- While others might direct and manage the organization and interact with patient and family communities in a different manner than Dr. Woodcock, it is difficult to argue that CDER has been unsuccessful under her leadership. A vast array of new drugs approved during her tenure is benefitting patients, including a host of significant advances using a variety of expedited programs. Further, this litany of therapeutic successes has been accomplished without compromising overall standards. Under Dr. Woodcock's leadership, commitment to due process and mutual review of scientific data have been major parts of CDER culture and are making a significant impact on drug development.

- It is inevitable that in some of these situations, highly qualified experts will disagree. In the face of profound changes in science and social interactions related to drugs, under Dr. Woodcock's leadership CDER enjoys broad public support, largely due to the constant, healthy atmosphere of transparency and debate that characterizes the documentation in this appeal. A review of Dr. Woodcock's record reveals extraordinary courage in the face of extreme pressure on many occasions, including from Congress, the press, patient and patient advocacy groups, and industry. She has taken and supported unpopular decisions when appropriate and is well-known for not relenting to pressure. Further, I find no pattern that indicates that this decision is part of a trend for lowering the standard for drug approval—a trend that would be unacceptable in any event.

Conclusions Regarding Additional Concerns

Overall, while I recognize the strain created by political and public pressures, given Dr. Woodcock's well-documented history of not bowing to such influences and a record in this case showing her close consideration of all relevant scientific evidence, **I do not find that she deviated from her responsibilities as Center Director, nor do I find that she succumbed to pressure from the patient community, the public, the press, or others.²³ Further, I do not find the general pattern of discourse and involvement to be atypical for Dr. Woodcock's management of the Center, nor do I find that her conduct was in conflict with the job requirements for Center Directors at the FDA.**

Additional Context: Accelerated Approval

It is important to note that the debate about this application is taking place in the context of an accelerated approval. Even under the best circumstances, accelerated approval may lead to decisions that are not verified upon further examination. These limitations are a reason accelerated approval is available only for a limited group of drugs: those intended to treat serious or life-threatening illnesses when the drug is expected to provide a meaningful benefit over existing therapy. In accelerated approvals, the surrogate is not a validated surrogate. As noted in FDA's Guidance on Expedited Programs for Serious Conditions – Drugs and Biologics, page 17:

For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Depending on the strength of the evidence supporting the ability of a marker to predict clinical benefit, the marker may be a surrogate endpoint that is

²³ I was troubled by statements on page 16 of the SDR Board memo that Dr. Woodcock's decision to approve eteplirsen may have been inappropriately motivated by concerns over the sponsor's financial well-being. To address to my own satisfaction any questions that Dr. Woodcock's statements in the SDR Board memo might raise, I have discussed this issue directly with Dr. Woodcock, who said that she was aware of the financial pressures on the company, but that her decision was based on the science. Based on the record and our conversation, I am satisfied that her decision is indeed based on her scientific evaluation of the evidence.

known to predict clinical benefit (a validated surrogate endpoint that could be used for traditional approval), a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit (and that could therefore be used as a basis for accelerated approval), or a marker for which there is insufficient evidence to support reliance on the marker as either kind of surrogate endpoint (and that therefore cannot be used to support traditional or accelerated approval of a marketing application).²⁴

Dr. Unger's and Dr. Borio's significant concerns about the implications of approving eteplirsen on the basis of the current data, even under the accelerated approval pathway, are evident.²⁵ As noted previously, Dr. Woodcock has explained that approval here will rely on "...the greatest flexibility possible for FDA."²⁶ The record amply reflects that the evidence here is not as strong as everyone involved in this dispute wishes it were. The record also reflects, however, that Dr. Woodcock has fully considered the patient population, lack of alternative therapies, and relevant information and analyses, and has concluded that the data are sufficient to meet the accelerated approval standard. Therefore, while I understand the concerns expressed by Drs. Unger and Borio regarding the implications of lowering of the standard for approval, I defer to Dr. Woodcock's conclusion that accelerated approval in this case does not represent such a lowering of the bar.

Opportunities for Process Improvement

I agree that there are many aspects of the history of eteplirsen that we must avoid in the future. Given the distinguished careers, time-proven expertise, and sincere concerns of Drs. Unger, Borio, Jenkins, and Woodcock, it is critical to review the following key lessons from this experience:

- All reviewers point to serious flaws in the eteplirsen drug development program. I personally have had many experiences in drug development and the assessment of therapeutics; it is common for problems to emerge that can be identified easily in

²⁴ More expansive discussion of these important issues on definitions of biomarkers and surrogates is included in a joint document from FDA and the National Institutes of Health, which can be found at: <http://www.ncbi.nlm.nih.gov/books/NBK326791>.

²⁵ In her capacity as Acting Chief Scientist, Dr. Borio notes: "Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies—both by discouraging others from developing effective therapies for DMD and by encouraging other developers to seek approval for serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit." Dr. Unger concludes: "If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients. In essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous." Dr. Jenkins expressed the same concerns, both in written documents and in follow-up discussions I have had with him.

²⁶ Woodcock Decisional Memorandum at 12.

retrospect. Clinical development involves numerous human decisions and compromises engendered by the fact that clinical trials involve human research participants who must be respected independently of the many others who design, conduct and judge the research. Furthermore, the diverse interests of sponsors, patients and families, investigators, and regulators must be melded into a few protocols for human studies, so that no protocol represents 100% agreement. Accordingly, any retrospective criticism should be expressed with humility. However, the flaws in the eteplirsen program are serious and worthy of attention by others developing drugs for serious rare diseases.

- Specifically, the poor quality of many of the biopsies and the failure of the sponsor to implement a high-quality procedure for assay validation led to a situation in which only a fraction of the data could be used to make the regulatory decision. Given the serious nature of the disease and the invasiveness of the procedures, any studies must be conducted according to the highest standards, so that each child and parent who volunteers can be confident that they have contributed as much as possible to the generalizable knowledge needed to provide effective treatment based on high-quality evidence. Such attention to standards of quality in study conduct is a critical element of respect for research participants.
- Further, all reviewers agree that had the sponsor conducted properly-controlled, randomized trials with dose escalation from the beginning, we would by now likely have access to definitive information that would have resolved the disagreement. Dr. Woodcock points out that "... [t]here is no such thing as an 'exploratory study' for a serious, life-threatening disease without therapeutic options. Randomization should be performed very early in the development program and open-label studies should be avoided."²⁷ Time after time, we see the over-hyping of preclinical results playing into misguided arguments that prevent the generation of high-quality evidence because of unrealistic expectations of benefit, which ultimately fosters continued uncertainty about the clinical value of therapeutics.
- It is unfortunate that the sponsor touted an academically based study that had unreliable measures of the assay, thereby greatly overstating the degree of protein expression in the follow-up biopsies. Blinded experts assembled by the FDA fundamentally debunked this study, which has yet to be retracted and continues to be cited.²⁸ Dr. Woodcock identified the lack of a reliable assay as the primary defect in this "seriously deficient" development program, and Dr. Unger comments multiple times on the uncertainties in the assay and the manner in which poor methodology undermined the results presentation.²⁹ It is critical that we continue to improve the entire pipeline of translational research to introduce more rigorous and reliable methods, even in academically-conducted

²⁷ Woodcock Decisional Memorandum at 11.

²⁸ In view of the scientific deficiencies identified in this analysis, I believe it would be appropriate to initiate a dialogue that would lead to a formal correction or retraction (as appropriate) of the published report.

²⁹ *Id.*

translational research. Likewise, it is equally important that we continue to work on ways to purge discredited research in a manner that reduces inappropriate citation and follow-on research based on the incorrect assumption of the accuracy of the precedent studies.

- Dr. Unger also points out that data from primate studies suggest that a substantial increase in dose (approximately a log order) might well produce the 10% of normal dystrophin levels that Dr. Unger feels would meet criteria for an effect that is “reasonably likely to predict clinical benefit.”³⁰ This view that much higher doses are likely to be beneficial is shared across the entire FDA hierarchy, yet studies have not been done in humans at higher doses. However, the FDA must make a decision based on available data.
- As Drs. Unger, Woodcock, and Borio all point out, the risk of lowering the bar for new drug approval is a serious concern. We must remember that over 90% of drugs that enter clinical trials do not make it to market, usually due either to inadequate beneficial effect or unexpected toxicity.³¹ Lowering the regulatory hurdle could expose unsuspecting patients to the harmful effects of these drugs that would have failed if proper development had been done. But the statute and regulations clearly demarcate accelerated approval as a special situation in which a range of evidence from various sources and unvalidated surrogates may be used to determine whether the demonstrated effect on a surrogate endpoint is reasonably likely to predict clinical benefit, requiring an additional judgment on the part of the FDA. **Thus, I am confident that this unique situation will not set a general precedent for drug approvals under the accelerated approval pathway, as the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information.**

The Path Forward

Given the approval status of eteplirsen, it is critical for the well-being of patients with DMD that the course of action fulfills the intent of accelerated approval and that the very best methods are used. As required for post-marketing studies for products approved under the accelerated approval program, the sponsor must conduct the required confirmatory trial with due diligence to evaluate whether eteplirsen has the predicted clinical benefit. It is notable that Dr. Unger and Dr. Woodcock agreed on several key points regarding further study of eteplirsen, regardless of the approval decision:

- The low doses currently employed are regarded as a starting point, as it seems likely that significant increases in dose could lead to desirable ranges of dystrophin production. Accordingly, a dose-finding study at much higher doses (as much as a log order increase)

³⁰ Appeal at 27.

³¹ Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. *Nat Biotechnol.* 2014;32:40-51.

is needed to find the dose most likely to lead to maximal clinical improvement, as will be reflected in the approval letter for eteplirsen³²:

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

Dr. Unger points out that Study 301 could be converted to a randomized trial in which one arm remains on the current dosing regimen and the other(s) receive higher doses in the range that might be expected to produce much higher dystrophin levels.³³ A study with only a modest increase in dose that found no difference would be non-informative. Accordingly, the difference in doses in a post-approval trial should be enough to create clear separation in dystrophin levels.

- Dr. Woodcock notes that the sponsor is also conducting a randomized trial of eteplirsen versus no therapy in other forms of DMD.³⁴ The utmost attention should be paid to optimizing the methodological rigor of this trial and the trial evaluating higher doses discussed above.
- It is essential that the clinical and patient communities not be misled by exaggerated claims, given the poor quality of the studies in the sponsor's application and the fact that the approval is based on a non-validated surrogate and that clinical benefit has not yet been established. The applicable statutory and regulatory provisions governing accelerated approval, which require sponsors to submit promotional materials to FDA for pre-dissemination review, should be helpful in this regard.

Summary

In conclusion, I defer to Dr. Woodcock in her role as Center Director to make the decision to approve eteplirsen under the accelerated approval provisions. I find merit and reason on both sides of the disagreement, and despite the intensity of the argument, I believe that the quality of thinking on both sides reflects the importance of clinical and scientific expertise coupled with due process within the FDA. I find no basis for a view that Dr. Woodcock was unduly influenced by involvement with the patient community or other external pressures, and note that our understanding about how to include patients in the regulatory process is evolving. In addition, serious shortcomings present in the eteplirsen development program should not be allowed to establish a broad precedent for therapeutic development in rare diseases. In the end, we have

³² Draft Approval Letter for eteplirsen, as of September 9, 2016.

³³ Appeal at 27.

³⁴ Woodcock Decisional Memorandum at 10.

significant agreement on the science, but a disagreement on the integration of all the evidence as to whether the small changes in dystrophin levels induced by these doses of eteplirsen are “reasonably likely” to predict clinical benefit. Considering that a substantially flawed development program contributed to the difficulty coming to resolution in this case, we must redouble our efforts to move the therapeutic development ecosystem to use methods that will produce high-quality evidence from the outset.

For the reasons set forth above, CDER’s final decision, as set forth in Dr. Woodcock’s July 14, 2016 Memorandum, is upheld. This matter is remanded to CDER for action consistent with this decision.

 Sept. 16th, 2016

Robert M. Califf, M.D., Commissioner of Food and Drugs

Philips, Howard

From: Unger, Ellis
Sent: Monday, September 19, 2016 10:58 AM
To: CDER-ODE1-ALL
Subject: FW: eteplirsen approval press release and documents

To All,

The eteplirsen documents are on line: Dr. Califf's memo, Dr. Lu Borio's (Chief Scientist) memo, my appeal, Dr. Woodcock's approval memo, and my CR memo.

Ellis

From: Walsh, Sandy
Sent: Monday, September 19, 2016 10:35 AM
To: Unger, Ellis; Dunn, Billy
Cc: Choy, Fannie (Yuet); Bastings, Eric; Temple, Robert
Subject: eteplirsen approval press release and documents

Here are the decisional documents that have been posted.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf

Sandy Walsh

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669
Sandy.Walsh@fda.hhs.gov



Philips, Howard

From: Choy, Fannie (Yuet)
Sent: Monday, September 19, 2016 11:19 AM
To: CDER-APPROVALS
Cc: Choy, Fannie (Yuet); Ware, Jacqueline H
Subject: NDA Approval: Exondys 51
Attachments: NDA206488_Aproval Ltr_ labeling_091916.pdf; Division Director_Eteplirsen DNP summary memo.pdf; Office Director Memo Eteplirsen_7-16-16.pdf; Woodcock final decisional memo 20160714.pdf

Dear Colleagues:

The following application has been approved under accelerated approval on September 19, 2016.

NDA number: NDA 206488

- Product Name: Exondys 51 (eteplirsen)
- Applicant Name: Sarepta Therapeutics, Inc.
- Approval Date: September 19, 2016
- Classification codes: Original NDA 505(b)(1), NME, Priority Review, Rolling Review, Fast Track designation, orphan designation
- Indication: EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on dystrophin increase in muscle tissue. An effect of EXONDYS 51 on ambulatory function has not been established. Continued approval for this indication may be contingent upon demonstration of an effect on ambulatory function in confirmatory trials.
- Route of administration: Injection
- Prescription

Attached to this email are the approval letter with attachment, the Office Director and Division Director Summary Reviews. The applicant has acknowledged receipt of the approval letter and attachment by email on 9/19/16. Please note that the attachments have not yet been redacted.

Attachments:

- Approval letter
- Division Director summary memo
- Office Director summary memo (Dr. Unger and Dr. Woodcock)

Thank you,

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration

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Philips, Howard

From: Unger, Ellis
Sent: Monday, September 19, 2016 10:27 AM
To: Dunn, Billy; Bastings, Eric; Ware, Jacqueline H; Freed, Lois M; Kozauer, Nicholas; Breder, Christopher D; Hawver, David; Choy, Fannie (Yuet); Peters, Tracy; Lowy, Naomi
Cc: Temple, Robert; Locicero, Colleen L; Stockbridge, Norman L; Grant, Stephen; Mathis, Mitchell; Farchione, Tiffany
Subject: RE: Eteplirsen SDR Board's Memo, Commissioner's Memo

Also – my email to Dr. Califf, disagreeing with the penultimate draft of his memo.

Ellis

Rob,

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

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

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

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

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

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

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

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

Importantly, this discrepancy, raising important doubts about all of the immunohistochemistry data, was not known to Dr. Woodcock at the time she filed her approval memo on 7/14/16. (I had not performed these analyses until the evening of 7/15/16.) Her issuance of a decisional memorandum prior to careful consideration of my final review represents a critical deviation from protocol. As pointed out in the SDR memo (page 10): “Dr. Woodcock conceded to the SDR Board that she was

leaning toward granting approval in light of the available data as early as 2014,” and page 20: “...at the conclusion of the review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level.”

It follows, therefore, that:

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

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

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

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

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

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

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

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

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

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

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

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

I thank you for your consideration in all of this.

Ellis

Temple, Robert

From: Unger, Ellis
Sent: Tuesday, September 20, 2016 7:24 PM
To: Dunn, Billy; Bastings, Eric; Jenkins, John K
Cc: Temple, Robert
Subject: eteplirsen commentary

My father read the documents on the web today. His thoughts:

wow spent the best part of the day reading the transcripts from so many publications including the FDA. I'm dizzy.

As I see it the Commissioner was protecting his underlings appropriately as were you and Bastings and Jenkins. The flaw was Janet not because she ignored the science but because she did not back up her group.

She deserves nothing from the patients who will not improve, from the insurance companies who have to pay out excessive monies for a useless drug, from her underlings who she would not back up, from every person in the country whose medical rates will go up, and from (God Forbid) the uninsured who cannot afford to pay for a worthless drug but will worry that they are letting their children down. This last part makes her despicable for the heartaches she will cause these parents. Only the company and its stockholders will ever gain from her decision.

eteplirsen

Francer suggested that action by FDA on payer communications and use of real-world data should not wait until after it holds a public hearing on off label communications in November. (Also see "[Off-Label Debate Between FDA, Industry To Formally Begin After Election](#)" - Pink Sheet, 31 Aug, 2016.)

In fact, Francer suggested that the meeting appears to be focused on a potentially more difficult area to address – communication of information to prescribers on what are more clearly off-label uses.

Communications to prescribers on “medically accepted alternative uses” would be a third step in redefining FDA’s communications policies, he said.

Alternative uses would include those “that are different from the approved indication but are medically accepted in that they may be in federal recognized [clinical] compendia or recognized clinical practice guidelines and they may even be the standard of care – some of the oncology drugs are the standard of care in ways that are outside their labeling.”

“We believe that additional sharing of this information can help patients by providing responsible information to health care professionals.” Although this may not be accomplished in the short term, “sooner or later FDA is going to have to grapple with the First Amendment decisions ... that plainly allow for the truthful, non-misleading communication about this kind of information,” Francer said.

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Accelerated Approval After Eteplirsen: A Lowered Bar Or A Unique Event?

- 20 Sep 2016
- Analysis

Sue Sutter [@PinkSheetSutter](#) sue.sutter@informa.com

Executive Summary

What CDER Director Woodcock saw as a flexible and reasonable approach to approval of Sarepta's muscular dystrophy drug, ODE I Director Unger viewed as a threat to the substantial evidence standard.

FDA's internal disagreement over the adequacy of [Sarepta Therapeutics Inc.](#)'s efficacy evidence for *Exondys 51* (eteplirsen) evolved into a debate over the intent, utility and future of the accelerated approval regulatory pathway.

Office of Drug Evaluation I Director Ellis Unger and others within the agency worried that granting eteplirsen accelerated approval for Duchenne muscular dystrophy would lower the efficacy bar for drugs approved under the pathway, eliminate the incentive for companies to invest in high-quality trials and lead to approval of new rare disease treatments without substantial evidence of effectiveness.

In contrast, Center for Drug Evaluation and Research Director Janet Woodcock and FDA Commissioner Robert Califf said the accelerated approval pathway was appropriate in a situation like the one at hand, where there is some uncertainty around the evidence for a new treatment in a serious disease with high unmet need.

With eteplirsen now approved for patients with an exon 51-skipping DMD gene, the final verdict on its efficacy may not be written until 2021, when results of the randomized, confirmatory trial required under accelerated approval are to be submitted to FDA. (Also see "[Duchenne Development: Six-Minute Walk Losing Favor?](#)" - Pink Sheet, 20 Sep, 2016.)

If that trial produces negative or equivocal results on clinical benefit, FDA could be facing a new internal debate, not to mention a fight with the DMD patient community, about what to do with eteplirsen.

Debating How Much Dystrophin Is Enough

Woodcock granted eteplirsen accelerated approval Sept. 19 over the objections of reviewers and senior staff within CDER. Califf had declined to overrule the CDER director's decision after Unger appealed to the commissioner's office. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)" - Pink Sheet, 19 Sep, 2016.)

Califf also said he was satisfied with Woodcock's statement that her decision was based on science, and not Sarepta's financial pressures. (Also see "[Woodcock's Consideration of Sarepta Financial Issues Raises Eyebrows](#)" - Pink Sheet, 19 Sep, 2016.)

At the heart of the dispute between Unger and Woodcock was whether the quantity of dystrophin production demonstrated in eteplirsen clinical trials was an effect that is reasonably likely to predict clinical benefit.

Unger said that although there was evidence from the interim data for Study 301 that eteplirsen induces dystrophin production in the muscle cells, the effect size was inadequate.

"I find no evidence that the increase in dystrophin demonstrated in Study 301 is reasonably likely to predict clinical benefit (mean 0.3%, range 0 to 1.3%)," Unger wrote in his July 18 appeal. The ODE I director said that dystrophin levels of 10% or more would be needed to affect the clinical course of DMD.

In a July 14 memo, Woodcock said that Western blot data following 48 weeks of treatment in Study 301 "clearly shows, using adequate controls, that the drug increases dystrophin protein production in some patients." When combined with 180-week data from an earlier trial, "I conclude that there is substantial evidence from Western blot experiments of increased dystrophin protein production, albeit at a low level."

The CDER director rejected the notion of a 10% minimum threshold for clinical benefit.

She rejected the idea of a 10% minimum threshold for clinical benefit. "I find no evidence of a threshold value for protein content and expression of a DMD phenotype, although the majority of DMD patients reported in the literature have dystrophin that is undetectable by the Western blot assays used."

Evidence from Western blots and other experiments show "that protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation," Woodcock wrote.

In addition to the biochemical data, Woodcock said the long-term clinical experience with eteplirsen provides support for the conclusion that low-level increases are reasonably likely to predict clinical benefit.

However, Unger asserted Woodcock failed to meet the burden of explaining "why production of a near-zero level of dystrophin" is reasonably likely to predict clinical benefit.

"I believe the available evidence leaves open the possibility that some patients *could* benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit," Unger said. "I can find no precedent of an accelerated approval for a marketing application where the effect size of the surrogate endpoint is as small as 0.3%."

Is It Flexibility ...

The internal memos reflect a philosophical debate over the flexibility envisioned for the accelerated approval pathway versus the need for substantial evidence.

The FDA Safety and Innovation Act of 2012 essentially codified the agency's accelerated approval regulations, providing specific authority to approve drugs on the basis of a surrogate endpoint reasonably likely to predict clinical benefit. The statute encouraged FDA to use innovative and flexible approaches to assessing products under accelerated approval for patients with serious or life-threatening diseases or conditions or unmet medical needs. However, FDASIA did not alter the substantial evidence standard for approval.

The issue of flexibility is highlighted repeatedly by Woodcock in her decisional memo and in other review documents that reflect her opinion on the eteplirsen application.

"Given the deficiencies that have been identified in the development program, my conclusion to rely on the surrogate endpoint ... represents the greatest flexibility possible for FDA while remaining within its statutory framework," Woodcock's memo states.

"In this case, the flexibility is warranted because of several specific factors, including: the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a fatal disease in children," Woodcock said. "Of note, the therapy has been relatively safe in the clinic, although intravenous administration always carries risk."

Woodcock was critical of the Office of New Drugs' failure to issue clear guidance on what constitutes a sufficient drug effect to be reasonably likely to predict clinical benefit, FDA's Borio said.

An Aug. 8 memo by FDA Acting Chief Scientist Luciana Borio also discusses the reasoning Woodcock provided to the scientific dispute resolution review board that considered Unger's appeal.

Woodcock "thought that the review team was unreasonable in its position on a threshold for predicting clinical benefit in this case," Borio said. "She acknowledged that there were clear weaknesses in the data but that accelerated approval should not be limited to 'sure bet' drugs and that confirmatory trials are required for a reason."

"Dr. Woodcock emphasized her view that the agency needs to accept more uncertainty when granting accelerated approval," Borio said. "She also criticized [the Office of New Drugs] for not issuing clear guidance

on what constitutes a sufficient drug effect to be 'reasonably likely to predict clinical benefit,' as she had suggested for an extended period of time."

... Or A Lowering Of The Bar?

What Woodcock saw as a flexible and reasonable approach, Unger viewed as a threat to the substantial evidence standard.

In his appeal, Unger argued that accelerated approval of eteplirsen "would lower the evidentiary standard for effectiveness to an unprecedented nadir."

"The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin," Unger said. "If a statistically significant change of 0.3% – a mere 3 parts out of a thousand – is considered adequate to support accelerated approval here, then the question arises as to whether there would be any statistically significant change that would be too small to be considered 'reasonably likely' to support accelerated approval."

Accelerated approval of eteplirsen "would lower the evidentiary standard for effectiveness to an unprecedented nadir." – ODE I Director Unger

If FDA were to adopt the concept that accelerated approval for rare diseases could be supported by any statistically significant change in an appropriate surrogate, it would enable accelerated approval of myriad drugs, Unger said.

"No doubt there are some who would applaud this as an advance," he said. "But a standard this low would undercut FDA's ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act."

Changing Drug Development For Rare Diseases

Unger also predicted eteplirsen's accelerated approval could detrimentally affect drug development.

"Traditional drug development for rare diseases might be replaced by a system where small, baseline-controlled, proof-of-concept studies designed to show any change in a surrogate marker would provide a basis for accelerated approval, assuming that the pathogenesis of the disease was well understood and that the surrogate was directly on the causal path," Unger said.

"There would be little reason to pursue adequately controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of failure would provide a disincentive to conduct such trials."

Borio raised similar concerns about the precedent that would be set by eteplirsen's accelerated approval.

"Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies – both by discouraging others from developing effective therapies for DMD and by encouraging other developers to seek approval for serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit," she said.

Withdrawal Might Be Difficult

Unger also cautioned about the difficulty FDA would face in trying to withdraw eteplirsen if the confirmatory trial does not demonstrate clinical benefit.

CDER learned this lesson the hard way when it sought to withdraw the breast cancer claim for [Genentech Inc.'s Avastin](#) (bevacizumab) after trials failed to confirm the magnitude of benefit seen in earlier studies that led to accelerated approval. Genentech fought the move and was the first sponsor to take such a dispute to the public hearing stage. CDER ultimately prevailed when then-FDA Commissioner Margaret Hamburg ordered the claim withdrawn in November 2011.

The Avastin experience led some FDA officials to call for an easier process of withdrawing drugs that fail their confirmatory trials. (Also see "[Lessons From Avastin: Accelerated Approval Needs "Easy On, Easy Off" Mechanism, Pazdur Says](#)" - Pink Sheet, 26 Nov, 2012.)

"In reality, it is difficult to withdraw ... a drug that is deemed to be effective, or possibly effective, by patients with severe diseases and limited treatment options," Unger said.

Califf: Eteplirsen A 'Unique Situation'

Although Califf said he understood the concerns raised by Unger and Borio about lowering the approval standard, "I defer to Dr. Woodcock's conclusion that accelerated approval in this case does not represent such a lowering of the bar."

Although the evidence was not as strong as everyone would have liked, the record reflects that Woodcock "fully considered the patient population, lack of alternative therapies and relevant information and analysis" in concluding the data were sufficient for accelerated approval, Califf said in a Sept. 16 memo.

The commissioner also did not view eteplirsen's approval as a precedent-setting event that would lower the bar for other drugs.

"I am confident that this unique situation will not set a general precedent for drug approvals under the accelerated approval pathway, as the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information," Califf said.

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Duchenne Development: Six-Minute Walk Losing Favor?

- 20 Sep 2016
- Analysis

Derrick Gingery [@dgingery](#) derrick.gingery@informa.com

Executive Summary

Sarepta relied on the endpoint to get accelerated approval for eteplirsen, but the interim CEO says trials for follow-on products could use walk-run tests or other measures instead.

[Sarepta Therapeutics Inc.](#) may find itself on the forefront of endpoint development in Duchenne muscular dystrophy after FDA's accelerated approval of *Exondys 51*.

With confirmatory trials on the horizon, the company said it is looking beyond potentially using the six-minute walk test to explore other measures of function.

FDA does not appear ready to retire the six-minute walk as a Duchenne endpoint, but has questioned it, even though most sponsors use it. The agency may want to use Sarepta's and other sponsors' trials in the disease to develop other, potentially better endpoints.

Sarepta interim CEO and Chief Medical Officer Edward Kaye said he has not heard specifically that FDA wants to move away from using the six-minute walk test for Duchenne trials. But he said the agency is interested in "exploring other endpoints."

"There's a lot of exploration to other types of endpoints and I think one of the things that will be interesting is how well these endpoints correlate to things like dystrophin," Kaye said during a Sept. 19 conference call on Exondys 51's approval.

"I think we're in the early phases of looking at some of these endpoints and as we go through, we'll obviously want to make sure we have the most sensitive and most robust endpoint that will demonstrate clinical efficacy."

FDA announced on Sept. 19 that Exondys 51 (eteplirsen) had received accelerated approval for treatment of Duchenne patients amenable to exon 51 skipping in a 30mg/kg per week dose.

The product on average will cost \$300,000 per year after discounts, compliance rates and weight-based dosing is taken into account. The company has not announced the higher list price.

Sarepta also received a pediatric rare disease priority review voucher as part of the approval. (Also see "[Duchenne Surprise: Sarepta Prices Exondys 51 Below Expectations](#)" - Scrip, 19 Sep, 2016.)

The confirmatory trial and another trial listed as a post-marketing commitment require use of the North Star Ambulatory Assessment as the primary endpoint, according to the [approval letter](#). Both trials will compare various doses of the product.

Sarepta used the six-minute walk test, which measures the distance a Duchenne patient walks during the period, in the trials submitted as part of its NDA.

The results were not convincing for FDA, raising concerns about whether Exondys 51 was effective. (Also see "[Duchenne Muscular Dystrophy: Second Product Isn't The Charm](#)" - Pink Sheet, 15 Jan, 2016.)

There also are questions about dystrophin production and whether it is an adequate biomarker for effectiveness in Duchenne. (Also see "[Sarepta Setback: FDA Doubts About DMD Biomarker Crushes Early Approval Dreams](#)" - Pink Sheet, 19 Nov, 2013.)

Walk-Run Tests Could Be Used, Kaye Says

Kaye said the company is considering some other potential endpoints as functional measures in younger boys, in part to expand the cohort of patients that could engage with the test.

Kaye said younger patients cannot perform the six-minute walk test, so other measures like the Bayley Scales of Infant and Toddler Development could be used for participants less than four years old.

As part of the confirmatory trials, several other measures could be used to try and demonstrate the success of the treatment, he said. Those include the 100-meter walk-run test, as well as the 10-meter walk-run.

Kaye said the details still need to be worked out with FDA in terms of the trial protocols.

"Obviously we're continuing to collect a lot of data," he said. "As we get more and more data, we'll compile it and then we'll have discussions with the agency to make sure we have a trial that will meet their needs."

The Peripheral and Central Nervous System Drugs Advisory Committee, during its consideration Exondys 51, voted overwhelmingly that 10-meter walk/run and rise time data had no effect on the persuasiveness of the results of Sarepta's studies.

The group also said the North Star Ambulatory Assessment data also had no effect or weakened the findings. (Also see "[Sarepta, FDA And The Dangers Of Strong Early Results](#)" - Pink Sheet, 2 May, 2016.)

Function tests can be problematic, in part because there are human factors that could affect results. Patient motivation can affect walking distance.

The issue was raised during the advisory committee meeting on [BioMarin Pharmaceutical Inc.](#)'s former Duchenne candidate drisapersen.

FDA was concerned that injection site reactions may have inadvertently unblinded patients as to whether they were receiving study drug, which could have motivated them to try harder during the test. (Also see "[FDA Can't Find Efficacy For BioMarin's Drisapersen](#)" - Pink Sheet, 20 Nov, 2015.)

Guidance Says Activity Measures Useful

FDA told the Pink Sheet that its [draft guidance](#) on developing drugs in Duchenne states there is no defined set of required or recommended clinical outcome measures for dystrophinopathy studies. And while outcome measures have been developed in the area, FDA said it also will consider proposals for new measures that can determine clinically meaningful effects in patients.

The draft guidance also says that in ambulatory children age four to seven, "timed function tests such as time to climb four stairs or time to walk or run 10 meters, among others" can be useful.

In addition, the guidance says that efficacy endpoints based on function can be measured in a variety of ways, including a patient's ability to perform certain activities or time to perform them.

Agency officials also noted in the guidance that Duchenne endpoints "should have the ability to detect improvement from baseline, as well as decline, to capture the spectrum of beneficial drug events."

Parent Project Muscular Dystrophy, a Duchenne patient advocacy group, submitted a proposed draft guidance for drug development in the disease for FDA consideration.

The agency later released its own version based in part on the group's suggestions. (Also see "[Duchenne Muscular Dystrophy: FDA Supports Broader Outcome Measures, Biomarkers](#)" - Pink Sheet, 10 Jun, 2015.)

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FDA Oncology Advisory Committee Is Still Pazdur's Center of Excellence

- 20 Sep 2016
- Opinion

Michael McCaughan [@RPMReportMike](#) michael.mccaughan@previsionpolicy.com

Executive Summary

Richard Pazdur is moving to a new role in FDA as part of a reorganization driven by the Cancer 'Moonshot.' The most recent Oncologic Drugs Advisory Committee meeting, however, demonstrates that he is still very much in command of cancer drug reviews.

The Oncologic Drugs Advisory Committee's unanimous rejection of Spectrum's proposed bladder cancer therapy apaziquone followed a tried-and-true template for cancer drug reviews in the "Breakthrough" era.

A new drug application with clear problems was brought to the meeting largely to allow FDA's negative review to be aired publicly. And along the way, Office of Hematology & Oncology Products Director Richard Pazdur uses the application to drive home a broader message about cancer drug development.

Pazdur openly acknowledges that FDA's Oncologic Drugs Advisory Committee (ODAC) is largely reserved for "problem" applications; there is, in his view, generally little justification for the delay necessitated by an advisory committee stop when a new drug for cancer could get to market even a few weeks faster.

But, through the years, Pazdur has also used the ODAC meeting as an opportunity to offer important messages to sponsors. Drug developers have learned to pay careful attention to those meetings for insights into Pazdur's thinking on topics like the limits of progression-free survival endpoints, efficacy bars in different disease settings, or the expectations for accelerated approval.

The recent news that Pazdur is transitioning to a new role at FDA – leading an "Oncology Center of Excellence" to integrate cancer reviews across the traditional FDA drug, biologic and device centers – raises questions

ACLA also insisted that statutory and regulatory provisions developed under a new framework should be designed to avoid duplication of oversight of test development and laboratory operations to ensure continued patient access to clinical laboratory services. -- Erin Durkin (edurkin@iwpnews.com)

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Woodcock Wanted Drug Approved Before Review Completed: FDA

09/20/2016

Janet Woodcock had made up her mind to approve ([see earlier story](#)) Sarepta's controversial Duchenne drug Exondys 51 (eteplirsen) well before she had completed its review — in fact, she had written an approval memo before reviewers even submitted their review memo and summary. These actions are detailed in a [review summary](#) that illustrates her unprecedented involvement and interference in the NDA review, actions that senior reviewers have driven by her succumbing to Congressional, patient, company and other outside pressures to get the drug approved. Pressure from Woodcock was so bad that at least two members of the review team were leaving FDA or had left the agency, the summary indicates.

Office of Drug Evaluation 1 director Ellis Unger questioned her involvement in the submission and appealed her decision to override his review that did not meet the standard for accelerated approval, Woodcock became defensive and critical of the review team's expertise. During the appeal, the Scientific Dispute Process Review (SDR) Board that the review team did a poor job framing the issues during their advisory committee presentations were confusing and poorly worded. During her interview with the SDR Board, Woodcock opined that the review team "did not put its best foot forward in the review team's presentation of the IHC data, contending that its failure to highlight the clinical data made the questions on conventional approval difficult for the committee members to understand.

Unger said that, to his knowledge, this could be the first time a Center director has overruled a review team (and an advisory committee) on a question of accelerated approval that has been demonstrated. On the suggestion of Office of New Drugs director John Jenkins, Unger urged that FDA commissioner Robert Califf eventually adjudicated the internal staff challenge in Woodcock's favor ([see story](#)).

Unger said allowing eteplirsen's accelerated approval would "lower the evidentiary standard for effectiveness to an unprecedented nadir. The benefit produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change is 3 parts out of a thousand — is considered adequate to support accelerated approval here, then the question arises as to whether there would be a change that would be too small to be considered 'reasonably likely' to support accelerated approval... If we were to adopt the concept that, for rare diseases, accelerated approval could be supported by any statistically significant change in an appropriate surrogate, or a response in a single patient, we would enable a myriad of drugs for rare diseases. No doubt there are some who would applaud this as an advance. But a standard this low would undercut FDA's ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1980 Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.

Unger said that the accelerated approval of this NDA," Unger continued, "there would be highly detrimental effects on drug development. Traditional drug development is replaced by a system where small, baseline-controlled, proof-of-concept studies designed to show any change in a surrogate marker would provide accelerated approval, assuming that the pathogenesis of the disease was well understood and that the surrogate was directly on the causal path. There would be no adequately controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of failure would provide a disincentive to invest in a drug. For example, a gene therapy designed to produce a missing clotting factor could receive accelerated approval on the basis of a tiny yet inconsequential response, or a more robust response in a single patient. In short, the precedent set here could lead to the approval of drugs for rare diseases without substantial evidence."

A review team member (RTM) told the SDR Board that, in his or her view, the review team was never sure whether they were discussing science, policies, or politics. Unger and the RTM, Dr. Woodcock frequently conveyed that she thought the review team was being unreasonable and encouraged [them] to find a way to approve the eteplirsen NDA," the summary says. "Both Dr. Unger and the RTM told the SDR Board that Dr. Woodcock seemed focused on the pressure from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of the need to be more flexible for ultra-rare diseases).

ny years of experience in Office of Drug Evaluation 1, the Center director's direct involvement with this drug, compared to other development projects," Unger told the board. He said he found it "unfortunate that the Center director made clear her intent to approve the drug at a briefing with CDER, before she had seen drafts of the Division's final review memorandum or my review memorandum. Prior to reading our reviews, Dr. Woodcock '...reached a different conclusion...' than the review team."

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Lawyers Discuss FDA Bias Concern on Chantix Study

09/20/2016

A briefing document prepared for a joint advisory committee meeting that voted 10-9 to recommend removal of a Boxed Warning for Pfizer's Chantix relating to potential psychiatric risks, including suicide and suicidal ideation, raised CDER medical reviewer concerns that data from a company post-marketing study were biased depending on how money the company gave the investigators. Three Hogan Lovells attorneys write in an online blog [post](#) that the study results appeared to show that the drug did not significantly increase the incidence of suicide and suicidal thoughts.

"FDA suggested that money given to investigators from Pfizer may have influenced the study results," the post says. "According to the briefing document, in sites where investigators received \$25,000 or more in speaking and consulting fees from the company, only 1.8% of patients who had already been diagnosed with a psychiatric disorder were reported to have side effects, such as anxiety, agitation, hostility, or suicidal thoughts, during the trial. On the other hand, at locations where physician/investigators received less money or no payments at all from Pfizer, 6.4% of patients were reported to experience such side-effects."

The attorneys say that the agency's briefing document message was essentially clear — the study results may not be trustworthy given how the data were collected and analyzed, and due to conflicts of interest related to payments to investigators. "This briefing document is the first time we are aware of agency disclosure of concerns about bias from industry payments to clinical investigators," they write. "We will be watching closely for other indicators of concern by the agency regarding such payments.... Given that reviewers have expressed concerns about the data used to support the removal, this regulatory decision will be particularly interesting and one that could influence conflicts of interest disclosure policy going forward."

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FDA Draft Guide on Determining When REMS is Necessary

09/20/2016

FDA has released a [draft guidance](#) on "FDA's Application of Statutory Factors in Determining When a REMS Is Necessary" that is intended to clarify how it applies factors in determining whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks. The agency says the document is one of several being developed to fulfill performance goals it agreed to during the last user fee reauthorization in 2012.

[FDA to Encourage Seamless Designs for Cancer Clinical Trials](#)

[FDA Approves First Duchenne Treatment, Sarepta's Exondys 51](#)

[Patient Engagement Stressed by Health Council in Advice to Next President](#)

[BsUFA II Seeks to Improve Review Process, Restructure Fees](#)

(FDA Webview)

[FDA Rescinds Teva SPA After Dosing Changed](#)

[KemPharm Seeks Dispute Resolution of Pain Drug Denial](#)

[FDA Contest for Developing Naloxone Mobile App](#)

[Woodcock Upheld by Califf in Duchenne Drug Appeal](#)

(BioCentury Extra)

[FDA approves Sarepta's eteplirsen, first DMD drug](#)

[Amgen pushes for access to biosimilar information](#)

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Sarepta's Eteplirsen Approved After Contentious Internal Debate

- 19 Sep 2016
- News

Sue Sutter [@PinkSheetSutter](#) sue.sutter@informa.com

Executive Summary

CDER Director Woodcock grants accelerated approval after FDA Commissioner Califf refuses to overturn her finding that the drug's effect on dystrophin is reasonably likely to predict clinical benefit in Duchenne muscular dystrophy.

FDA Commissioner Robert Califf deferred to Center for Drug Evaluation and Research Director Janet Woodcock on the accelerated approval of [Sarepta Therapeutics Inc.](#)'s *Exondys 51* (eteplirsen) even though her favorable view of the Duchenne muscular dystrophy drug was opposed by the clinical review team, other senior personnel within the drugs center and the agency's acting chief scientist.

Temple, Robert

From: CDER Trade Press
Sent: Tuesday, September 20, 2016 10:16 AM
To: CDER Trade Press
Subject: CDER Trade Press News Update September 20, 2016



CENTER FOR DRUG EVALUATION AND RESEARCH

Trade Press Update

Recent news from trade publications highlighting CDER-related issues.

Today's Headlines (click to go directly to the article):

(The Pink Sheet – NOTE: Informa publications including, the Pink, Tan, and Gold Sheets along with the RPM Report and Scrip Regulatory Affairs significantly changed their format. Those publications are now all included under the "Pink Sheet" banner)

[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)

[Woodcock's Consideration of Sarepta Financial Issues Raises Eyebrows](#)

[Eteplirsen Review Timeline: CDER Director Was Involved Early And Often](#)

[Teva Leads Generic Rivals In First-To-File ANDAs By A Long Shot](#)

[Pediatric Opioid Development Faces Grim Outlook After Advisory Cmte.](#)

(Scrip)

[Duchenne Surprise: Sarepta Prices Exondys 51 Below Expectations](#)

(Regulatory Focus)

[Sarepta Wins Controversial FDA Approval for First DMD Drug](#)

(Inside Health Policy)

[GPhA Head Rails Against Brand Drug Makers For Anti-Generic Lobby](#)

[FDA Seeks To Prevent Opioid Overdoses Through Its First-Ever Mobile App Challenge](#)

[Duchenne Drug Approval Reveals Unprecedented Internal FDA Battle Over Patient Role](#)

[FDA Goes Against Advisory Committee, Approves Duchenne Drug](#)

(FDA News)

The agency granted accelerated approval Sept. 19 of eteplirsen, an antisense oligonucleotide, for treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

The approval followed an unusual appeal by Office of Drug Evaluation I Director Ellis Unger that went all the way to the commissioner's office. Unger and Woodcock disagreed on the key question of whether the quantity of dystrophin produced by eteplirsen is an effect that is reasonably likely to predict clinical benefit, such that it can serve as a surrogate endpoint supporting accelerated approval.

Woodcock – a 30-year agency veteran who has headed CDER for a total of 19 years – clearly put her reputation on the line with her aggressive push for accelerated approval of eteplirsen, a drug with limited clinical trial data that FDA officials have described as having major flaws.

"The approval of Exondys 51 reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases – while remaining within our statutory framework," Woodcock said.

"The approval of Exondys 51 reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases – while remaining within our statutory framework," Woodcock said in an email to CDER staff announcing the approval."

"In this case, flexibility is warranted because of the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a life-limiting disease of children," she said. "These factors, combined with the dystrophin production data – and the drug's low risk profile – led the agency to approve the drug under the accelerated approval pathway."

[Memos](#) released concurrent with the approval paint a picture of Woodcock taking a highly activist role, both before and after NDA submission, in the effort to get eteplirsen approved as the first drug treatment for DMD, an ultra rare genetic disorder characterized by progressive muscle deterioration and weakness that is often fatal.

The CDER director made known her inclination to grant accelerated approval before other reviews had been completed, was very involved in the advisory committee meeting and believed the review team was not doing enough to take advantage of the agency's regulatory flexibility to speed new treatments to market, the documents show.

On the other side of the argument were Unger and review team members who believed that Woodcock was overly concerned with external pressures on FDA from the DMD patient community, with whom she had interacted frequently, and Congress to approve the drug, as well as with the financial viability of Sarepta if it received a complete response letter. (Also see "[Woodcock's Consideration of Sarepta Financial Issues Raises Eyebrows](#)" - Pink Sheet, 19 Sep, 2016.)

In the end, Califf opted neither to overrule Woodcock nor convene an independent review of the scientific issues in dispute between the director and her staff.

FDA history includes a "consistent precedent of final decision-making about medical products at the center level," Califf said in a Sept. 16 memo.

"Overruling the center director is exceedingly rare and, in my view, would be appropriate only if the center director's decision could not be supported by the available data and information," the commissioner said. "In the present case, the scientific uncertainties lead to a situation in which the decision is a matter of reasoned expert opinion and judgment."

Scientific Dispute Board Appeal ...

Eteplirsen has had a difficult development and regulatory review, with the robustness of the efficacy data underlying questions about the drug's approvability. The initial NDA submission included only one 12-patient controlled clinical study to support efficacy. (Also see "[Duchenne Muscular Dystrophy: Second Product Isn't The Charm](#)" - Pink Sheet, 15 Jan, 2016.)

Despite the questions about clinical efficacy, the drug has garnered an extraordinary amount of support from patients, advocates and Congress. (Also see "[Sarepta's Eteplirsen Review Delay Emboldens Duchenne Community](#)" - Pink Sheet, 25 May, 2016.)

The controversy ended up on Califf's desk because Unger, who heads the office that oversees the Division of Neurology Products, submitted a scientific dispute resolution appeal challenging Woodcock's decision to award accelerated approval.

In a July 14 memorandum, Woodcock concluded there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells.

Evidence from Western blot and other experiments show that protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, she said. Furthermore, both the biochemical data and the eteplirsen clinical data lead to the conclusion that an increase in dystrophin production is reasonably likely to predict clinical benefit in DMD, she said.

Unger and numerous other FDA staff disagreed with Woodcock's view that the findings on the dystrophin surrogate endpoint for eteplirsen are reasonably likely to predict clinical benefit (*see box*).

FDA Staff Opposed To Accelerated Approval

- Office of Drug Evaluation I Director Ellis Unger
- Division of Neurology Products review team
- Office of Biometrics
- Office of Clinical Pharmacology
- Office of New Drugs Director John Jenkins
- Acting Chief Scientist Luciana Borio

Unger's appeal was heard by the agency's Scientific Dispute Process Review Board, a standing committee chaired by acting Chief Scientist Luciana Borio. The board reviewed the eteplirsen NDA administrative file and interviewed Unger, Woodcock, an unidentified review team member and CDER Ombudsman Virginia Behr.

In an Aug. 8 memo to Califf, Borio said the board determined the process followed by CDER gave Unger adequate opportunity to present his scientific views and that the drug center considered all relevant evidence.

... Sparks Call For Substantive Review

However, the board urged the commissioner to conduct "a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit."

Borio's memo describes Woodcock's involvement in issues related to the eteplirsen IND and NDA, including numerous center director briefings and multiple meetings with patient advocacy groups, as well as her active role in the advisory committee review. (Also see "[Eteplirsen Review Timeline: CDER Director Was Involved Early And Often](#)" - Pink Sheet, 19 Sep, 2016.)

At the April advisory committee meeting, panelists voted narrowly against accelerated approval and more firmly against regular approval. (Also see "[Sarepta, FDA And The Dangers Of Strong Early Results](#)" - Pink Sheet, 2 May, 2016.)

Woodcock's involvement in the NDA review "appears to have upended the typical review and decision-making process," the board found.

On June 3, Woodcock requested Sarepta provide additional data from an ongoing trial (Study 301) that included comparisons of biopsy samples obtained at week 48 to their respective baseline samples. If the data showed a meaningful increase in dystrophin, FDA expected to be able to grant accelerated approval within four business days of receiving the data, Woodcock's letter stated.

The scientific dispute board concluded that Woodcock had an extensive and early role in the NDA review process that was troubling. "Indeed, her involvement here appears to have upended the typical review and decision-making process."

"By all accounts, Dr. Woodcock made clear her views that CDER should lean toward finding that eteplirsen met the standards underlying accelerated approval nearly from the outset of her involvement," Borio's memo states. "By May 4, 2016, she had orally communicated her intention to grant accelerated approval for eteplirsen, even though she had not yet seen even the draft review memoranda from the review team or a decisional memorandum from Dr. Unger.

"Then, when she requested data from Study 301 from Sarepta, she communicated to the sponsor a compressed timeframe for CDER's review. Although she later expanded the timeframe for review when the data proved to be disappointing, she apparently analyzed the data on her own, conducted her own additional search of the scientific literature, and took only six or seven business days to orally communicate to the review team her decision to grant approval," the memo states.

Despite the irregularities in process, Woodcock did consider all relevant evidence in reaching her scientific conclusion, the board found. "Based on her own medical judgment, she simply has a difference of opinion with Dr. Unger – both with respect to the scientific conclusion and the sufficiency of the underlying rationale."

Nevertheless, in a section of the memo titled "Considerations From the Acting Chief Scientist," Borio suggests she shares Unger's viewpoint on the underlying scientific issues.

"By any meaningful objective standard ... the overall evidence derived from eteplirsen's limited clinical development program does not support that the levels of dystrophin produced by eteplirsen at the doses studied are reasonably likely to provide clinical benefit," Borio said.

Review Involvement Reflects Management Style

Califf's memo states it is "highly unusual" for a center director's decision on a product application to be appealed to the commissioner's office, and a footnote points out the established dispute resolution process "does not contemplate a substantive decision on the disputed issue by the commissioner."

With regard to Woodcock and Unger, Califf concluded that "qualified experts with extensive experience in FDA decision-making and stellar track records can assimilate the same scientific evidence and disagree about the extrapolation to whether the evidence supports a conclusion that the treatment has an effect that is 'reasonably likely' to predict clinical benefit."

"Given that I do not have technical expertise beyond those already involved in this decision and the record contains adequate evidence to support her conclusion, I defer to the judgment of the center director," he said.

Contrary to the assertions of Unger and other review staff, Califf said he found no basis for the view that Woodcock was unduly influenced by involvement with the patient community or other external pressures.

Woodcock's involvement with the eteplirsen review fits within her longstanding, "hands on" management approach, Califf said.

Califf also addressed the concerns raised by the review board with regard to the CDER director's involvement in the early stages of review and advisory committee and her decision to approve before other reviews had been completed.

Woodcock has had a "hands on" management style during her entire career at FDA, Califf said. "She is well known for interacting with staff at all levels and expressing her opinions." While her involvement with the eteplirsen review might have been more intensive than usual, "such a focus does fit within a longstanding management approach."

Furthermore, "it is difficult to argue that CDER has been unsuccessful under her leadership," he continued. "A vast array of new drugs approved during her tenure is benefitting patients, including a host of significant advances using a variety of expedited programs."

Under Woodcock's leadership, CDER has enjoyed broad public support, Califf said. She has shown "extraordinary courage in the face of extreme pressure on many occasions, including from Congress, the press, patient and patient advocacy groups and industry. She has taken and supported unpopular decisions when appropriate and is well known for not relenting to pressure."

"Further, I find no pattern that indicates that this decision is part of a trend for lowering the standard for drug approval – a trend that would be unacceptable in any event," Califf said.

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Woodcock's Consideration of Sarepta Financial Issues Raises Eyebrows

- 19 Sep 2016

- **News**

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Executive Summary

CDER Director tells FDA appeals board that Duchenne muscular dystrophy development could suffer if Sarepta's drug not approved.

CDER Director Janet Woodcock gave a candid opinion of the importance of the approval of the Duchenne muscular dystrophy drug *Exondys 51* (eteplirsen), as well as the health of its sponsor, [Sarepta Therapeutics Inc.](#), during FDA's internal battle over the decision.

Woodcock admitted to colleagues that the company may need the product approved for its financial health as well as drug development in the space, an issue that is not supposed to play a role in FDA decision-making.

The issue emerged because Woodcock overruled the review team's decision against approving Exondys 51 even though there were questions about its efficacy. Woodcock's decision was appealed ultimately to FDA Commissioner Robert Califf, who sided with her. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)" - Pink Sheet, 19 Sep, 2016.)

Sarepta also gained a pediatric rare disease priority review voucher as a result of the approval. It and the required confirmatory studies could affect the company's health going forward. (*See related story in Scrip.*)

Duchenne Surprise: Sarepta Prices Exondys 51 Below Expectations

By Derrick Gingery 19 Sep 2016

It sparked at least one analyst to question how Sarepta came up with a price for FDA's first approved Duchenne muscular dystrophy treatment.

[Read the full article here](#)

Documents outlining the extraordinary appeal of Woodcock's decision to approve Exondys 51 indicate that Woodcock "was looking at the broader picture for the development of these types of drugs in very limited patient populations" and said "there needed to be some path forward for such innovative products."

Woodcock suggested that "Sarepta in particular 'needed to be capitalized.'"

"Dr. Woodcock cautioned that if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline," according to a memo from Acting Chief Scientist Luciana Borio on the scientific dispute resolution appeal. Documents outlining the [appeal](#) were posted Sept. 19 along with the Exondys 51 [label](#) and [approval letter](#).

"[Woodcock] stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would 'lapse into a position of' self-treatment."

Woodcock's statement about the impact on the drug development may hold some merit. Duchenne drug development could have been in trouble with another denial.

If Exondys 51 had not been approved, Sarepta could have faced severe financial problems. Its stock price plummeted after FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted against a recommendation that the evidence presented warranted accelerated or full approval. (Also see "[Patients Can't Rescue Sarepta's Eteplirsen](#)" - Pink Sheet, 25 Apr, 2016.)

And another proposed Duchenne candidate, [BioMarin Pharmaceutical Inc.](#)'s drisapersen, already had received a complete response letter. (Also see "[BioMarin's Drisapersen 'Compete Response' Shows FDA Flexibility Still Limited](#)" - Pink Sheet, 14 Jan, 2016.)

Califf 'Troubled'

Califf did not determine that Woodcock "succumbed to pressure from the patient community, the public, the press, or others" in overruling the review division. But he also was concerned about the implication that Sarepta's financial health played a role in the decision.

"I was troubled by statements ... that Dr. Woodcock's decision to approve eteplirsen may have been inappropriately motivated by concerns over the sponsor's financial well-being," Califf wrote in a footnote. "I have discussed this issue directly with Dr. Woodcock, who said that she was aware of the financial pressures on the company, but that her decision was based on the science.

"Based on the record of our conversation, I am satisfied that her decision is indeed based on her scientific evaluation of the evidence."

Woodcock has been among FDA's strongest proponents of flexibility when it comes to reviewing drugs for orphan diseases like Duchenne. The agency also has a long track record of flexibility with evidentiary standards for orphan product approvals. (Also see "[FDA Orphan Approval Flexibility Remains Steady As Pressure Increases](#)" - Pink Sheet, 27 Oct, 2014.)

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Eteplirsen Review Timeline: CDER Director Was Involved Early And Often

- 19 Sep 2016
- News

Sue Sutter [@PinkSheetSutter](#) sue.sutter@informa.com

Executive Summary

Review documents show eight center director briefings during the IND phase and seven after NDA submission of Sarepta's DMD drug.

FDA review documents released in connection with the accelerated approval of [Sarepta Therapeutics Inc.](#)'s *Exondys 51* (eteplirsen) describe Center for Drug Evaluation and Research Director Janet Woodcock's involvement with review activities during the IND and NDA stages of the Duchenne muscular dystrophy drug.

In his appeal to the Scientific Dispute Process Review Board, Office of Drug Evaluation I Director Ellis Unger lists a total of 15 center director briefings associated with eteplirsen's development, more than half of which occurred prior to NDA submission. Some of the briefings during the IND stage also included discussion of other DMD drugs under development.

"The center director's direct involvement with this drug, compared to other development programs, has been unprecedented," Unger said.

In his memo refusing to disturb Woodcock's decision to grant accelerated approval, FDA Commissioner Robert Califf said that while the CDER director's involvement was "more intensive than usual," it fit within her longstanding "hands on" management approach. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)" - Pink Sheet, 19 Sep, 2016.)

Below is a list of the center director briefings and other key events in the review of the eteplirsen NDA, as drawn from agency documents.

Date	Action
IND Chronology	
3/13/2013	End-of-Phase II meeting
7/17/2013	Center director briefing
10/18/2013	Center director briefing
10/28/2013	Center director briefing (continuation of 10/18/2013 meeting)
11/17/2014	Center director briefing
2/6/2014	Center director briefing
3/5/2014	Center director briefing
3/19/2014	Sponsor meeting with CDER director on study design and path forward
4/2/2014	Center director briefing
NDA Chronology	
6/26/2015	Eteplirsen NDA submitted
12/9/2015	Center director briefing
1/13/2016	Center director briefing
1/22/2016	Originally scheduled meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (postponed due to snowstorm)
2/10/2016	Center director briefing
4/15/2016	Center director briefing
4/25/2016	Advisory committee meeting; panel votes 7-6 there is not substantial evidence from adequate,

	well-controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit, and 7-3 (3 abstentions) that clinical results of a single historically controlled study do not provide substantial evidence of efficacy
5/4/2016	Center director briefing to discuss the advisory committee meeting and plan of actions for the NDA; CDER Director Janet Woodcock informs review team she intends to grant accelerated approval
5/24/2016	ODE I Director Ellis Unger meets privately with Woodcock to discuss eteplirsen decision
5/31/2016	Center director briefing to discuss reviews and initial draft of Woodcock's decisional memorandum based primarily on the data from Study 201/202
6/3/2016	In a letter signed by Woodcock, FDA requests additional data from Study 301, including comparisons of biopsy samples at baseline and week 48; if results show a meaningful increase in dystrophin by Western blot analysis, FDA expects to be able to grant accelerated approval within four business days of receiving the data
6/27/2016	Sarepta submits requested data
7/5/2016	In email to Woodcock, Unger requests formal appeal to the commissioner
7/6/2016	Center director briefing on levels of dystrophin observed in ongoing trial and whether they can be interpreted as reasonably likely to predict clinical benefit and used as a surrogate endpoint
7/11/2016	Woodcock provides draft of her final decisional memo to review team for comments
7/14/2016	Woodcock finalizes her decisional memo
7/16/2016	Unger finalizes his decisional memo
7/18/2016	Unger files scientific dispute resolution appeal
8/8/2016	Acting chief scientist's memo says Scientific Dispute Process Review Board finds Unger had an opportunity to present his scientific views; board encourages FDA Commissioner Robert Califf to conduct a substantive review of the scientific dispute or convene a panel of relevant experts
9/16/2016	Califf memo defers to Woodcock on eteplirsen's accelerated approval
9/19/2016	Eteplirsen receives accelerated approval under brand name Exondys 51

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Teva Leads Generic Rivals In First-To-File ANDAs By A Long Shot

- 19 Sep 2016
- Analysis

Jessica Merrill [@Jessicaemerrill](#) Jessica.merrill@informa.com

Purdue's Stacy Baldrige defended the product's labeling, pointing to the company's clinical trials of OxyContin with pediatric patients at the meeting, noting that subjects were carefully selected, as well as an enrollment rate of 7.6%. Additionally, 40% of pediatric patients prescreened but not enrolled either failed to meet requirements related to minimum dosage or duration of use.

Baldrige also said in a statement to the Pink Sheet that Purdue is not promoting to pediatricians or other prescribers the pediatric safety and dosing information for OxyContin.

"While we are not promoting the indication, we believe it is critical for prescribers to have the necessary safety information when making prescribing decisions," Baldrige said. "It is important to study treatments for children with pain so that doctors can make good, evidence-driven decisions."

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Duchenne Surprise: Sarepta Prices Exondys 51 Below Expectations

- 19 Sep 2016
- Analysis

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Executive Summary

It sparked at least one analyst to question how Sarepta came up with a price for FDA's first approved Duchenne muscular dystrophy treatment.

[Sarepta Therapeutics Inc.](#) may have given payers a break when it priced its newly approved Duchenne muscular dystrophy treatment *Exondys 51* (eteplirsen).

The announced \$300,000 annual price was not as high as some had estimated and prompted Sarepta's Interim CEO and Chief Medical Officer Edward Kaye to explain the company's reasoning behind it.

FDA announced Sept. 19 that it had granted accelerated approval for Exondys 51 for treatment of Duchenne in patients amenable to exon 51 skipping, which is about 13% of the Duchenne population. The product is available through a once-weekly intravenous infusion of 30mg/kg.

Sarepta also received a rare pediatric disease priority review voucher, which could allow a priority review for any future application it chooses or be sold to another sponsor.

Center for Drug Evaluation and Research Director Janet Woodcock decided to overrule the review division's recommendation to deny approval. It prompted an extraordinary appeal process that reached FDA

Commissioner Robert Califf, who sided with Woodcock. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)" - Pink Sheet, 19 Sep, 2016.)

Some of Woodcock's reasoning for her decision also raised concerns among others at FDA. (Also see "[Woodcock's Consideration of Sarepta Financial Issues Raises Eyebrows](#)" - Pink Sheet, 19 Sep, 2016.)

The commercial launch of Exondys 51 will begin immediately, Sarepta said in a statement.

Sarepta said the quoted price takes into account weight-based dosing over time, as well as compliance rates and mandatory government discounts.

The number seemed to surprise one analyst from Leerink Partners, who during a conference call on the approval asked about the assumptions used to determine the price, including whether the company considered a similar price for future indications. He said other analysts had expected a higher figure.

Kaye responded that the price was reasonable and took into account research and development spending, as well as post-marketing requirements and production costs.

"What we're trying to do is be as thoughtful as possible," he said. "Given the sensitivity to pricing, we've tried to be very what we think is reasonable given all of the costs for this and even the innovation that goes into manufacturing. The focus is really to try to make sure that all the patients can gain access to it."

The price may still be expensive, but couching it as lower than expected may not draw much criticism or scrutiny, although orphan products usually do not warrant intense pricing complaints.

Because orphan treatments are difficult to develop and target small populations, there seems to be an understanding that they will be expensive, especially when they are the first for a debilitating disease.

Advocates also want to balance affordability with encouraging drug development in the sector.

Parent Project Muscular Dystrophy said in a statement that it "remains focused on ensuring all patients who are candidates for eteplirsen obtain affordable access to the drug while it continues to support the development of additional tools and resources to drive forward approvals of additional therapies and treatments."

Post-Marketing Trials Required

Some of the revenue from sales likely will help pay for the Exondys 51 confirmatory study, which will determine whether the evidence used to grant accelerated approval leads to a clinical benefit. If not, FDA could pull the drug from the market.

FDA directed Sarepta to conduct a two-year randomized, double-blind, controlled trial in Duchenne patients amenable to exon 51 skipping that compares the approved 30mg/kg per week dose to one "that provides significantly higher exposure," such as the same dose daily, according to the [approval letter](#).

Trial completion is expected in November 2020 and a final report in May 2021, according to FDA's approval letter.

Protocols have yet to be discussed with FDA, including the comparison dose for the confirmatory study, and won't be finalized by 2017, Kaye said during the conference call.

Another trial studying patients with exons 45 or 53 looking at two "well-separated doses" also is part of the *post-marketing commitments*.

Approval Creates Confidence For Other Developers

The accelerated approval is expected to open doors for eventual expansion of the indication, such as the other exon groups.

Kaye said in Sarepta's statement that the company "will continue to leverage what we have learned from Exondys 51 to facilitate future development of potential new treatments targeting additional exons with the goal of one day treating all DMD patients amenable to exon skipping."

Debra Miller, president and CEO of CureDuchenne, an advocacy group that provided early funding for eteplirsen's development, said in an interview that she wanted to see trials in other exons to be fast-tracked going forward.

Miller also said the approval will give other sponsors more confidence to invest in Duchenne treatments.

"It goes to small companies that have one drug and have been watching this process with horror basically," she said. "Now, they have confidence to put resources [into development] and hopefully we have a new paradigm that is more human and allows patients to get the drugs they need."

Sarepta has travelled a difficult road to approval for Exondys 51.

After FDA made its concerns about the drug's efficacy known, the Peripheral and Central Nervous Systems Drugs Advisory Committee voted against recommending that the evidence was sufficient for an accelerated or full approval. (Also see "[Patients Can't Rescue Sarepta's Eteplirsen](#)" - Pink Sheet, 25 Apr, 2016.)

Then, FDA asked for more data and missed its review goal. (Also see "[Sarepta's Eteplirsen Review Delay Emboldens Duchenne Community](#)" - Pink Sheet, 25 May, 2016.)

Voucher To Be Sold Soon

The priority review voucher is another benefit of the approval, and could generate a significant cash infusion that Sarepta could use for additional research or other expenses, should it be sold.

Sarepta said during the conference call that it intends to sell it and already has reached out to several potential buyers.

Leerink analysts said in a note they expect \$350m capital inflow from sale of the voucher.

Vouchers have been commanding hundreds of millions recently, but their price may have peaked.

Most recently, [Gilead Sciences Inc.](#) paid less than \$338m for a voucher, a drop from the \$350m [AbbVie Inc.](#) paid in 2015.

It is likely that the increased number of available vouchers is driving their price down. The pediatric rare disease voucher program has been very popular with sponsors. (Also see "[Priority Review Vouchers Appear To Be Dropping In Price](#)" - Pink Sheet, 27 Jul, 2016.)

The program will expire on Oct. 1 if Congress does not renew it. Orphan drug advocates are pushing for an extension, but FDA does not want the program to continue. (Also see "[Pediatric Rare Disease Voucher Program Faces Expiration](#)" - Pink Sheet, 10 Sep, 2016.)

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Sarepta Wins Controversial FDA Approval for First DMD Drug

Posted 19 September 2016 By [Zachary Brennan](#)

The US Food and Drug Administration (FDA) on Monday approved Sarepta Therapeutics' first drug to treat patients with Duchenne muscular dystrophy (DMD), a rare genetic disorder that causes progressive muscle deterioration and weakness in young children.

The approval is highly controversial after a [FDA advisory committee voted against approval](#) in April as the outside experts said there was not substantial evidence that the drug is effective in providing clinical benefit, which is the standard for traditional approval. Before that vote and afterwards, the DMD patient community protested vigorously.

DMD, occurring in about one out of every 3,600 male infants worldwide, is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. The first symptoms are usually seen between the ages of three and five, and worsen over time.

The agency said that following the hearing, Sarepta submitted additional data "showing substantial evidence of dystrophin production, although the amount of dystrophin produced was only a small fraction of the normal level."

The injection, known as Exondys 51 (eteplirsen), is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, who constitute approximately 13% of the population with DMD. Sarepta said late Monday that the average cost per patient will be \$300,000.

Ultimately, the new injection, known as Exondys 51, was approved under FDA's accelerated pathway reserved for drugs to treat serious or life-threatening diseases, and where there is a lack of other treatment options.

"Based on the data submitted by the applicant, the Agency has concluded that there is a statistically significant increase in dystrophin production in indicated patients who are exposed to the drug that meets the accelerated approval requirement," FDA said Monday.

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Disagreement

That approval followed a contentious scientific disagreement inside of FDA pitting Janet Woodcock, director of the Center for Drug Evaluation and Research (who was in favor of approval) against Ellis Unger, director of the Office of Drug Evaluation.

The fight boiled down to what should be considered a "statistically significant increase in dystrophin, the surrogate endpoint," and, according to Unger, whether "an exceptionally small magnitude" implies clinical benefit, according to the [126-page approval letter](#).

"This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed 'reasonably likely to predict clinical benefit.' Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated," Unger wrote in an email to Woodcock.

In his appeal of Woodcock's decision to override the advisory committee's vote and other reviewers' qualms with the application, Unger noted that the position of the review team in the Division of Neurology Products, the Office of Biometrics, the Office of Clinical Pharmacology, the Office of Drug Evaluation-I, and the Office of New Drugs "(verbal acknowledgement from Dr. John Jenkins) is that the applicant has not provided evidence that this drug is effective at the dose studied."

↑ Wrong - Did not give evidence

However, FDA Commissioner Robert Califf noted in his letter on the dispute that he deferred to Woodcock on the approval decision.

New Trial

Moving forward, FDA said it is requiring Sarepta (company's stock increased in value by more than 80% as of Monday morning and the company also won a rare pediatric priority review voucher as a result of the approval, which it says it will sell) to conduct a clinical trial to show that the drug preserves motor function, with eteplirsen being compared to placebo.

The required study is designed to assess whether Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. If the trial fails to verify clinical benefit, FDA said it "may initiate proceedings to withdraw approval of the drug.

"In this case, flexibility is warranted because of the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a life-limiting disease of children. These factors, combined with the dystrophin production data – and the drug's low risk profile – led the Agency to approve the drug under the accelerated approval pathway," FDA said.

GPhA Head Rails Against Brand Drug Makers For Anti-Generic Lobby

September 19, 2016

The head of the generic drug lobby called out representatives of brand and biologics industries for lobbying against a handful of pro-generic policies on Capitol Hill and trying to shift the blame for price hikes on generics while claiming to support competition. The official blasted brand makers for undermining legislation that would prevent use of REMS to delay generics, pushing policies to thwart biosimilar uptake and advocating an industry-wide exemption for the inter-partes review of weak patents shielding branded drugs.

Generic Pharmaceutical Association CEO Chip Davis complained "some interests are engaged in a campaign to try and place blame on generics for pricing problems" when in fact these drugs are part of the solution, on a conference call Monday (Sept. 19).

"From our perspective at GPhA, the recent focus and attention focused on drug prices has the potential to bear some positive results in our view," Davis said. He emphasized that ensuring generic and biosimilar competition and the harmonization of international regulatory pipelines are important planks to encourage affordable drug prices.

"But in the midst of this critical opportunity to make progress on pricing and reducing costs, certain representatives for the brand and biologic industries are driving an agenda that would - if enacted - ultimately leave vulnerable patients without access to affordable medicines. These industry representatives are saying one thing publicly about the need for competition, but advocating in Congress for something quite different. The policies they are advocating would actually increase barriers for generic entry, leading to less competition and increased costs to the system," Davis said.

Davis also said he wanted to put to rest a suggestion by some that generic drug price hikes are a major contributor to rising prices. "Lastly, let me address one issue head on since it is being used to try and steer the decision-makers and the media in the wrong direction. A conversation about percent increases in a small minority of generic drugs distracts from the overarching reality that generic drugs experience deflation and save the American health care system \$5 billion week," he said.

The generic drug trade group similarly lashed out against the brand drug industry in a National Journal op-ed piece last week.

"Brand drug companies have proven time and again they will do anything they can to preserve their market monopolies at the expense of patients seeking access to affordable medicines," the op-ed piece said.

Duchenne Drug Approval Reveals Unprecedented Internal FDA Battle Over Patient Role

September 19, 2016

Background documents surrounding FDA's approval of a controversial Duchenne muscular dystrophy drug reveal drug center chief Janet Woodcock, backed by commissioner Robert Califf, made the decision despite strong opposition from the acting chief scientist and a top FDA reviewer, who argued Woodcock was heavily influenced by patient groups and Congress, rather than science. The documents indicate that Woodcock saw the move as an overarching policy shift to offer flexibility on ultra-rare disease treatments, but the review team chief said it set a dangerous precedent for patients.

Califf noted FDA's "understanding about how to include patients in the regulatory process is evolving," and concluded Woodcock did not succumb to pressure from patients, the public, the press or others. But the top reviewer disagreed, saying Woodcock was changing the bar on efficacy and this likely marked the first time a center director overruled a review team on whether effectiveness was demonstrated.

Woodcock, conversely, felt the review team "downplayed and undercut" the views of the patient advocates. But the other officials felt approval of the drug could affect future therapy development, with the review team official describing eteplirsen as "a scientifically elegant placebo," and arguing that approval would send a signal that political pressure and intimidation guide FDA decisions.

The documents reveal there were initial scientific disagreements between the director of the Office of Drug Evaluation-I, Ellis Unger, and Woodcock around the approval of the drug. According to a memo sent to the agency officials from Califf on Friday (Sept. 16), Unger, the review team and Acting Chief Scientist Luciana Borio concluded that the demonstrated levels of dystrophin are not "reasonably likely" to predict clinical benefit.

The memo notes that Woodcock, using "...the greatest flexibility possible for FDA while remaining within its statutory framework," found eteplirsen is reasonably likely to predict clinical benefit.

"She is clearly employing and interpreting the full range of appropriate information, comprising a 'totality of evidence' approach in determining that the clinical trials demonstrated an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit," said Califf.

The dispute was sent to Califf in August by Borio, who chairs the Agency Scientific Dispute Process Review Board (SDR Board). The board was told that under Woodcock's direction, the review team joined her in meetings with patient advocacy groups for DMD on multiple occasions from very early on in the review process.

"The [review team member] described the meetings with the patient advocacy groups, which frequently included boys with DMD and their parents, as 'intense,' 'personal,' and 'intimidating,'" Borio's memo states.

Unger thought that Woodcock's early interest and involvement in the approach to guiding the development of eteplirsen was based in part on the enthusiasm in the DMD community to an article published about the initial findings of a study that Unger and Woodcock now agree are misleading and unreliable.

in fresh produce. However, this is the first time that FDA has created a challenge to create a mobile app intended to be used by lay persons.

FDA also highlighted the progress that has been made in increasing access to Naloxone, namely that the number of lay-users has nearly tripled from 2010 to 2014, despite the fact that the drug is only available by prescription.

However, Lurie declined to answer a question from *IHP* on progress being made on an agency effort, announced Aug. 11, [to encourage a switch of Naloxone to OTC](#).

FDA's announcement is part of President Obama's Prescription Opioid and Heroin Epidemic Awareness Week being held from Sept. 19 to 24. The week of advocacy was announced Friday (Sept. 16) by presidential proclamation.

The proclamation called on Congress to approve President Obama's FY 2017 budget request for \$1.1 billion in mandatory funds over two years, intended primarily to support cooperative agreements with states to expand access to medication-assisted opioid treatment.

"My Administration is steadfast in its commitment to reduce overdose deaths and get more Americans the help they need," states the proclamation. "That is why I continue to call on the Congress to provide \$1.1 billion to expand access to treatment services for opioid use disorder ... Although Federal agencies will continue using all available tools to address opioid use disorder and overdose, the Congress must act quickly to help more individuals get the treatment they need -- because the longer we go without congressional action on this funding, the more opportunities we miss to save lives."

On a White House press call held Monday, Department of Agriculture Secretary Tom Vilsack announced USDA is providing \$4.7 million in grants "to support 18 projects in 16 states for rural communities to use communications technology to expand access to healthcare, substance use treatment, and advanced educational opportunities." Of these 18 grants, 11 deal with distance learning and seven are telemedicine grants, according to Vilsack.

Speakers also echoed calls for action on the president's budget and questioned the effectiveness of recent congressional action to address opioid abuse.

Michael Botticelli, director of the Office of National Drug Control Policy, called Congress' lack of appropriated funds for the Comprehensive Addiction and Recovery Act, which was signed into law on July 22, "reprehensive."

Don Flattery, a Virginia parent of a son who died from an opioid overdose, echoed criticisms made by Botticelli, calling passage of CARA a "hollow gesture." Flattery also made a personal plea to Congress to approve the \$1.1 billion in mandatory funds requested by the president. -- *Nicholas Florko* (nflorko@iwppnews.com)

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“Indeed, Dr. Woodcock told the SDR Board that she became involved because of the broader public interest the article generated, along with encouragement from the Commissioner of Food and Drugs at the time and her long-held belief that [Office of New Drugs] has been very conservative in evaluating drugs for accelerated approval,” Borio said.

Unger believed that Woodcock was inclined to grant approval from very early in the process, and a review team member that agreed to speak to the SDR Board anonymously said the review team was never sure whether they were discussing science, policies or politics.

“According to both Dr. Unger and the RTM, Dr. Woodcock frequently conveyed that she thought the review team was being unreasonable and encouraged [Division of Neurology Products] to find a way to approve the eteplirsen NDA. Both Dr. Unger and the RTM told the SDR Board that Dr. Woodcock seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of overarching policy (e.g., the need to be more flexible for ultra-rare diseases),” the memo states.

Borio also revealed that the anonymous team member said at least two team members were leaving FDA or had left the agency in the wake of both the decision-making process within the drug center and the pressures exerted by outside forces.

Unger, in a July memo to Office of Scientific Integrity Director G. Matthew Warren, argued the approval of the drug would send the signal that political pressure and even intimidation -- not science -- guides FDA decisions, with extremely negative consequences.

“The ramifications here are profound. The public will perceive that it was their unprecedented lobbying efforts that made the difference and earned eteplirsen its accelerated approval. For the future, this will have the effect of strongly encouraging public activism and intimidation as a substitute for data, which is one of the worse possible consequences for communities with rare diseases. This type of activism is not what was envisioned for patient-focused drug development,” he said.

Borio's memo stated that Unger expressed surprise at the extent of Woodcock's involvement in the advisory committee meeting, adding that she advocated for changing the order of the questions posed to the advisory committee in April and wanted the question on conventional approval to come before the one on accelerated approval. Woodcock allegedly requested a longer than is typical for the open public hearing portion of the meeting as well.

Woodcock told the SDR Board that she thought the review team did a poor job framing the issues during their presentation and that the questions were confusing and poorly worded. She also said that the team's failure to highlight the clinical data made the questions on conventional approval and accelerated approval difficult for the committee members to understand.

“Dr. Woodcock also criticized the review team for how it downplayed and undercut the views of the patient advocates,” the memo states.

Unger, in a July email to Woodcock, states: “This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed 'reasonably likely to predict clinical benefit.' Moreover, to my knowledge, this could be the first time

a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.”

Woodcock told the SDR Board that she was looking at the broader picture for the development of these kinds of drugs for very limited patient population in the United States.

“She opined that Sarepta in particular 'needed to be capitalized.' She noted that the sponsor's stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would 'lapse into a position of' self-treatment,” the Borio memo states.

Califf said that he was troubled by these statements, but he discussed the issue with Woodcock who maintained her decision was based on science. “Based on the record and our conversation, I am satisfied that her decision is indeed based on her scientific evaluation of the evidence,” he said.

Borio in personal comments to the commissioner noted that there are currently no specific drugs to treat DMD patients and a complete response letter may cause uncertainty on whether eteplirsen would continue to be developed.

“However, approving products based on hope, on subjective clinical judgment, or on theoretical constructs that are not anchored in data leads to irreparable damage to patients. Approval at this time could deter others from pursuing the development of truly effective treatments, both for DMD and other serious, life-threatening conditions,” said Borio.

She also argued that granting accelerated approval for the drug could encourage other developers to seek approval for serious conditions before investing the time and research necessary to establish whether a product is likely to deliver clinical benefit.

Unger's memo states that by allowing the marketing of an ineffective drug, “essentially a scientifically elegant placebo,” thousands of patients and their families would be given false hope. He argued this would be unethical and counterproductive. -- Erin Durkin (edurkin@iwpnews.com)

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FDA Goes Against Advisory Committee, Approves Duchenne Drug

September 19, 2016

FDA granted accelerated approval to a controversial Duchenne muscular dystrophy drug Monday (Sept. 19) after an emotional hearing in April where an advisory panel voted against approval of the drug causing a backlash from an audience of DMD patients, parents, doctors and advocates. Agency officials had left the door open in April to approve the drug based on testimony from patients and their parents, leading some to view the product as a test for how much flexibility FDA has to weigh patient testimony regarding medical need.

In a memo to FDA staff Monday, drug center chief Janet Woodcock said Sarepta Therapeutics submitted additional data after the advisory committee meeting.

The agency is requiring Sarepta Therapeutics to conduct a clinical trial to confirm the drug's clinical benefit. The study will assess whether Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. "If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug," FDA said in a press release.

Woodcock said in April that it would be appropriate to consider patient testimony. "I think that's fair," Woodcock said. "The standard is adequate and well-controlled trials. That's in the statute. We are instructed in flexibility on how to interpret that based on medical need."

At the time, Billy Dunn, director of the Division of Neurology Product in FDA's drug center, also signaled the agency would seriously consider the patients' testimony.

"The emotion and passion in the room during the discussion is clear, and I mentioned at the beginning of the day that we listen and we listen carefully. While I recognize there's great concern about the discussion and the results of the votes, I assure we listened very carefully to some very meaningful testimony today. We've observed the panel be highly influenced by that testimony. I assure that we will take the information we learned here today under very serious consideration as we adjourn this meeting," said Dunn.

FDA had delayed its decision on the drug in May, according to the drug maker Sarepta Therapeutics, while lawmakers questioned the agency over how it ran the advisory committee that voted against approval of the product.

GOP Sens. Ron Johnson (WI) and Dan Coats (IN) wrote to FDA that they were concerned with how the agency posed questions to the advisory committee, alleging the questions were framed in a way that made it difficult for members to vote in favor of the application being approved. -- *Erin Durkin* (edurkin@iwppnews.com)

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FDANEWS

FDA to Encourage Seamless Designs for Cancer Clinical Trials

To achieve the national cancer moonshot's goal of accelerating cancer research, the FDA is planning to encourage more seamless, adaptive clinical trial designs for oncologic drugs.

The agency is looking to speed up the regulatory pathway, possibly shifting away from traditional Phase I, II, and III development, wrote Richard Pazdur, acting director of the FDA's Oncology Center of Excellence, in [a blog post](#) on the agency's website.

"Adopting this approach could complement FDA's expedited regulatory programs such as breakthrough designation and accelerated approval to get products to patients in the most efficient manner possible,"

Pazdur wrote. He said the new emphasis on clinical trial design stems from recent advances in the scientific understanding of cancer.

Pazdur also proposed sharing a common control arm among evaluations of multiple drugs in the same indication — possibly involving products from multiple companies — and said that larger, simpler trials with easily measured endpoints would be more efficient uses of clinical resources.

In addition, he wrote that he wants to revisit patient eligibility criteria, possibly expanding the number of people who qualify for clinical trials, while maintaining patient safety.

Meanwhile, the National Cancer Institute has launched a clinical trials search portal that allows prospective patients to find appropriate trials in their area. Additionally, HHS issued a rule last week mandating that certain clinical trial results be made public, online at ClinicalTrials.gov ([DID, Sept. 16](#)).

Pazdur also highlighted upcoming public workshops with academia and industry. On Sept. 22, the FDA will host a [forum](#) on assessing cardiotoxicity in oncology trials; and in October, the agency will hold a joint [workshop](#) with the American Association for Cancer Research on immunotherapy drug development. — Conor Hale ([Return to Top](#))

FDA Approves First Duchenne Treatment, Sarepta's Exondys 51

The FDA granted accelerated approval to Sarepta's Exondys 51—the first drug indicated for the treatment of Duchenne muscular dystrophy—despite reservation from FDA staff and an advisory panel.

The approval is based on a surrogate endpoint of increased dystrophin levels in the skeletal muscle of patients treated with the drug. In its review of the clinical evidence, the FDA found that Exondys 51 promoted dystrophin production in some patients, which is “reasonably likely to predict clinical benefit.”

Given the available evidence, however, a clinical benefit for the drug—such as improved motor function—has not been established, the FDA said. To confirm whether the drug provides a clinical benefit, Sarepta will have to submit additional data from a confirmatory study that will evaluate the drug's effect on motor function.

An accelerated approval is provisional and requires a confirmatory study. If the study indicates that the drug does not provide a clinical benefit, the FDA can rescind its decision.

The FDA's decision comes after the drug faced approval delays and unfavorable reviews from FDA staff and an advisory committee, who both questioned the effectiveness of the drug and requested more clinical evidence ([DID, April 26](#)).

In May, the FDA extended its review of the drug application indefinitely, following pleas from two Republican senators that the FDA “exercise the broadest flexibility” in its review of the drug ([DID, May 26](#)). Another delay came in June, when the FDA asked for data on dystrophin levels from 13 patient biopsies ([DID, June 8](#)).

can connect opioid users experiencing an overdose with nearby carriers of the prescription drug naloxone – the antidote for an opioid overdose. The contest builds on work announced in the agency’s Opioids Action Plan and the U.S. Department of Health and Human Services’ [Opioid Initiative](#) to take concrete steps toward reducing the impact of opioid misuse, dependence and overdose on American families and communities by making naloxone more accessible.

“The goal of this competition is to develop a low-cost, scalable, crowd-sourced mobile application that addresses this issue of accessibility,” FDA associate commissioner **Peter Lurie** is quoted in a [release](#) as saying. “Mobile phone applications have been developed to educate laypersons on how to recognize an overdose and administer naloxone, and to connect bystanders with individuals in need of other medical services, such as CPR. To date, however, no application is available to connect carriers of naloxone with nearby opioid overdose victims.”

Teams and individuals wishing to participate in the competition will have until 10/7 to register. On 10/19-20, FDA will host a two-day code-a-thon for registered entrants to develop their concepts and initial prototypes. All coding will be made open-source and publicly accessible, and collaboration will be encouraged, the agency says. A panel of judges will eventually evaluate submissions and the highest-scoring entrant will receive an award of \$40,000.

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Woodcock Upheld by Califf in Duchenne Drug Appeal

09/19/2016

After surviving an internal staff challenge adjudicated in her favor by FDA commissioner **Robert Califf**, CDER director **Janet Woodcock** made final her decision to approve Sarepta Therapeutics’ Duchenne muscular dystrophy (DMD) drug Exondys 51 (eteplirsen) under the agency’s accelerated approval process 9/19. It’s unprecedented for such a high-level Center decision to be internally appealed and decided by a politically appointed commissioner.

The internal challenge was brought before the FDA Scientific Dispute Process Review Board chair and acting chief scientist **Luciana Borio**, who sided with appellant Office of Drug Evaluation 1 director **Ellis Unger**. Unger disagreed with Woodcock’s decision that the NDA’s data met the standard for accelerated approval. The board subsequently asked Califf to review the scientific merits of the case.

In a [summary review document](#), Califf notes that it is “highly unusual” for a Center director’s application decisions to be appealed to the commissioner’s office. After reading Unger’s appeal, Woodcock’s final decision, and the appeal board’s recommendation, Califf said he performed a thorough review of the clinical science and decided to defer to Woodcock’s “judgment and authority.” A key point in the Woodcock and Unger dispute is whether the amount of dystrophin protein produced by eteplirsen is sufficient to be “reasonably likely” to predict clinical benefit, according to the document. Califf concluded that Unger and Woodcock each “exercised reasonable scientific judgment in reaching differing conclusions on whether the effect on dystrophin production seen in the studies... reasonably predicts clinical benefit... There is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence, including the detailed views of Dr. Unger and the review team; yet she came to a different conclusion.”

Califf also noted that Woodcock in her approval decision is “clearly employing and interpreting the full range of appropriate information, comprising a ‘totality of evidence’ approach in determining that the clinical trials demonstrated an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Because of the uncertainties in this situation with a surrogate that has not been validated, it is clear that Dr. Woodcock’s decision also utilized the flexibility afforded under the relevant statutory provisions, including consideration of the life-threatening nature of the disease and the lack of alternative treatments.”

The appeal board, based on Unger’s complaint, also raised concern about Woodcock’s “level of involvement in the NDA review.” According to the summary document, the board said her “extensive, early involvement in the review process” ... appears to have upended the typical review and decision-making process.” It further cautioned that “care should be taken to avoid the appearance of interfering with the integrity of scientific reviews at the lower levels of a Center.” The board concluded that “Dr. Woodcock herself was the one who conducted that review and resolved the conflict in her own favor.” Califf did not falter in his support of Woodcock. He endorsed her “hands on” approach during her entire career at FDA. “She

Earlier this year, Teva and its development partner Active Biotech confirmed that the highest dose arms in two MS trials and one trial in Huntington's Disease were discontinued at the recommendation of a data monitoring committees. Subsequently, Teva submitted an amendment to the SPA to account for this change. However, under FDA's regulatory process, the SPA was rescinded as all changes must be agreed to prior to implementation of the change. "This requirement could not be fulfilled in the current case, since the DMC recommendation triggered an immediate action to withdraw the 1.2 mg dose for the treatment of RRMS in the interest of patient safety" Active Biotech says.

The CONCERTO trial continues with one dose (0.6mg/day) vs. placebo on the original schedule, and Teva plans to use this pivotal study to support filing for marketing approval for laquinimod in the U.S. and EU. Teva has completed two Phase 3 trials with the 0.6mg daily dose in MS and continues long-term extension studies at this dose.

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KemPharm Seeks Dispute Resolution of Pain Drug Denial

09/19/2016

KemPharm has decided to file a formal dispute resolution request over a June FDA complete response letter on an NDA label claim of abuse deterrence for Apadaz (benzhydrocodone and acetaminophen), an investigational abuse-deterrent product candidate for the short-term management of acute pain. The company expects it could take up to 12 months to complete all parts of the dispute resolution request.

The complete response letter was in response to an NDA amendment that the company filed earlier this year ([see story](#)) that sought to strengthen the drug's labeling related to its abuse-deterrent properties. The amendment presumably addressed concerns expressed by members of the FDA Anesthetic and Analgesic Drug Products Advisory Committee when they voted in May 16-4 to recommend approval for the drug. During the committee meeting, FDA asked the advisors to vote on whether data submitted by the company support a labeling claim that Apadaz is an abuse-deterrent product. On an 18-2 vote, committee members said Apadaz should not be labeled as abuse-deterrent. They acknowledged that the available data suggest the potential for a marginal benefit in preventing abuse via the intranasal route and encouraged the company to continue studying the drug's abuse-deterrent properties to acquire data that in the future could reach the standards needed for a labeling claim. KemPharm says it decided to seek dispute resolution in order to address and resolve certain disagreements with CDER's interpretation of the "Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling" and the data provided within the Apadaz NDA related to its abuse-deterrence properties. The issues for the dispute resolution are "solely related to the abuse-deterrence properties of Apadaz and what constitutes abuse-deterrence in the context of a label claim," it says. Minutes from an end-of-review meeting also confirmed that the review division is focused primarily on "Category 3 data in determining whether an IR opioid product is eligible for any abuse-deterrent label claims," the company adds. "Though we believe the data submitted in the Apadaz NDA supported important elements of the Category 3 criteria, the data did not meet the endpoints of greatest relevance to the division," it says. KemPharm says it developed the drug using its proprietary Ligand-Activated Technology, which creates a new prodrug by chemically attaching one or more molecules, or ligands, to an FDA-approved parent drug. "Once administered, human metabolic processes, such as those in the gastrointestinal tract, separate the ligand from the prodrug and release the parent drug, which can then provide its therapeutic effect," it says.

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FDA Contest for Developing Naloxone Mobile App

09/19/2016

FDA has announced a Naloxone App Competition, a public contest focused on developing a mobile phone application that

is well-known for interacting with staff at all levels and expressing her opinions," he said in the summary. "This development program may represent a point of particular focus for Dr. Woodcock with the result that her involvement was more intensive than usual and correspondingly had an effect upon the review team, but such a focus does fit within a longstanding management approach."

Califf concluded that Woodcock did not deviate from her responsibilities, nor did she succumb to pressures from the patient community, the public or others. "Further, I do not find the general pattern of discourse and involvement to be atypical for Dr. Woodcock's management of the Center, nor do I find that her conduct was in conflict with the job requirements for the Center directors at the FDA."

As for the accelerated approval, this is the first drug approved to treat patients with Duchenne. The drug is indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13% of the DMD population. "Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval," Woodcock said in a [news release](#).

The approval comes 10 days after the departure of CDER Division of Neurology Products clinical team leader **Ronald Farkas**, who joined clinical research organization Parexel 9/9. Farkas was one of the harshest critics of Sarepta's NDA during an April advisory committee meeting that voted 7 to 6 ([see story](#)) that the company did not provide substantial evidence from adequate and well controlled studies that the drug induces production of dystrophin to a level that is reasonably likely to predict clinical benefit in patients.

In June, the company agreed to an agency request that it provide dystrophin data, as measured by western blot, from biopsies already obtained from an ongoing confirmatory study of eteplirsen (PROMOVI). The company said at the time that it planned to submit data from 13 patient biopsy samples, at baseline and week 48, to the agency within a few weeks. In a [statement](#), Sarepta said it expected this would "facilitate a prompt decision on the NDA by the agency."

Eteplirsen is designed to address the underlying cause of Duchenne's by restoring the dystrophin messenger RNA (mRNA) reading frame, and enabling the production of a shorter, functional form of the dystrophin protein, according to the company.

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FDA approves Sarepta's eteplirsen, first DMD drug

[Sarepta Therapeutics Inc.](#) (NASDAQ:SRPT) soared \$20.79 (74%) to \$48.94 on Monday after FDA granted accelerated approval to the company's Exondys 51 eteplirsen ([AVI-4658](#)) to treat Duchenne muscular dystrophy (DMD) amendable to exon 51 skipping.

Sarepta will price the drug at an expected net annual cost of \$300,000 for a 25 kg boy, taking into account changes in weight-based dosing over time and expected compliance rates. A 2 mL vial of the drug will cost \$1,600, and a 10 mL vial will cost \$8,000. The approved dose is 30 mg/kg once weekly.

FDA based its approval on the surrogate endpoint of [dystrophin](#) increase in skeletal muscle seen in some DMD patients treated with Exondys 51. In April, FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted 7-6 that Sarepta had not shown substantial evidence that eteplirsen induces dystrophin expression "to a level that is reasonably likely to predict clinical benefit." The panel voted 7-3, with three abstentions, that data from a Phase IIb placebo-controlled trial and its open-label extension did not provide "substantial evidence" that eteplirsen is effective ([see BioCentury, May 2](#)).

In a summary review [document](#) describing the scientific dispute among FDA staff regarding Exondys 51,

Commissioner Robert Califf said he deferred to the judgment of Janet Woodcock, director of FDA's Center for Drug Evaluation and Research, in her decision to grant accelerated approval to the drug. Califf weighed in on the decision after FDA's Ellis Unger, director of FDA's Office of Drug Evaluation I, appealed Woodcock's decision to the commissioner's office.

Califf wrote that Unger and Woodcock "have each exercised reasonable scientific judgment in reaching differing conclusions" about Exondys 51's effects, and that overruling Woodcock would be appropriate only if her decision "could not be supported by the available data and information."

In its approval [letter](#), FDA said Sarepta must conduct a two-year confirmatory study of Exondys 51 evaluating North Star Ambulatory Assessment (NSAA) as the primary endpoint. The study is to compare Exondys 51's approved dosage with a dosage providing "significantly higher exposure, e.g. 30 mg/kg daily," the letter said. The deadline for a draft protocol submission is next month.

FDA extended its review of Exondys 51 well past its May 26 PDUFA date. In June, the agency requested additional data from PROMOVI, an ongoing Phase III trial of Exondys 51 in which six-minute walk distance is the primary endpoint ([see BioCentury Extra, June 7](#)).

Sarepta expects PROMOVI to be a confirmatory study for European approval of Exondys 51. Sarepta said Monday it plans to submit an MAA by year end.

The company expects it will take DMD patients 30-90 days to receive reimbursement for Exondys 51. The company declined to provide guidance for sales of the drug, a phosphorodiamidate morpholino oligomer (PMO) that induces skipping of exon 51 in dystrophin mRNA.

Sarepta received a rare pediatric disease Priority Review voucher upon Exondys 51's approval. The company intends to sell the voucher for a non-dilutive source of funding for its R&D programs.

Two companies with clinical DMD programs posted gains Monday. [PTC Therapeutics Inc.](#) (NASDAQ:PTCT) added \$1.88 (21%) to \$10.99, and [Santhera Pharmaceuticals Holding AG](#) (SIX:SANN) rose CHF3.30 to CHF53.80.

In February, FDA issued a refuse to file letter for PTC's [Translarna](#) ataluren. In July, the agency told Santhera it would not support its planned submission of [Raxone](#) idebenone seeking accelerated approval without Phase III data. ([Return to Top](#))

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Amgen pushes for access to biosimilar information

In an appellate brief filed in federal court, [Amgen Inc.](#) (NASDAQ:AMGN) said a U.S. District Court's failure to force the [Hospira Inc.](#) unit of [Pfizer Inc.](#) (NYSE:PFE) to supply manufacturing information for a biosimilar "threatens to undermine the entire balance" of the Biologics Price Competition and Innovation Act (BPCIA). Amgen filed the brief in the U.S. Court of Appeals for the Federal Circuit (CAFC), where it is challenging a lower court's ruling regarding [Retacrit](#), Hospira's proposed biosimilar of [Epogen](#) epoetin alfa from Amgen and [Procrit](#) epoetin alfa from the Janssen Biotech unit of [Johnson & Johnson](#) (NYSE:JNJ).

In the brief, Amgen argued that a prior CAFC ruling obligates biosimilar developers to provide reference drug sponsors with access to manufacturing information via the discovery process if a reference product sponsor files a lawsuit. Denying access, Amgen argued, would allow biosimilar sponsors to "unilaterally control" which patents may be challenged through selective disclosures. CAFC ruled last year that biosimilar developers are not required to provide BLAs and manufacturing information ([see BioCentury Extra, July 21, 2015](#)).

Amgen sued Hospira last year to delay the approval and launch of Retacrit, claiming that Hospira infringed two Epogen patents and violated BPCIA by failing to provide manufacturing information. The U.S. District Court of the District of Delaware denied Amgen's motion to force Hospira to produce the information, saying it was not relevant to the patents contested in the lawsuit ([see BioCentury Extra, Sept. 23, 2015](#)).

Philips, Howard

From: Bastings, Eric
Sent: Tuesday, September 20, 2016 5:52 PM
To: Califf, Robert; Unger, Ellis; Dunn, Billy; Temple, Robert; Jenkins, John K
Subject: Forbes' analysis of the eteplirsen action

A lot of what we worried about is discussed in this article.

<http://www.forbes.com/sites/matthewherper/2016/09/20/approving-a-muscular-dystrophy-drug-ignites-civil-war-at-the-fda/#7c49ac9e353d>

Eric

Philips, Howard

From: Woodcock, Janet
Sent: Tuesday, September 20, 2016 10:13 AM
To: Nelson, Robert 'Skip'
Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)
Subject: RE: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

I agree. My understanding is that the division has had discussions with the sponsor about this issue, and they are aware that the use of a portacath for placebo in the US is not considered acceptable. My understanding is that [REDACTED] (b) (4)

[REDACTED] (b) (4)

The “confirmatory” study for exon 51 is a dose-comparison and as you say, does not raise the ethical issues, but does need a final agreement on the protocol. jw

From: Nelson, Robert 'Skip'
Sent: Monday, September 19, 2016 8:52 AM
To: Woodcock, Janet
Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)
Subject: RE: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

Janet,

In looking at the latest records in DARRTS for NDA 206488, it does appear that the PMC for exon 45 and 53 is described [REDACTED] (b) (4) and notes that the use of a placebo control may not be feasible (and, if so, recommends the use of an untreated concurrent control). However, the protocol submitted to INDs 118086 (exon 45) and 119982 (exon 53) is a double-blinded placebo-controlled [REDACTED] (b) (4)

(<https://www.clinicaltrials.gov/ct2/show/NCT02500381>). As currently written, placebo will be administered as an IV infusion once a week for up to 96 weeks. I also see that the PMR for skipping exon 51 suggests a dose-ranging study. A [REDACTED] (b) (4) study in which all patients would receive active product [REDACTED] (b) (4) does not raise the same ethical concerns as the infusion of a placebo for almost two years. If FDA believes that a [REDACTED] (b) (4) study would be informative (which it would be if a difference was noted), then [REDACTED] (b) (4)

[REDACTED] An IR to clarify the Sponsor’s intentions would be useful.

Again, happy to discuss further.

Skip Nelson
Deputy Director and Senior Pediatric Ethicist
Office of Pediatric Therapeutics, FDA
Office: WO32-5152; Tele: (301) 796-8665; E-mail: Robert.Nelson@fda.hhs.gov

From: Woodcock, Janet
Sent: Friday, September 16, 2016 6:37 PM
To: Nelson, Robert 'Skip'
Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)
Subject: RE: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

They are not using the (b) (4) It is a postmarket commitment per the approval letter, but much of the protocol is to be developed. My understanding is that they are (b) (4). jw

From: Nelson, Robert 'Skip'
Sent: Friday, September 16, 2016 10:57 AM
To: Woodcock, Janet
Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)
Subject: RE: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

I will double-check, but my understanding is that the trial is a double-blinded (b) (4) using a placebo infusion (thus raising the issue about central line access for a two year trial). An open label trial with a concurrent no treatment control would not raise the same ethical concerns (but may be uninformative given the use of the (b) (4)).

Skip Nelson
Deputy Director and Senior Pediatric Ethicist
Office of Pediatric Therapeutics, FDA
Office: WO32-5152; Tele: (301) 796-8665; E-mail: Robert.Nelson@fda.hhs.gov

From: Woodcock, Janet
Sent: Friday, September 16, 2016 10:41 AM
To: Nelson, Robert 'Skip'
Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)
Subject: RE: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

My understanding of the current protocol is that is a randomized (b) (4) controlled study in which the control arm is not treated, at least in the US. jw

From: Nelson, Robert 'Skip'
Sent: Friday, September 16, 2016 10:22 AM
To: Woodcock, Janet
Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)
Subject: FW: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)
Importance: High

Dear Janet,

DNP suggested I forward my concerns (detailed below) to you as you are leading the review of this application. My recommendation is to send an IR to the Sponsor asking about the IRB review of the planned ESSENCE trial. I appreciate the sensitivity of this recommendation given the issues surrounding the review of this product. Please let me know if I can answer any questions you may have about this recommendation. Thank you for your attention to this request.

Skip Nelson
Deputy Director and Senior Pediatric Ethicist
Office of Pediatric Therapeutics, FDA
Office: WO32-5152; Tele: (301) 796-8665; E-mail: Robert.Nelson@fda.hhs.gov

From: Nelson, Robert 'Skip'
Sent: Thursday, August 18, 2016 3:20 PM
To: Farkas, Ronald; Bastings, Eric

Cc: Dunn, Billy; Choy, Fannie (Yuet)

Subject: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

Importance: High

Dear Ron and Eric,

I am writing to express a concern about the ESSENCE trial based on our previous communication and conversations I have had with parents of boys with DMD. Although I appreciate that any communication with the sponsor, Sarepta, may be delayed until after a decision is made about the pending NDA application; however, I believe an Information Request should be sent ASAP to the sponsor asking why the ESSENCE protocol has not been referred by the (b) (4) IRB to FDA for review under 21 CFR 50.54. Let me explain my reasoning.

(1) On July 5, 2016, the sponsor sent the following communication: (b) (4)

(b) (4)

From this communication, I conclude that the (b) (4) IRB thought that the use of central venous catheters in the US may be necessary, and could be justified on scientific and ethical grounds.

- (2) As you know, the use of implantable central venous catheters for the administration of placebo is not in compliance with 21 CFR 50.53 (as it presents more than a minor increase over minimal risk without the prospect of any direct benefit). As such, absent federal panel review, a local IRB in the US is unable to approve such a procedure. In addition, absent federal panel review, FDA considers such a procedure an “unreasonable risk.” Our regulations, however, have a process under 21 CFR 50.54 by which these procedures can be reviewed by a federal panel and approved, if appropriate, by the FDA Commissioner (in essence, determining that the risk is “reasonable” given the context). An IRB may refer a protocol for federal panel review if “the IRB finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.” I can only assume, based on the Sponsor’s characterization of the (b) (4) IRB assessment, that this criterion for referral has been met. The US is the only country I know of that has this regulatory framework limiting the authority of local IRBs with respect to approving these procedures, so I am not surprised by the different decisions being made in the EU.
- (3) Parents of boys with DMD appreciate the likelihood that many if not most of the DMD boys will require central venous access to be able to tolerate weekly infusions for the length of this study (nearly two years). Questions have been raised (to me in conversation) as to whether the decision not to refer the study for federal panel review under 21 CFR 50.54 is a back-handed way to assure that the clinical trial is not feasible in the US. At the very least, it would place these DMD boys at risk without the potential compensating benefit of a sufficiently long course of the investigational product to be able to see a meaningful clinical benefit. I consider this a serious ethical issue that FDA should not even implicitly endorse by failing to send an IR.

Given these concerns, I strongly recommend that FDA send an IR to the sponsor, Sarepta, asking why the (b) (4) IRB has not referred the protocol for review under 21 CFR 50.54 given their assessment of the protocol. I will not speculate on what recommendation(s) might emerge from such a review, which is conducted by the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, as I am the person responsible for coordinating the AC meeting. However, I consider it a serious ethical breach of the responsibility of the (b) (4) IRB (and perhaps other reviewing IRBs) to make a finding that merits referral under 21 CFR 50.54 and yet not make that referral.

Let me know if I can answer any questions.

Skip

Robert "Skip" Nelson, MD PhD

Deputy Director and Senior Pediatric Ethicist, Office of Pediatric Therapeutics, FDA

Tele: (301) 796-8665; Mobile: (240) 328-7146; Fax: (301) 847-8619

E-mail: Robert.Nelson@fda.hhs.gov

Website: <http://www.fda.gov/pediatrics>

Mailing Address:

WO/Building 32, Room 5152

10903 New Hampshire Avenue, Silver Spring, MD 20993-0002

This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

Temple, Robert

From: Unger, Ellis
Sent: Wednesday, September 21, 2016 9:33 AM
To: Bastings, Eric; Jenkins, John K; Temple, Robert
Subject: Re: FDA Webview

[Pink sheet today has more coverage.](#)

[Sent from my BlackBerry.](#)

From: Bastings, Eric
Sent: Wednesday, September 21, 2016 8:54 AM
To: Jenkins, John K; Unger, Ellis; Temple, Robert
Subject: FDA Webview

Woodcock Wanted Drug Approved Before Review Completed: FDA Records

09/20/2016

CDER director **Janet Woodcock** had made up her mind to approve ([see earlier story](#)) Sarepta's controversial Duchenne drug Exondys 51 (eteplirsen) well before the Center review team had completed its review — in fact, she had written an approval memo before reviewers even submitted their review memo and summary. This and other disturbing actions are detailed in a [review summary](#) that illustrates her unprecedented involvement and interference in the NDA review, actions that senior agency officials suggested was driven by her succumbing to Congressional, patient, company and other outside pressures to get the drug approved. Pressure from Woodcock and other outsiders was so bad that at least two members of the review team were leaving FDA or had left the agency, the summary indicates.

When CDER Office of Drug Evaluation 1 director **Ellis Unger** questioned her involvement in the submission and appealed her decision to override his review team's opinion that the NDA data did not meet the standard for accelerated approval, Woodcock became defensive and critical of the review team's expertise. During the appeal, Woodcock told the internal Scientific Dispute Process Review (SDR) Board that the review team did a poor job framing the issues during their advisory committee presentations and that the panel questions were confusing and poorly worded. During her interview with the SDR Board, Woodcock opined that the review team "did not put its best foot forward." She criticized the review team's presentation of the IHC data, contending that its failure to highlight the clinical data made the questions on conventional approval and accelerated approval difficult for the committee members to understand.

Unger noted that, to his knowledge, this could be the first time a Center director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated. On the suggestion of Office of New Drugs director **John Jenkins**, Unger urged that FDA commissioner **Robert Califf** evaluate the appeal too. Califf adjudicated the internal staff challenge in Woodcock's favor ([see story](#)).

In his appeal, Unger said allowing eteplirsen's accelerated approval would "lower the evidentiary standard for effectiveness to an unprecedented nadir. The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change of 0.3% — a mere 3 parts out of a thousand — is considered adequate to support accelerated approval here, then the question arises as to whether there would be any statistically significant change that would be too small to be considered 'reasonably likely' to support accelerated approval... If we were to adopt the concept that, for rare diseases, accelerated approval could be supported by any statistically significant change in an appropriate surrogate, or a response in a single patient, we would enable accelerated approval of a myriad of drugs for rare diseases. No doubt there are some who would applaud this as an advance. But a standard this low would undercut FDA's ability to ensure that drugs that are approved are

effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.

"With accelerated approval of this NDA," Unger continued, "there would be highly detrimental effects on drug development. Traditional drug development for rare diseases might be replaced by a system where small, baseline-controlled, proof-of-concept studies designed to show any change in a surrogate marker would provide a basis for accelerated approval, assuming that the pathogenesis of the disease was well understood and that the surrogate was directly on the causal path. There would be little reason to pursue adequately controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of failure would provide a disincentive to conduct such trials. For example, a gene therapy designed to produce a missing clotting factor could receive accelerated approval on the basis of a tiny yet inconsequential change in levels of the factor, or a more robust response in a single patient. In short, the precedent set here could lead to the approval of drugs for rare diseases without substantial evidence of effectiveness."

A review team member (RTM) told the SDR Board that, in his or her view, the review team was never sure whether they were discussing science, policies, or politics. "According to both Dr. Unger and the RTM, Dr. Woodcock frequently conveyed that she thought the review team was being unreasonable and encouraged [the review division] to find a way to approve the eteplirsen NDA," the summary says. "Both Dr. Unger and the RTM told the SDR Board that Dr. Woodcock seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of overarching policy (e.g., the need to be more flexible for ultra-rare diseases).

"Based on my years of experience in Office of Drug Evaluation 1, the Center director's direct involvement with this drug, compared to other development programs, has been unprecedented," Unger told the board. He said he found it "unfortunate that the Center director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division's final review memorandum or my review memorandum. Prior to reading our reviews, Dr. Woodcock stated that she had already '...reached a different conclusion...' than the review team

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Temple, Robert

From: Unger, Ellis
Sent: Thursday, September 22, 2016 11:32 AM
To: Choy, Fannie (Yuet); Dunn, Billy; Bastings, Eric; Farkas, Ronald; Breder, Christopher D; Freed, Lois M; Hawver, David; Heimann, Martha R; Wilson, Wendy; Woody, Dahlia; Men, Angela; Wu, Ta-Chen; Jin, Kun; Ling, Xiang; Ware, Jacqueline H; Rao, Ashutosh; Bhattaram, Atul; Rogers, Hobart; Grimstein, Christian; Zerislassie, Ermias; Krudys, Kevin; Mehta, Mehul U; Hung, Hsien Ming J; Rao, Ashutosh; El Hage, Antoine N; Alfaro, Cara; Khin, Ni Aye; Peters, Tracy
Cc: Jenkins, John K; Locicero, Colleen L; Kelley, Laurie; Temple, Robert; Brown, Paul C; Lowy, Naomi; CDER-OND-120-CSO; Bastings, Eric; Bergmann, Kenneth; Boehm, Gerard A; Breder, Christopher D; Buracchio, Teresa; Dinsmore, Steven; Dunn, Billy; Fitter, Heather; Getzoff, Natalie; Goldstein, Susanne R.; Green, Jody; Hershkowitz, Norman; Hosford, David; Hughes, Alice; Jawidzik, Laura; Kapcala, Leonard P; Kasim, Suhail; Kozauer, Nicholas; Mani, Ranjit B; Marler, John; Mentari, Evelyn; Paine, Rainer; Peters, Tracy; Podskalny, Gerald; Raman, Ramesh; Rodichok, Lawrence; Sheridan, Philip; Tandon, Veneeta; Villalba, Lourdes; Yasuda, Sally; CDER-OND-120-PHARMTOX; Kindle, Gretchen; Lewis, Ashley; Wade, Donna
Subject: Review of Eteplirsen NDA 206488

All,

As the dust settles following the eteplirsen approval, I want to thank each of you for your extraordinary perseverance and dedication to your careful review work. Your reviews were based on rational science, despite considerable pressure to succumb to emotional influences. Many of you were pummeled with derisive emails from the public, and some of you felt physically threatened. The personal protection provided for the review team to travel to the College Park advisory committee meeting is testament to the huge public pressure and raw emotions in play here.

I presume that by now you have read the negative comments conveyed in Dr. Borio's memo with respect to the performance of the review team, and I know that some of you find those comments demoralizing. In my opinion, however, your work was superb, despite a process that, through no fault of your own, was highly dysfunctional.

I feel certain that this review process will be a one-off; it will not be repeated. We have raised a number of important points in our appeal of the action, and they have not been lost on the public. In particular, the publication of preliminary results from independent investigators that cannot be substantiated, the inappropriate lobbying from the public, and problems with the review process are now receiving the public attention they deserve. I believe that public scrutiny will continue, and these conversations and commentaries will result in positive changes.

Please know that, despite the outcome, you fought the good fight for science here, and we all must continue to stand ready to protect the public health. You remain the main line of defense for the US public, some 300 million people, against drugs that don't work and drugs that are unsafe. There is no one else to take on this work, and no one is trained better than you to do it. I am extraordinarily proud of all of you for doing all that you do.

Ellis

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation-I
Office of New Drugs

Philips, Howard

From: Unger, Ellis
Sent: Thursday, September 22, 2016 1:33 PM
To: Wade, Donna
Cc: Temple, Robert; Locicero, Colleen L
Subject: FW: Review of Eteplirsen NDA 206488

Is this something I can do?

From: Unger, Ellis
Sent: Thursday, September 22, 2016 1:21 PM
To: Bhattaram, Atul
Cc: Bastings, Eric
Subject: Re: Review of Eteplirsen NDA 206488

Excellent idea. Let me see if I can make it happen.

Sent from my BlackBerry.

From: Bhattaram, Atul
Sent: Thursday, September 22, 2016 1:11 PM
To: Unger, Ellis
Cc: Bastings, Eric
Subject: RE: Review of Eteplirsen NDA 206488

Hi Ellis

Thank you for your email. Very helpful. I read the document again closely to understand how the review team might feel. Given that I don't know how everyone feels, it would be a good idea to write a time-off award for the eteplirsen review team. It could be for 16 h (Just making up a number). Lower will not sound right. Also when the FDA awards nominations are announced, we should write a team award for this submission.

I am not sure who can help you with these in OND, but I can certainly help you if needed. I have written FDA awards nominations in the past for my colleagues. I am not sure about the time off award process in OND.

Just a suggestion. Let me know if you need help.

Atul

Philips, Howard

From: Unger, Ellis
Sent: Wednesday, September 28, 2016 10:54 AM
To: Breder, Christopher D; Bastings, Eric; Dunn, Billy
Cc: Temple, Robert; Locicero, Colleen L; Lowy, Naomi
Subject: FW: Thanks

See below.

From: Borio, Luciana
Sent: Wednesday, September 28, 2016 10:44 AM
To: Unger, Ellis; Jenkins, John K
Subject: Fw: Thanks

Dear Ellis, John - please see below message.

Sent from my BlackBerry 10 smartphone.

From: John Porter <john.porter@myotonic.org>
Sent: Wednesday, September 28, 2016 7:08 AM
To: Borio, Luciana
Subject: Thanks

Luciana,

Thanks for giving the talk at HRA yesterday and taking the time to speak with me afterwards. As I said yesterday, I've followed the Duchenne candidate therapeutic regulatory process closely during my time at NINDS/NIH, then at PPMD, and now with MDF.

When I was a program director at NINDS (covering muscular dystrophy and SMA), I worked on the rigor/reproducibility effort with Shai Silberberg and very much believe in establishment of adequate scientific rationale to launch clinical development programs and to obtain marketing approval. You may be interested that Richard Harris, an NPR science reporter, took a year sabbatical to write a book on rigor and reproducibility in preclinical science--it should be published early next year. I'm encouraging him to take a hard look at rigor in clinical trials.

I've also given 'lessons learned' talks on the experiences with the three dystrophin drugs at the CureSMA conference this year and at the Drug Development Roundtable at our MDF Conference two weeks ago, and [REDACTED] (b) (5). One lesson is to strive to avoid the hype that produces therapeutic misconception--which clearly went off the rails here. Our organization has developed an industry engagement policy to try to have myotonic dystrophy travel a higher road.

I wanted to reiterate my comments from yesterday that, in the face of everything that staff at DNP has encountered with the BioMarin, PTC, and Sarepta programs, and your own efforts with the SDR Board for Sarepta, there are many of us "out here" that appreciate all of those efforts. While virtually every neuromuscular disease is in dire need of safe and effective therapeutics, drugs that fail to meet both of those standards don't help anyone. Rigor is the buzz word. Thanks.

John

John D. Porter, Ph.D. | Chief Science Officer | Myotonic Dystrophy Foundation
1004A O'Reilly Avenue, San Francisco, California 94129
w/c: [REDACTED] ^{(b) (6)} | john.porter@myotonic.org | www.myotonic.org

Philips, Howard

From: Temple, Robert
Sent: Wednesday, September 28, 2016 5:26 PM
To: Ware, Jacqueline H; Dunn, Billy
Cc: Blount, Aprile
Subject: RE: HOLD for possible call with (b) (4)

Looks like I am free that half hour

From: Ware, Jacqueline H
Sent: Wednesday, September 28, 2016 3:16 PM
To: Dunn, Billy; Temple, Robert
Subject: RE: HOLD for possible call with (b) (4)

Hi Billy and Bob,

Please let me know if you are available for this call with (b) (4) next week. All other invites have accepted. I don't want to schedule with (b) (4) until I know that everyone is available.

Thanks,
Jackie

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

From: Ware, Jacqueline H
Sent: Tuesday, September 27, 2016 7:36 PM
To: Ware, Jacqueline H; Locicero, Colleen L; Temple, Robert; Dunn, Billy; Bastings, Eric; Kozauer, Nicholas
Cc: Unger, Ellis; CDER 120 Calendar
Subject: HOLD for possible call with (b) (4)
When: Tuesday, October 04, 2016 12:00 PM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: TBD

(b) (4)

[Scheduled by J. Ware on 9/27/16; 301.796.1160]

Philips, Howard

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 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.

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On efficacy, what puzzled me is that the treatment of dystrophin production as a valid surrogate seems less credible when viewed in context the Biomarlin drug, and that did not seem to be incorporated into the review decision. Biomarlin conducted a pretty substantial, rigorous, well-controlled trial so they did some pretty substantial work on this. In essence, the Biomarlin 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.

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Outrage of the Month: FDA Senior Leader Ignores Science, A...

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THE BLOG

Outrage of the Month: FDA Senior Leader Ignores Science, Approves Ineffective Drug for a Rare Disease

10/03/2016 01:10 pm ET

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Michael Carome, M.D.

Director of Public Citizen's Health Research Group.

[Read more in Public Citizen's October Health Letter](#)

On Sept. 19, 2016, the Food and Drug Administration (FDA) [approved](#) eteplirsen (brand name Exondys 51) — the first drug approved for treating Duchenne muscular dystrophy (DMD) — despite a disturbing lack of evidence that the drug is actually effective. The approval decision ultimately was made by Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research (CDER) — the center that reviews and approves drugs — over the strong [objections](#) of scientific experts at the agency who had reviewed the new drug application for eteplirsen.

In 1962, Congress dramatically strengthened the process for approval of new drugs by passing a [law](#) requiring not only proof of safety but also "substantial evidence" of effectiveness for a drug's intended use. The law stipulates that such evidence must come from "adequate and well-controlled" studies. This approval standard revolutionized prescription drug regulation in the U.S. and has remained unchanged for more than a half-century.

[Sarepta Therapeutics](#), the maker of eteplirsen, submitted data to the FDA from three very small clinical trials involving a total of 25 subjects with DMD. The drug is intended to boost the production of a key muscle protein called dystrophin, which is almost completely absent from the muscles of DMD patients.

FDA staff, including Woodcock, [agreed](#) that there were "[m]ajor flaws in both the design and conduct" of the three trials. Moreover, the trials found no meaningful improvement in subjects' physical performance and only minuscule increases in muscle dystrophin levels. [FDA scientists](#) also identified serious problems with the integrity of key tests used to measure changes in dystrophin levels in patients enrolled in the clinical trials.

As a result, a team of FDA scientific experts, including physicians and pharmacologists, [concluded](#) that the trials failed to provide substantial evidence from adequate and well controlled trials that eteplirsen is effective or that the

not she?

changes seen in muscle dystrophin levels were likely to predict effectiveness. They therefore recommended against approval. *reg andly*

Dr. Ellis Unger, the senior FDA official who supervised the team of scientists reviewing the data on eteplirsen, agreed with the team's assessment, as did his supervisor, Dr. John Jenkins, director of the Office of New Drugs; the agency's acting chief scientist, Dr. Luciana Borio; and the majority of the members of an FDA advisory committee that evaluated the clinical trial data on April 25, 2016.

Despite this overwhelming opposition to the approval of eteplirsen, Woodcock overruled the FDA's scientific experts and decided to approve the drug.

In a highly unusual move, Unger formally appealed Woodcock's decision to FDA Commissioner Robert Califf. But in a display of cowardice, Califf rejected the appeal and deferred to Woodcock, allowing the approval to go forward.

In his written appeal to Califf, Unger made a number of remarkably blunt statements highlighting the adverse impact on public health that would result from Woodcock's decision to approve eteplirsen. They include:

- "By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk. I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs — if not to patients, to society." (Sarepta has announced that the average price for one year of treatment will be \$300,000.)
- "With the false perception that eteplirsen is effective, patients who are gaining benefit from steroids but experiencing untoward side effects might be inclined to taper or stop them, which could lead to more rapid disease progression."
- "False scientific conclusions have the potential to mislead the field of medicine, slowing progress in finding and developing therapies that actually are effective." [Emphasis in original]
- "Accelerated approval [of eteplirsen] would lower the evidentiary standard for effectiveness to an unprecedented nadir."

Unger characterized Woodcock's involvement in the review of eteplirsen as "unprecedented," including her extensive involvement in the planning of, and her participation in, the April 25 advisory committee meeting. Unger also raised concerns about Woodcock's issuance of her decision memo before he had finished his own decision memo on behalf of the team of FDA scientists who had conducted the review of the drug.

Echoing Unger's concerns, Borio wrote:

"Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages. As a consequence, the regulatory reviews did not start at the staff level with scientific reviews and then proceed through the chain of command for concurrence or non-concurrence at all appropriate levels within the management structure, as would be the typical course of decision-making for a regulatory decision grounded in science. Indeed, before the reviewers had

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even completed their draft scientific reviews, Dr. Woodcock had told them —
Outrage of the Month: FDA Senior Leader Ignores Science, Approves Ineffective Drug fo...
on May 4, 2016 — that she intended to grant accelerated approval.

Kelly Ayotte Thinks
Donald Trump Is A
Good Role Model,
But She Still Won't
Endorse Him

Finally, alluding to intense pressure on the FDA from [Congress](#) and [patient advocates](#) to approve eteplirsen, Unger [noted](#), "Approval of [eteplirsen] would send the signal that political pressure and even intimidation — not science — guides FDA decisions, with extremely negative consequences." He continued:

Georgia Elementary
School Educator
Fired After Allegedly
Calling Michelle
Obama A 'Gorilla'

"The ramifications here are profound. The public will perceive that it was their unprecedented lobbying efforts that made the difference and earned eteplirsen its accelerated approval. For the future, this will have the effect of strongly encouraging public activism and intimidation as a substitute for data, which is one of the wors[t] possible consequences for communities with rare diseases. This type of activism is not what was envisioned for patient-focused drug development."

Trump Gave 10
Times The Personal
Max To Florida
Attorney General

Woodcock's decision to overrule so many agency experts represents a dangerous, unparalleled capitulation to pressure from politicians and patients and a stunning disregard of the scientific evidence. Her action eviscerates the FDA's long-standing (but, under Woodcock, already declining) approval standards for new drugs, threatens public health and demonstrates that she is unfit to serve as CDER director.

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Philips, Howard

From: Unger, Ellis
Sent: Friday, October 07, 2016 12:14 PM
To: Temple, Robert; Dunn, Billy; Bastings, Eric; Jenkins, John K
Subject: Fw: Anthem declares Exondys50 "investigational and not medically necessary"

Sent from my BlackBerry.

From: Southworth, Mary Ross <MaryRoss.Southworth@fda.hhs.gov>
Sent: Friday, October 7, 2016 11:59 AM
To: Unger, Ellis
Subject: Anthem declares Exondys50 "investigational and not medically necessary"

https://www.anthem.com/medicalpolicies/policies/mp_pw_c192386.htm

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of New Drugs/CDER/FDA
(o) 301 796-0539



Temple, Robert

From: Unger, Ellis
Sent: Wednesday, October 19, 2016 3:53 PM
To: Temple, Robert
Subject: FW: FDA Chief Defends Controversial Drug Approval

From: Borio, Luciana
Sent: Tuesday, October 18, 2016 11:07 AM
To: Unger, Ellis; Warren, Matthew
Cc: Jenkins, John K
Subject: FW: FDA Chief Defends Controversial Drug Approval

FYI.

From: Mair, Michael
Sent: Tuesday, October 18, 2016 10:47 AM
To: Borio, Luciana
Subject: FDA Chief Defends Controversial Drug Approval

CQ NEWS
Oct. 17, 2016 – 12:19 p.m.

FDA Chief Defends Controversial Drug Approval

By Andrew Siddons, CQ Roll Call

The Food and Drug Administration commissioner on Monday defended the agency's approval of a controversial drug to treat Duchenne muscular dystrophy, saying that the decision was based on science and free from the influence of Congress and patient groups that pushed for the drug's approval.

Speaking at a meeting of the National Organization for Rare Disorders, Commissioner Robert Califf said he removed himself from the decision-making about the drug in deference to Janet Woodcock, a longtime FDA official who oversees the agency's Center for Drug Evaluation and Research.

"Setting a precedent of political appointees intervening in decisions that belong in a scientific process would risk opening the door to a potentially dangerous temptation for others," Califf said.

Approval of the drug, eteplirsen, followed an emotional campaign from the families affected by Duchenne. They argued that eteplirsen represented a rare hope for slowing the disease's progression and enhancing the lives of affected boys before they succumb to the disease in their teens or early adulthood. Congress was also actively involved in lobbying for the drug's approval, with hundreds of lawmakers from both chambers and parties signing letters urging FDA approval.

The drug, eteplirsen, was given conditional approval by the FDA last month after an extended review period in which scientists inside and outside of the FDA questioned whether the drug actually worked. In light of these concerns and minimal information about effectiveness, the FDA granted an approval that will require follow-up clinical trials to gather further evidence.

Califf said there are often differences of opinion within the FDA, but that Woodcock had the experience and the track record to make a good decision.

"I think Dr. Woodcock made a reasonable judgment, and I also think that those who thought otherwise were not unreasonable; they also had a reasonable point of view. But that's why you have a hierarchy in an organization," he said.

Califf said that the law gives the FDA “enormous latitude” for how it considers certain types of evidence when it comes to rare diseases like Duchenne, but there are aspects of this policy he would like to see “more discussion, more writing, more going back-and-forth and testing it out so it’s not totally wide open.”

With the drug’s approval, the FDA must ensure that the manufacturer follows through with additional testing. If the results of those clinical trials do not indicate that the drug works, the FDA can rescind its approval.

But the FDA has been criticized in the past about whether it can effectively monitor the results of follow-up studies for drugs that are already on the market. Califf acknowledged that criticism but argued the agency is now doing an effective job monitoring these follow-up tests.

“Coming into the FDA, I had a perception that the majority of post-market commitments to conduct definitive trials were not met” by the manufacturer, he said. “The ecosystem is doing much better than I expected with post-market commitments and we’re making progress in publishing the results.”

Temple, Robert

From: Unger, Ellis
Sent: Thursday, October 20, 2016 10:23 AM
To: Grant, Stephen; Temple, Robert; Stockbridge, Norman L
Cc: Dunn, Billy; Bastings, Eric
Subject: RE: NORD Slides

Nothing public that I know of, but Billy and Eric have heard complaints and concerns from a number of sponsors.

Here's the article of the day:

Forbes Op-Ed: Former FDA Official Critical of FDA' Decision on Eteplirsen as FDA's "Self-Serving Risk-Aversion" In an opinion piece for [Forbes](#), former FDA official Henry Miller, the Robert Wesson Fellow in Scientific Philosophy and Public Policy at Stanford University's Hoover Institution, and John Cohrssen, former Associate Director of the President's Council on Competitiveness and counsel to the House E&C Committee, write that the FDA errs more often "by delaying or denying approval of a beneficial product, rather than by approving a dangerous one" because the FDA protects itself from public criticism "at all costs." As an example, Miller and Cohrssen highlight the recent example of eteplirsen, which they say was approved only after Dr. Woodcock "overruled her subordinates and one of the drug's primary antagonists resigned his position." The authors write that these "unnecessary delays are a tragedy not only for the subset of victims of Duchenne muscular dystrophy for whom the drug is intended," but also "for victims of other diseases who lack access to promising new medicines when no treatments are available." They conclude that they "have all been victimized not only by illness but often also by the FDA's thirst for control and its excessive, self-serving risk-aversion."

From: Grant, Stephen
Sent: Wednesday, October 19, 2016 4:38 PM
To: Temple, Robert; Unger, Ellis; Stockbridge, Norman L
Subject: RE: NORD Slides

Who are these sponsors who are dismayed by the eteplirsen development program? And why don't they make their objections public?

From: Jenkins, John K
Sent: Wednesday, October 19, 2016 3:31 PM
To: CDER-OND-SLT-II
Subject: FW: NORD Slides

Folks

I gave a presentation at the NORD annual meeting yesterday on regulatory flexibility in reviewing rare diseases and also lessons learned from the recent eteplirsen approval for DMD. The slides are posted on our website. I wanted to share so you can see the message I tried to convey to the rare disease community yesterday on these topics. I have had a lot of positive comments on the messages, including from sponsors who were dismayed by the eteplirsen development program.

John

From: Shreeve, Chris
Sent: Wednesday, October 19, 2016 11:23 AM
To: Jenkins, John K
Subject: FW: NORD Slides

Your slides are online. [Link below.](#)

From: Winthrop, Sally
Sent: Wednesday, October 19, 2016 11:00 AM
To: Shreeve, Chris
Cc: Taira, Helene
Subject: RE: NORD Slides

Chris,
This is now online on the Presentation page,
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm074833.htm>
Direct link,
<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM525805.pdf>
Sally

From: Shreeve, Chris
Sent: Wednesday, October 19, 2016 8:42 AM
To: Winthrop, Sally
Cc: Taira, Helene
Subject: FW: NORD Slides

Sorry. [Here you go.](#)

From: Jenkins, John K
Sent: Wednesday, October 19, 2016 8:26 AM
To: Shreeve, Chris
Subject: FW: NORD Slides

Chris

Here are the slides I used at yesterday's NORD meeting if you want to post to the CDER presentations website.

John

From: Jenkins, John K
Sent: Tuesday, October 18, 2016 8:54 AM
To: Jenkins, John K; Catlett/Jenkins
Subject: NORD Slides

Philips, Howard

From: Unger, Ellis
Sent: Friday, October 21, 2016 11:10 AM
To: CDER-ODE1-ALL
Subject: Dr. Califf on the eteplirsen approval

All,

There was a NORD summit meeting on rare diseases in Arlington earlier this week, where Drs. Califf and Jenkins gave talks; both talked about the eteplirsen approval. The two articles, below, summarize Dr. Califf's thinking.

Dr. Jenkins gave a "lessons learned" talk (here's the link:

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM525805.pdf>). See, in particular, what he says about recruitment and retention in the last slide.

Ellis



Political Appointees Shouldn't Influence Approval Decisions, Califf Says

- 20 Oct 2016
- ANALYSIS

[Derrick Gingery@dgingery](mailto:Derrick.Gingery@dgingery) derrick.gingery@informa.com

Executive Summary

FDA commissioner offers new details about why he left final decision on Sarepta's controversial Duchenne muscular dystrophy drug to FDA's expert bureaucrats.

FDA Commissioner Robert Califf did not want politics interfering with the controversial approval of **Sarepta Therapeutics Inc.**'s Duchenne muscular dystrophy drug *Exondys 51* and decided to stay out of it.

"While it is essential for FDA to be collaborative with the community of patients, advocates, academia and industry during development, one of the most important issues is the preservation of independence of the FDA as a regulatory and public health agency from the vicissitudes of political influence," Califf

said during an Oct. 17 address to the National Organization for Rare Disorders' Rare Diseases and Orphan Products Breakthrough Summit.

"And for decision-making about market approval and final approval of labeling, external influence should be kept to a minimum."

It was an amplification of the reasoning Califf gave in official documents outlining why he deferred to the judgment of Center for Drug Evaluation and Research Director Janet Woodcock in deciding to approve Exondys 51 (eteplirsen).

The circumstances surrounding the approval put FDA in an awkward position during the conference.

The agency normally would want to trumpet the decision as an example of its commitment to rare diseases and regulatory flexibility. (Also see "[FDA Orphan Designations At Record Levels; Resources Need To Keep Up](#)" - Pink Sheet, 29 Feb, 2016.) But in this case, FDA also had to raise all the problems it found with the development program and related lobbying efforts.

Office of New Drugs Director John Jenkins, one of those opposed to approval, said during the conference that Exondys 51 should not be a model for development going forward. (Also see "[No More Sarepta-Like Development, FDA Officials Say](#)" - Pink Sheet, 20 Oct, 2016.)

A 'Dangerous Temptation'

There were a number of agency concerns about the evidence that Sarepta presented in its application, including whether efficacy had been shown.

Multiple FDA officials within CDER opposed approval. Woodcock overruled them and decided to allow Exondys 51 on the market anyway. It led to a dispute resolution process being initiated within FDA in which Califf was the final arbiter. He wrote that he was not qualified and deferred to Woodcock. (Also see "[Woodcock's Consideration of Sarepta Financial Issues Raises Eyebrows](#)" - Pink Sheet, 19 Sep, 2016.)

In his speech at NORD, Califf indicated that his lack of technical expertise was not the only reason he did not give his opinion on Exondys 51's approval.

He said a "political meddling would undermine confidence and introduce the type of bias that is not helpful."

"Setting a precedent of political appointees intervening in decisions that belong in a scientific process would risk opening the door to a potentially dangerous temptation for others, including political appointees within government and other non-FDA groups, to intervene more frequently," Califf said.

Califf added that it should be the career product center staff, who have been thoroughly vetted for financial conflicts of interest, that should decide.

"The main point I'm making is that there are career people whose job it is to weigh all these factors who build a track record and become leaders of organizations based on their proven track record," Califf said in response to an audience question after the speech. "Political appointees come and go and may be influenced by a variety of other factors. So I really respect the view of this administration and all previous administrations that political appointees stepping in should be kept to an absolute minimum."

Politics Didn't Affect Woodcock, Califf Says

Califf also did not think Woodcock's decision was politically motivated.

"I think Dr. Woodcock made a reasonable judgment and I also think that those who felt otherwise were not unreasonable," he said in response to an audience member's question. "But that's why you have a hierarchy in an organization with a method of escalation."

However, among the issues raised about Woodcock's decision to approve the product was that it would encourage political interference in FDA reviews. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)" - Pink Sheet, 19 Sep, 2016.)

While it is rare, there have been political appointees overruling FDA's decisions.

Among the more recent was for [Teva Pharmaceutical Industries Ltd.](#)'s emergency contraceptive *Plan B One-Step*. FDA decided that the product could be made over-the-counter, but then HHS Secretary Kathleen Sebelius overruled FDA and kept it behind the pharmacy counter. (Also see "[HHS Overrules FDA On Plan B OTC, Sends Teva Back To Drawing Board](#)" - Pink Sheet, 7 Dec, 2011.)

Some Critics' Behavior 'Unseemly'

Raising the level of awkwardness of the moment, Califf also admonished some of the tactics used during the campaign pushing for Exondys 51's approval.

The commissioner said some critics "devolved into name calling and taunting of FDA employees. ... Such personal attacks on public servants is unseemly and inappropriate," Califf said.

While it was his only comment, it was a strong rebuke to stakeholders considering the model for their own advocacy efforts.

Patients and advocates were particularly active during the Exondys 51 advisory committee meeting, both by dominating the public hearing and cheering for what they viewed as positive comments on the product. (Also see "[Patients Can't Rescue Sarepta's Eteplirsen](#)" - Pink Sheet, 25 Apr, 2016.) They also asked members of Congress to lobby FDA for its approval. (Also see "[Sarepta's Eteplirsen Is Centerpiece Of Senate Hearing On Expanded Access](#)" - Pink Sheet, 25 Feb, 2016.)

As a result, FDA's relations with patient groups could be damaged, at least in the short-term. (Also see "[Patient Advocacy With FDA Review Staff Will Be Tougher Post-Sarepta](#)" - Pink Sheet, 23 Sep, 2016.)

Not A Rare Disease Milestone?

Califf also warned that patients must be willing to accept that the data may show that Exondys 51 is not an effective treatment.

There can be variability in the natural history of many diseases and that some patients may do well and mistakenly attribute it to the proposed treatment. "All of this leads to reluctance to accept that a treatment may not be effective," he said.

FDA and stakeholders must also be able to accept when a drug candidate has failed. "Many times I saw research teams and pharmaceutical companies cling to the belief that the treatment was beneficial despite mounting evidence to the contrary," Califf said. "We must have the courage to evaluate without bias so that we can move on to better treatments when our current choices are suboptimal or ineffective and we can have confidence in celebrating therapeutic successes."

Skepticism about Exondys 51's approval has already been expressed in the market. [Anthem Inc.](#) recently decided not to cover the product, ruling that it was not medical necessary. (Also see "[Anthem Denies Coverage For Eteplirsen, Citing Lack Of Clinical Efficacy](#)" - Pink Sheet, 7 Oct, 2016.) ([Return to Top](#))

Oct. 21, 2016

Califf: He and Woodcock were Right on Duchenne Drug Approval

10/20/2016

FDA commissioner **Robert Califf** says he was right in upholding her action, and by extension CDER director **Janet Woodcock** also was right in overruling her subordinate Center medical officers to approve Sarepta Therapeutics' Duchenne muscular dystrophy drug Exondys 51 (eteplirsen). Addressing the same Arlington, VA meeting of the National Organization for Rare Diseases at which CDER new drug evaluation director **John Jenkins criticized the approval action**, Califf said the "complex process of drug and device development to provide the evidence needed to make a decision about approval and labeling has a long history replete with precedents and accumulated wisdom ... While it is essential for FDA to be collaborative with the community of patients, advocates, academia, and industry during development, one of the most important issues is the preservation of independence of the FDA as a regulatory and public health agency from the vicissitudes of political influence. And for decision-making about market approval and final approval of labeling, external influence should be kept to a minimum.

“This was,” he continued, “a critical part of my decision to defer to the Center director about accelerated approval of eteplirsen. Setting a precedent of political appointees intervening in decisions that belong in a scientific process would risk opening the door to a potentially dangerous temptation for others, including political appointees within government and other non-FDA groups to intervene more frequently. While it is true that FDA decision-making is difficult and imperfect, political meddling would undermine confidence and introduce the type of bias that is not helpful. In this regard, it is clear that the medical product center, comprised of professionals who are FDA employees and carefully vetted for financial conflicts, should make the decision. An admirable process with strong historical precedent enables the FDA to make decisions that are rational and defensible. An organized system of appeal allows those who disagree to be heard at higher administrative levels. In the history of FDA regulation of medical products, the politically appointed Commissioner or Secretary of HHS has rarely intervened to override a decision from a medical product center.”

In his presentation, Califf said he wants FDA, industry and academia to work together to reduce the number of drug development programs that fail. “Despite the remarkable progress, the latest data continue to indicate that the vast majority of drugs entered into early phase human testing will not make it to market. This is due to a complex combination of failure to demonstrate efficacy, unexpected toxicity, and difficulty with manufacturing... Therefore, while speed to access is vital to suffering people, we also must continue to develop and implement methods that ‘separate the wheat from the chaff,’ rapidly discarding therapies that are dangerous or ineffective and speeding along therapies that truly provide clinical benefit.”

Califf’s talk focused on the accelerated approval pathway and the statute’s approval allowance related to a biomarker showing it is “reasonably likely” to predict clinical benefit. “Accordingly, the statute allows enormous latitude for FDA to consider the spectrum of evidence about biological plausibility, clinical epidemiology, and fundamental knowledge that could link the biomarker of interest to the possibility of being a valid surrogate,” he said. “In the end, the FDA must make a judgment about whether the measurement in the biomarker plus associated data and information make it ‘reasonably likely’ that the treatment will have clinical benefit.”

Califf said more work is needed to define what “reasonably likely” actually means. “It is not defined either in statute or guidance,” he said. “Although scientifically the evaluation of the totality of evidence should lead one to a quantitative or probabilistic estimate, there is no guidance on whether ‘reasonably likely’ means that there is a 50%, a 75%, or a 95% chance that the change in the biomarker will lead to a clinical benefit. This approach necessarily vests a lot of public trust in FDA and emphasizes the clear need for the FDA to employ the very best people, and for its advisory committee system and other feedback mechanisms to enable very high quality scientific exchange. This is one of many reasons why my top priority at FDA has been to continue to develop and support our workforce, including working on the advisory committee system to assure that we get the best advice.”

Another area Califf said he is interested in is expanded access for desperate patients. He said FDA approves over 99% of such requests, but “when there is no possibility of enrolling in a trial, either because of eligibility criteria or logistics (as when the patient lives far away from the nearest study site and cannot travel), it is up to the company that manufactures the drug to decide whether the drug can be made available. We are working with the Reagan-Udall Foundation on developing a navigator system to make it even easier to access the system to find the best avenue for the patient. And we are following with interest efforts to increase the transparency of the policies of companies about their experimental drugs and biologics. Among many reasons to steer expanded access towards

appropriate clinical trials, when possible, is the fact that, as I mentioned before, the vast majority of therapies that enter clinical trials – more than 90% – have serious toxicity or lack clinical efficacy. So it is critical that we sort out the effective therapies from those that are ineffective or dangerous through high quality clinical trials.”

[\(Return to Top\)](#)

Temple, Robert

From: Unger, Ellis
Sent: Wednesday, October 26, 2016 11:18 AM
To: Bastings, Eric; Dunn, Billy; Temple, Robert; Jenkins, John K; Lowy, Naomi
Cc: Stockbridge, Norman L; Grant, Stephen; Mathis, Mitchell; Farchione, Tiffany
Subject: FW: Health Affairs: The FDA's Controversial Duchenne Drug Approval And The Moral Impulse To Rescue

[You might find this interesting.](#)

From: Borio, Luciana
Sent: Wednesday, October 26, 2016 10:52 AM
To: Warren, Matthew; Unger, Ellis
Subject: FW: Health Affairs: The FDA's Controversial Duchenne Drug Approval And The Moral Impulse To Rescue

The FDA's Controversial Duchenne Drug Approval And The Moral Impulse To Rescue

[Mildred Solomon](#)

October 25, 2016



What can we learn from the Food and Drug Administration's (FDA's) controversial approval of the first drug for Duchenne Muscular Dystrophy (DMD)?

Everybody at the FDA [agrees](#): "There were major flaws in the design and conduct of the clinical trials using eteplirsen (brand-name Exondys 51)." Nevertheless, against the recommendations of the FDA's expert panel, Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, approved the drug under the FDA's accelerated approval pathway for a subset of patients, approximately 13 percent of the DMD population with a gene mutation amenable to the drug's action. Upon appeal by agency scientists who disagreed with Dr. Woodcock, FDA Commissioner Robert Califf upheld her decision, saying that both sides, in reaching their

different conclusions, had exercised reasonable scientific judgment. One week later, he [called for retraction](#) of one of the papers that Sarepta Therapeutics, the maker of Exondys 51, had relied upon for data on the drug's effectiveness.

What's going on?

How can a regulator approve a drug, while simultaneously questioning the quality of the evidence about its efficacy?

Has the FDA succumbed to the pleas of desperate parents and in so doing, lowered its scientific standards? Or has it demonstrated compassion and a path forward that is justifiable?

My answer is that the controversial decision is defensible, but only if there is adequate follow through.

Compassionate response to the most vulnerable among us is a virtue, often described as emanating from the "rule of rescue," which calls on us to meet the needs of strangers in dire circumstances. Nothing is more dire than children living with fatal illnesses, like DMD. These children are terminally ill, there are no other viable alternatives, the drug seems to be safe, and while it is being used, it can be studied. Dr. Woodcock seemed to be making an explicitly compassionate argument based on the virtue of rescue, when [she noted](#) at a 2016 FDA advisory committee meeting that there is a great deal of effort that goes into avoiding the mistake of approving a drug that is not effective, but "there is often little consideration of another error, which is failing to approve a drug that actually works."

What's next?

But now there must be follow through. First, responsible drug development under accelerated approval calls for corporate restraint from hyperbolic claims. Indeed, in approving Exondys 51 for accelerated approval, Califf noted that statutory and regulatory provisions governing accelerated approval "require sponsors to submit promotional materials to the FDA for pre-dissemination review." Hopefully, as the Commissioner urged, the FDA will be vigilant in ensuring that packaging and marketing materials do not overstate what is known about the drug's efficacy.

Second, if the now-required post-marketing trial does not demonstrate clinical benefit, FDA approval must be withdrawn. There are [precedents](#) for withdrawing approved indications that are later discovered to be mistaken, like Avastin, which was approved in 2008, and had approval withdrawn in 2011, when subsequent trial data showed no benefit in overall survival or quality of life and significant life threatening side effects. Nevertheless, once approved, it is hard to roll back all the consequences of a premature approval. Medicare continues to pay for Avastin, and the National Comprehensive Care Network's 2014 guidelines for patients still list the drug as a treatment for Stage IV breast cancer.

Moreover, if evidence proves lacking, insurers will refuse to pay for it ([as Anthem already has](#)), and they will deserve back up from health policymakers and others to withstand the public controversy that will arise from coverage refusals.

If approval is ultimately withdrawn for Exondys 51, its use over the years until we have better evidence will have cost millions and burdened families, who—believing in it—may have had to make dire decisions about how to cover co-pays. Clinicians have a role to play here. Most, if not all of these children are under the care of physicians, who should make a point of explaining to parents how uncertain the science still is on this drug, helping to modulate false hopes and guide appropriate parental decision making.

Third, going forward, the FDA should do much more to insist that sponsors follow FDA advice earlier in the research process. In this case, the FDA alerted Sarepta that it needed a larger sample and controls, but that *advice* did not translate into action. More emphasis on the importance of complying with FDA advice about study design should be placed earlier in the process, so that sponsors follow FDA recommendations for study design before bringing applications for accelerated approval.

Patient Engagement: A Double-Edged Sword

This is some of what can be done to ensure the bar on scientific standards has not been lowered. But there is more that as a society we have to figure out. Patient engagement in science policy in general, and specifically in drug policy, is a principle we can, and should, embrace. Were it not for the AIDS activists of the 1980s and early 1990s, HIV/AIDS might not have transformed from a death sentence to a manageable chronic illness. Listening to patient experiences, even when the scientific evidence is scant, is a good policy that ensures the experts and the powerful stay alert to the human needs science aims to address.

However, patient engagement is a double-edged sword, especially when coupled with the financial interests of other stakeholders. Consider, for example, the hundreds of millions of dollars and the human pain and suffering that was caused by over-exuberant patients who were desperate and health systems that stood to make huge revenues, by too quickly embracing [unproven bone marrow transplantation](#) for the treatment of breast cancer. There is no substitute for the scientific method.

As this election cycle demonstrates, we are already in what has been called a “[post-fact](#)” world in our [political life](#). Let us hope that science and science policy do not find themselves in the same predicament — where evidence is pushed aside by the overly fervent.

That said, it would be naïve to think that evidence alone can be [determinative](#). It behooves us to find ways to engage patients, but we also should engage other more disinterested members of the public, who can be charged with considering a policy’s impact on a range of issues vital to the common good, not just on rescue. There are many questions that citizens should weigh in on — questions, like: Will approval of this drug impede, or even eliminate, our ability to gain important knowledge about it? Will approval limit the evidentiary standard the FDA should use? If a drug is being considered for approval on the basis of limited evidence, how will *both* the potential benefits and the full range of possible negative side effects be explained to patients?

Institutional integrity—and the very ability of our society to carry out the biomedical research enterprise in ethically appropriate ways—requires that scientists and policymakers withstand pressure from industry, patients, Congress, and the press. In drug development these pressures are intense and omnipresent, as desperate patients and their families seek rescue, research sponsors seek cures, and investors seek returns. Adherence to evidence must remain a *sine qua non*. In addition, we must find ways that experts, patients, and the public can examine evidence, weigh competing claims, and balance or prioritize values, so that together we can make the hard choices that confront us.

Tags: [clinical trial](#), [Duchenne Muscular Dystrophy](#), [FDA](#)

Philips, Howard

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Sent: Wednesday, October 26, 2016 10:27 AM
To: Unger, Ellis; Temple, Robert
Subject: JAMA article on eteplirsen approval

<http://jamanetwork.com/journals/jama/fullarticle/2572614>

I thought they included some interesting solutions to existing limitations:

One partial solution could be the adoption of novel regulatory models, such as limited approval with intensive collection of new clinical evidence, before a drug becomes universally available. As a further step, drugs that have not yet shown clinical outcome benefit could be made available at just the cost of production, or most profits could be kept in escrow, until adequate trials are completed.

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From: Temple, Robert
Sent: Wednesday, October 26, 2016 12:35 PM
To: Grant, Stephen; Unger, Ellis
Cc: Stockbridge, Norman L
Subject: RE: Health Affairs: The FDA's Controversial Duchenne Drug Approval And The Moral Impulse To Rescue

The HIV advocates, very much desiring drugs that would help them live, strongly urged good trials. My recollection is that they were better at this than the ID docs. In any case the AZT approval was based on a mortality difference, as I recall it of 16 vs 1 (final; at termination of study is was 9 vs 1). We later accepted viral load and CD4 surrogates but they were very reasonable

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Another example of the uselessness of most self-proclaimed bioethicists....substitutes hazy aspirations and bromides for serious analysis of the facts. "Compassionate response to the most vulnerable among us is a virtue"...as you used to hear in college "Man that's so heavy." And some of the 'facts' in this article aren't "Were it not for the AIDS activists of the 1980s and early 1990s, HIV/AIDS might not have transformed from a death sentence to a manageable chronic illness." Really? I have heard the reasonable argument that activists drew attention to the problem and so accelerated development of HAART by increasing funding but I have never heard and think not reasonable that effective treatments for AIDS would never have been developed without the activists.

And what to make of this paragraph? "That said, it would be naïve to think that evidence alone can be [determinative](#). It behooves us to find ways to engage patients, but we also should engage other more disinterested members of the public, who can be charged with considering a policy's impact on a range of issues vital to the common good, not just on rescue. There are many questions that citizens should weigh in on — questions, like: Will approval of this drug impede, or even eliminate, our ability to gain important knowledge about it? Will approval limit the evidentiary standard the FDA should use? If a drug is being considered for approval on the basis of limited evidence, how will *both* the potential benefits and the full range of possible negative side effects be explained to patients?" Evidence alone is not determinative? So much for FDA as a data-driven entity. We are supposed to know whether approval might in the future actually result in some useful information?

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Tags: [clinical trial](#), [Duchenne Muscular Dystrophy](#), [FDA](#)

Philips, Howard

From: Freed, Lois M
Sent: Wednesday, October 26, 2016 7:55 AM
To: Bastings, Eric; Dunn, Billy; Unger, Ellis; Temple, Robert; Kozauer, Nicholas
Subject: RE: Interesting article
Attachments: Kesselheim JAMA online 2016.pdf

Related link and article.

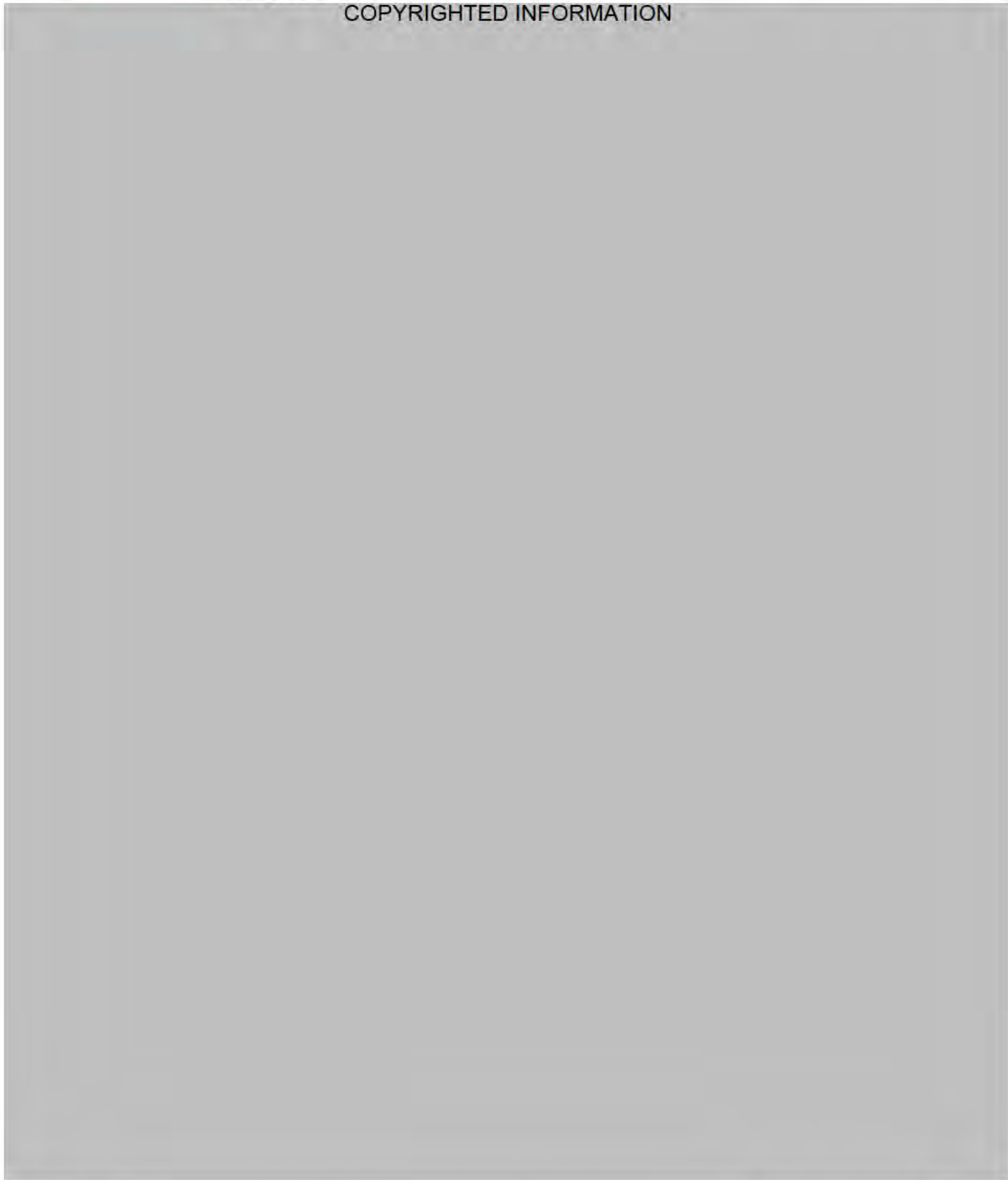
<http://www.fiercebiotech.com/biotech/jama-fda-expert-hit-out-at-sarepta-s-worrisome-model-for-approval>

From: Bastings, Eric
Sent: Wednesday, October 26, 2016 7:44 AM
To: Dunn, Billy; Unger, Ellis; Temple, Robert; Freed, Lois M; Kozauer, Nicholas
Subject: Interesting article

VIEWPOINT

Approving a Problematic Muscular Dystrophy Drug Implications for FDA Policy

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Philips, Howard

From: Lowy, Naomi
Sent: Wednesday, October 26, 2016 11:00 AM
To: Temple, Robert; Unger, Ellis
Subject: RE: JAMA article on eteplirsen approval

I think that's the point—why should they recoup their costs if the drug doesn't work? It sounds like they are advocating for a form of approval they are calling "limited" that does not allow them to market the drug in the way accelerated approval does. That would include delaying the company from profiting from drug sales, until confirmatory trials are done.

From: Temple, Robert
Sent: Wednesday, October 26, 2016 10:55 AM
To: Lowy, Naomi; Unger, Ellis
Subject: RE: JAMA article on eteplirsen approval

They can provide access now and recoup the cost of production. The available with new data sounds like accelerated approval, no?

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Subject: JAMA article on eteplirsen approval

<http://jamanetwork.com/journals/jama/fullarticle/2572614>

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Clifford B. Saper, M.D., Ph.D.
Editor-in-Chief
Annals of Neurology

c/o Managing Editor
330 Brookline Avenue
Boston, MA 02215
email: aon@bidmc.harvard.edu

Dear Dr. Saper:

This letter is in reference to the paper "Eteplirsen for the treatment of Duchenne muscular dystrophy," by Jerry R. Mendell, Louise R. Rodino-Klapac, Zarife Sahenk, Kandice Roush, Loren Bird, Linda P. Lowes, Lindsay Alfano, Ann Maria Gomez, Sarah Lewis, Janaiah Kota, Vinod Malik, Kim Shontz, Christopher M. Walker, Kevin M. Flanigan, Marco Corridore MD, John R. Kean, Hugh D. Allen, Chris Shilling, Kathleen R. Melia, Peter Sazani, Jay B. Saoud, and Edward M. Kaye, published in the *Annals of Neurology* (*Ann Neurol* 2013;74:637–647).

The principal conclusion of the study was: "Eteplirsen restored dystrophin in the 30 and 50 mg/kg/wk cohorts, and in subsequently treated, placebo-controlled subjects."

We believe that the reported findings for the 48-week study are based on unreliable data and that the conclusions, based on these erroneous findings, are misleading. We therefore urge that the paper be corrected or retracted from the *Annals of Neurology*.

In the course of FDA's review of a New Drug Application for eteplirsen for the treatment of Duchenne muscular dystrophy in patients with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, FDA inspected the Columbus, Ohio facility where the study had been conducted. As noted in documents posted on the internet subsequent to our September 19, 2016, approval,¹ a number of significant methodological problems were found that importantly affect the study results.

The Patients and Methods section of the publication states:

"To evaluate dystrophin-positive fiber levels, immunohistochemical staining was done on 10 µm frozen sections of 3 separate blocks of biopsy tissue separated by at least 200 µm and evaluated by blinded expert muscle pathologists. For dystrophin localization, sections were stained with MANDYS106 NCL, a mouse monoclonal antibody to amino acids 1749–2248,[15, 16] using standard immunofluorescence methodology.[9, 14] Dystrophin-positive fibers and total fibers were counted, and the percentage of dystrophin-positive fibers was calculated across all samples."

¹ Downloaded 9/29/16 from
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf

was it done
by Dr
group (also
30, 50) and
was not the
same seen?
FDACDER0005172

Note that the first sentence states that the tissues were evaluated by “blinded expert muscle pathologists,” implying more than one such evaluator. The third sentence explains that dystrophin-positive and total muscle fibers were counted, and because this sentence closely follows the first sentence and is in the same paragraph, there is the implication that the fiber counting was also performed by “blinded expert muscle pathologists.” In fact, the counting was performed by a single histotechnician.

The FDA inspectional findings pertinent to the fiber counting are reprinted from pp. 12 to 15 of the Office Director Decisional Memo.¹

“Although the technician had been blinded to treatment group, access to the treatment code was not protected with the kinds of safeguards and firewalls that one would ordinarily put in place for an adequate and well controlled trial. The immunohistochemistry images were only faintly stained, and had been read by a single technician using an older liquid crystal display (LCD) computer monitor in a windowed room where lighting was not controlled. (The technician had to suspend reading around mid-day, when brighter light began to fill the room and reading became impossible.) These issues are well described in a summary of inspectional findings in Dr. Breder’s clinical review (page 27). There was also concern that the reader, although masked to treatment assignment, was not masked to sequence/time (see below). Importantly, in a trial where all patients eventually received the active drug, knowledge of sequence could lead to the false appearance of a treatment effect, i.e., the appearance of increasing dystrophin expression with time, simply by having a lower threshold for calling fibers “positive” at later time points in the study.

what
that
week?

Having uncovered numerous technical and operational shortcomings in Columbus, our team worked collaboratively with the applicant to develop improved methods for a reassessment of the stored images. We suggested a re-read of all images by 3 independent masked readers, such that blinding could be assured and inter- and intra-observer variability could be characterized. We also suggested the use of better equipment, specifically, high-quality light-emitting diode (LED) computer monitors, in darkened rooms.

The applicant undertook a blinded re-analysis of the images on the server as FDA suggested. Unfortunately, the re-analyses failed to show a significant increase in dystrophin-positive fiber counts in eteplirsen treated patients (Figure 3). Note also that for patients who switched from placebo to eteplirsen at Week 24 (dashed red and black lines), there was no response between Weeks 24 and 48.”

The results of the original analysis (left) and the blinded re-analysis by 3 readers (right) are shown graphically below. These show actual percent positive fiber counts, without baseline subtraction. Note the marked differences between readings in the left and right plots, particularly at later time points.