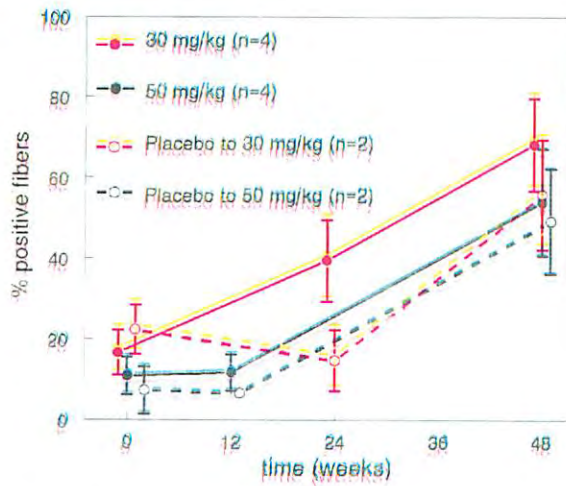
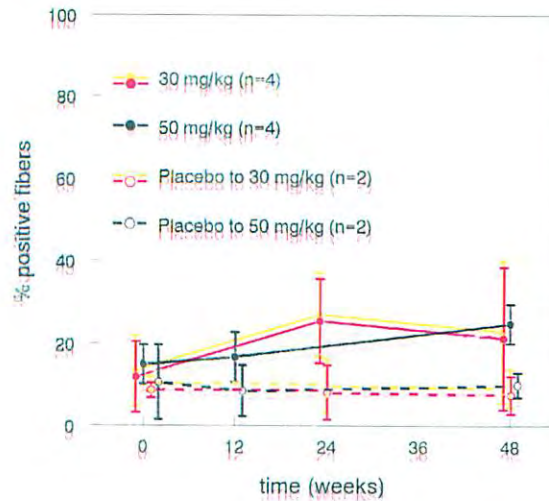


Original reading at
Nationwide Children's Hospital



Blinded re-read by 3 pathologists



The original results were shown in Table 2 of the paper as percent positive fibers; absolute change from baseline, reprinted below:

A

Cohort (n)	Week 12 Mean Change from BL, SE (p-value) †	Week 24 Mean Change from BL, SE (p-value) †	Week 48 Mean Change from BL, SE (p-value) †
All Eteplirsen (8)	NA	NA	47.3, 3.89 (≤0.001)
Eteplirsen 30mg/kg (4)	ND	22.9, 2.90 (≤0.002)	51.7, 3.54 (≤0.001)
Eteplirsen 50 mg/kg (4)	0.8, 3.55 (NS)	ND	42.9, 6.72 (≤0.008)
Placebo-Delayed Eteplirsen (4) †	-4.0, 2.92	-4.0, 2.92	37.7, 6.30 (≤0.009) †
Eteplirsen 30 mg/kg (2)	ND	-7.48, 1.00	33.6, 5.23
Eteplirsen 50 mg/kg (2)	-0.6, 5.16	ND	41.8, 13.30

Based on data received by FDA, the revised and markedly different results from the blinded re-read of 3 pathologists are shown using the same format:

	Week 12 Mean Change from BL (SE)	Week 24 Mean Change from BL (SE)	Week 48 Mean Change from BL (SE)
All Eteplirsen (8)	NA	NA	9.8, 2.33
Eteplirsen 30 mg/kg (4)		13.7, 2.04	9.6, 4.54
Eteplirsen 50 mg/kg (4)	1.8, 3.57	ND	10, 2.41
Placebo - delayed Eteplirsen (4)		-1.2, 1.69	-0.8, 1.96
Eteplirsen 30 mg/kg (2)	ND	-0.4, 3.4	-1, 2.02
Eteplirsen 50 mg/kg (2)	-2.1, 2.05	ND	-0.6, 4.34

Note that the absolute change from baseline originally reported was approximately 50% for all eteplirsen patients, whereas the percent change reported on independent re-analysis is approximately 10%. Many time points and treatment groups were examined here; given that there was no attempt to control the type-I error rate, we did not compute nominal *p*-values for these results. Importantly, the independent re-analysis did not confirm the results reported in the paper and is much less supportive of the stated conclusions.

Moreover, based on our comparison of the immunohistochemistry images in Figure 3 of the paper and the raw images of all photomicrographs collected from each patient biopsy received in the New Drug Application, the images in the publication appear markedly enhanced and thereby deceptive; certainly, the images in the publication are in no way "representative," as claimed by the authors.

Finally, we found technical problems with the supportive Western blot analyses reported in the paper. We have yet to post the details of our review on the internet; therefore, we cannot provide any specific comments with respect to the Western blot analyses at this time.

We believe that correcting these findings is important because they have been cited in a manner that overestimates the effect of eteplirsen on dystrophin. Furthermore, as human translational science advances and the time lag between discovery and human clinical trials shortens, we are seeing more critical evidence for new therapies emanating from academic laboratories. Accordingly, the numerous methodological shortcomings should be noted to assist others who may be involved in producing evidence of a quality needed for regulatory submissions.

In summary, the dystrophin-positive muscle fiber counting, as originally performed by the authors, was incorrect. In a blinded re-analysis by 3 readers, the original counts were shown to be markedly inflated, and these incorrect counts provided the basis for the conclusions of the study. In light of the above, we do not believe that the paper in its current form meets the high standards of *Annals of Neurology*.

Sincerely,

From: Staffa, Edward
Sent: Monday, November 07, 2016 7:02 AM
To: Woodcock, Janet; Throckmorton, Douglas C; Temple, Robert; Moscicki, Richard
Cc: Agajelu, Ogochukwu *; Bechtel, Christine; Bennett, Carol; Bernstein, Ilisa; Blount, Aprile; Bolek, Michelle; Buckman, Paul; Buckman-Garner, ShaAvhrée; Carpenter, Courtney; CDER Trade Press; Christl, Leah A; Clarke, Mary Beth; Clark-Lynn, Sarah; Colby, Tralisa; Corrigan, Dara; Cosgrove, Thomas; Dal Pan, Gerald; Echegoyen, Edwin; Elliott, Deborah; Fischer, Andrea (FDA); Frey, Patrick; Frydl, Andrea; Goldsmith, Jonathan; Guidos, Robert; Huang, Sheilyn; Hunter, Nina L; Ikenberry, Sarah; Iles, Irina *; Jackler, Karen; Jenkins, John K; Jerrick, Morgan; Keller, Melanie; Kim, Sarah; Kochel, Bridget; Kopcha, Michael; Kornegay, Cynthia J; Kremzner, Mary E; Labbe, Colleen; Lee, Tracey (FDA); Lilly, Trudy; Lister, Sherunda; Livornese, Deborah; Lowy, Naomi; McCune, Susan; Meyer, Lyndsay; Moeny, David; Mullin, Theresa; OGDREQUEST; O'Grady, Jordana; CDER OSE OCT; Pattee, Suzanne; Peddicord, Sarah; Pinheiro, Simone P; Rausch, Paula (FDA); Rawlings, Kimberly; Rowzee, Anne; Ruiz, Diane; Shaham, Lauren; Sherman, Rachel; Shreeve, Chris; Sims, Anthony E; Sipes, Grail; Sklamberg, Howard; Smith, Harry; Staffa, Edward; Staffa, Judy A; Staton, Anna; Stowe, Ginneh D.; Toigo, Theresa A; Uhl, Kathleen (CDER); Unger, Ellis; Unger, Monica; Wang, Cunlin; Whyte, John; Winthrop, Sally; Yu, Lawrence
Subject: FW: The FDA News Summary for Monday, November 07, 2016
Attachments: FDA161107.doc; FDA161107.pdf; WSJ - Rogue Synthetic Compounds.docx

[Good morning... in the clips today: WSJ: New Opioid-like Drugs Are Emerging at a One-A-Week Rate --- Often Ahead of DEA Scheduling... Roll Call: FDA "Remarkably Transparent" On Eteplirsen Approval... Generic Epinephrine Auto-Injector Often Not Substituted For EpiPen Because Pharmacists Would First Need To Call the Prescriber For Authorization... Patients Worldwide Turning To "Buyers Clubs" For Access To Hepatitis C, HIV Medications... Opinion: Strengthening FDA "Critical" To Combat Cancer, Congress Should Pass Cures Act... Opinion: FDA's All-Or-Nothing Drug Approval Process Needs Reform... FDA Advisory Panel Votes To Recommend Approval Of Experimental Antibiotic... Editorial: Revising Drug Marketing Rules For Off-Label Use Would Make Drug Spending Worse... Teleflex Issues Voluntary Recall For Naloxone Administration Device.](#)

WSJ: New Opioid-like Drugs Are Emerging at a One-A-Week Rate --- Often Ahead of DEA Scheduling. A front-page [Wall Street Journal](#) (see attached) article titled, *This Is U-47700, Once a Lab Experiment, Now a Killer Opioid*, reports new psychoactive drugs, including a number of synthetic opioids, are emerging at a rate of a drug per week on average, according to estimates by UN Commission on Narcotic Drugs. The article details one family's tragic story of death from U-47700, making a point that this drug is one of many being churned out by rogue chemists who often create the molecule based on abandoned research on drugs that never made it to market through legitimate approval channels. The extensive article points out many of the substances are from China... most are fentanyl spinoffs... and that because they are being created and released so quickly, many are on the streets before even being identified and banned by DEA as Schedule I Controlled Substances.

Roll Call: FDA "Remarkably Transparent" On Eteplirsen Approval. [Roll Call](#) reports that while the FDA has been "haunted" by its "controversial" approval of eteplirsen to treat Duchenne muscular dystrophy, "instead of shying away from the controversy, the FDA has been remarkably transparent." The article notes that the FDA released 300 pages of internal emails on Thursday and FDA officials discussed the decision on Friday. The article notes that Dr. Jenkins, told reporters, "We've moved on. The good news is, most decisions we make within the agency are not this controversial." The article

also notes Dr. Califf saying, "I hope people realize that a great thing for a federal agency that has to make hard decisions is to encourage people that have differences of opinion to express them." The emails showed the "debate" among Drs. Califf, Jenkins, Woodcock Unger and Pazdur, [STAT](#) also reports, providing a [link](#) to the 311 page document containing these emails, and analyzing details of the communications.

Generic Epinephrine Auto-Injector Often Not Substituted For EpiPen Because Pharmacists Would First Need To Call the Prescriber For Authorization. [CBS News](#) reports that while an FDA-approved generic EpiPen alternative exists, it is rarely fulfilled by pharmacists because it is "technically the authorized generic for a different brand, Adrenaclick." Dr. Mohamad Jalloh of the American Pharmacists Association said, "legally we would have to fill it as an EpiPen unless we call a prescriber to change it." According to the article, part of the low prescription activity for the generic alternative can also be explained by strong branding, whereby EpiPen has become accepted as a general term for an epinephrine auto-injector. Food Allergy Research & Education CEO Dr. James Baker urged more competition for the EpiPen, saying the "FDA has shown that if you have three or four drugs in the marketplace you're likely to have a more competitive market."

Patients Worldwide Turning To "Buyers Clubs" For Access To Hepatitis C, HIV Medications. [Reuters](#) reports that "thousands of patients from London to Moscow to Sydney are turning to a new wave of online 'buyers clubs' to get cheap generic medicines to cure hepatitis C and protect against HIV infection." The "buyers clubs... act as middlemen by providing details of trusted online pharmacies and drug manufacturers, exploiting a loophole in World Trade Organization patent rules that allows small-scale imports of medicines for personal use."

Opinion: Strengthening FDA "Critical" To Combat Cancer, Congress Should Pass Cures Act. In a [Washington Post](#) letter to the editor, Ellen Sigal, the founder and chairperson of Friends of Cancer Research and a member of the White House Moonshot Blue Ribbon Panel, praised the FDA role as "a vital player in speeding lifesaving treatments to those who need them," but lamented that "for nearly a decade, the FDA has been recruiting with one arm tied behind its back." To address the FDA's lack of sufficient funding, Sigal urged Congress to "pass the 21st Century Cures Act, which would unlock the agency's potential to compete for the most qualified scientific talent" and provide adequate staffing for "the Oncology Center of Excellence, a key pillar of the White House's visionary Cancer Moonshot."

Opinion: FDA's All-Or-Nothing Drug Approval Process Needs Reform. An op-ed in [Forbes](#) says that the FDA's current drug approval process compels the agency "to make all-or-nothing decisions based upon limited evidence." Instead, they advocated for "an alternative system that allows for partial approval," which would "help some patients who lose out when the FDA denies approval while potentially also benefiting future patients by reducing the uncertainties faced by drugs' developers."

FDA Advisory Panel Votes To Recommend Approval Of Experimental Antibiotic. The [AP](#) reports that an FDA advisory panel "has narrowly recommended approval" for Cempra's experimental antibiotic. The panel "voted 7-6 in favor of the drug, saying its effectiveness outweighed risks of liver toxicity seen in company studies." [Reuters](#) reports that the panel recommended the approval of solithromycin for the treatment of community-acquired pneumonia. Panelists did vote "unanimously that the drug works as well as the potent antibiotic moxifloxacin." Additional coverage is provided by the [Triangle \(NC\) Business Journal](#) and [Healio](#) also report.

Editorial: Revising Drug Marketing Rules For Off-Label Use Would Make Drug Spending Worse. An editorial for [Modern Healthcare](#) says that the FDA, "is considering dramatic changes to its drug marketing rules that threaten to make the problem of out-of-control drug spending even worse."

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Ostheimer said OTC homeopathic marketers can refer to previous FTC guidance on including disclaimers in ad claims and to the agency's recent public workshop that examined the testing and evaluation of disclosures companies make to consumers about advertising claims, privacy practices and other information.

The policy statement "is a guidance on how companies can comply," he said. "We've given guidance in other contexts that have to make clear and conspicuous disclosures and that guidance is available. It's not specific to the area of OTC homeopathy but it applies to disclosures and all sorts of contexts in advertising and labeling.;

"There's not going to be anything specific with respect to OTC homeopathic disclosures, but there has been guidance with respect to how to make disclosures clear and conspicuous."

Young considers FTC's statement sufficient for firms' compliance, partly because the policy is not a change from the commission's historic approach.

"This does simply rehash and explain the FTC's position and does so in such a way that the industry, I think, can understand what they're saying about the need for substantiation, when they make claims that require substantiation," he said.

"I don't think anything changes here, but it is better-articulated."

Homeopathic firms also might caution FTC and FDA that little room is available on drug product labels to add disclaimers. While print, digital or broadcast ads can be expanded as needed to include disclaimers or disclosures, drug product labels have finite space available, a point often noted about potential labeling needed for some Rx-to-OTC switches. (Also see "[Naloxone Switch: Door Opener For Other NDAs That Swing On Consumer Education](#)" - Pink Sheet, 13 Jul, 2015.)

FDA also is reviewing its oversight of homeopathic products, in both the Rx and OTC spaces, with the agency addressing concerns that consumers who use the products might not be receiving medical care needed for certain diseases or conditions. (Also see "[Homeopathic Divide: FDA Talks Pre-Market Approval As Industry Floats Label Changes](#)" - Pink Sheet, 6 May, 2015.)

From the editors of The Tan Sheet.

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Exondys 51's Development: Was Placebo-Controlled Trial Possible?

- 16 Nov 2016
- Analysis

[Derrick Gingery @dgingery derrick.gingery@informa.com](mailto:derrick.gingery@informa.com)

Executive Summary

Sarepta says US FDA said no, but agency repeatedly urged the company to pursue the approach.

[Sarepta Therapeutics Inc.](#) and FDA appeared at odds over whether a placebo-controlled trial should have, or could have, been conducted as part of the later development stages of *Exondys 51* in Duchenne muscular dystrophy.

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A Sarepta official said recently that the company, patients and physicians concluded that a Phase III placebo-controlled trial would not be appropriate given the promising results seen in previous studies, and that an FDA bioethicist agreed with that assessment.

But emails and other documents from the review indicate that FDA repeatedly told the company that placebo-controlled trials were preferable to the studies that ultimately were submitted. FDA repeated the warnings multiple times during the development phase, as well as mid-review.

During an Oct. 25 webinar on accelerated approval that was sponsored by the EveryLife Foundation for Rare Diseases, Shamim Ruff, Sarepta senior VP of regulatory affairs and quality, said once the company received the results from its Study 202 it did not think a Phase III study was advisable.

The 202 study was an open label extension study of study 201, a placebo-controlled efficacy study that did not show a significant difference between eteplirsen and placebo. One reason for not needing a Phase III study was that it would not be ethical to give some Duchenne patients a placebo knowing the potential of *Exondys 51*, Ruff said, and recruitment for a placebo-controlled study likely also would have been difficult.

"Due to the significant increase in dystrophin observed in the 202 study, physicians, patients and even the FDA bioethicist at one of our meetings, felt it would not be appropriate to conduct a Phase III placebo control study," she said.

"Patient recruitment would have been very, very challenging at the time," Ruff added. "There were a number of parallel studies ongoing for a competitor drug for the exact same subset of patients from DMD."

Ruff appears to be referring to [BioMarin Pharmaceutical Inc.](#)'s drisapersen, proposed trade name *Kyndrisa*. It, like Sarepta, was seeking approval for its product in Duchenne patients amenable to exon 51 skipping. Duchenne muscular dystrophy is a rare disease, with about 15,000 patients in the US. Exon 51 patients make up about 13% of all Duchenne patients.

BioMarin received a complete response letter for drisapersen after FDA had a number of concerns about its efficacy. The company decided to end the development program shortly thereafter. But in the wake of the *Exondys 51* approval, BioMarin has said that it is considering an appeal of the complete response. (Also see "[Sarepta's Shadow: BioMarin Mulls Turning The Extraordinary Into A Template](#)" - Pink Sheet, 15 Oct, 2016.)

Ruff also told FDA that the final stages of the review had to be completed quickly due to Sarepta's financial problems, although its SEC filings gave a different outlook. (Also see "[Sarepta Pressured FDA On Eteplirsen Due To 'Dire' Finances, Gave Investors Rosier Picture](#)" - Pink Sheet, 3 Nov, 2016.)

FDA Offered Potential Placebo Control Study

It is unclear when the conversation with FDA that Ruff described in fact occurred. Asked to provide a date or details, she said in an email to the Pink Sheet that "it serves to highlight the many challenges to consider when designing a clinical trial for a rare, progressive and fatal pediatric disease."

FDA review documents, including emails, memos and other correspondence between Sarepta and the agency, do not appear to indicate that the agency said a Phase III placebo-controlled study was not appropriate. In fact, the agency said exactly the opposite on several occasions and encouraged Sarepta that placebo-controlled trials were possible.

For example at the end-of-Phase II meeting, conducted in March 2013, Sarepta said its data from study 201 and 202 was showing treatment was resulting in "an unprecedented and clinically meaningful" six-minute walk test benefit and asked whether accelerated approval would be appropriate.

FDA was not as excited about the data as the company and said that if the clinical benefit is as good as the data already gathered, then a placebo-controlled trial would be possible.

"If it is true that eteplirsen leads to remarkable clinical benefit in even some patients, there is no doubt that a feasible placebo-controlled clinical study can be designed to demonstrate that benefit," the agency said according to the meeting minutes. "We remain eager to discuss such a possibility."

FDA also proposed a potential placebo-controlled design during the end-of-Phase II meeting that was essentially born out of convenience due to the company's manufacturing capacity. Sarepta indicated during the meeting that upon approval, Exondys 51 initially would only be available in limited quantities.

Sarepta could conduct a lottery to fairly determine which patients receive the drug, FDA said, and "if the details were properly designed, data derived from such a random lottery system could be a de facto randomized clinical trial."

"In the context of this setting ... a placebo-controlled design for the pivotal confirmatory trial would be justifiable," the agency said in the meeting minutes. "It is therefore important to consider potential endpoints based on patient/caregiver reported outcomes."

FDA Raises Concern About Sarepta View Of Approval Path

During a September 2014 pre-NDA meeting, in response to a Sarepta question about post-approval confirmation studies, the agency responded that "a placebo-controlled trial should be initiated immediately" in response to a question about confirmatory studies should accelerated approval be granted.

The agency also said that there were concerns about whether the data it planned to submit showed an effect. "We are concerned about the accuracy of your characterization of the possible approval pathway for eteplirsen that we outlined in the April 2014 letter," the agency wrote, according to the meeting minutes.

"We stated that based on our preliminary assessment of the possible effect size of eteplirsen (and other factors), we did not agree that the 48 week open-label trial that you proposed would be likely to provide a definitive demonstration of the efficacy of eteplirsen. Our more recent assessment of the 144-week efficacy data that are now available from study 201/202 suggests that functional decline may not be distinguishable from historical experience. This has increased our concern that any effect of eteplirsen, if present, may not to be large enough to provide interpretable evidence of efficacy in an open-label study of a design similar to what you have proposed."

During the October 2015 mid-review cycle meeting, Sarepta argued that placebo-controlled trials "of eteplirsen and similar drugs were not feasible because long-term administration of placebo to children through central venous catheters was not ethically acceptable."

FDA corrected the company again, according to the meeting minutes. "FDA clarified that it did not agree that placebo-controlled studies were infeasible and recommended that other types of access devices that did not enter central veins be used," the agency said.

Ruff also said during her presentation that while placebo-controlled trials have served industry well for several decades, it is time to find an alternative pathway to approval for smaller patient populations.

After the approval, FDA officials said that rare disease drug sponsors should strive to conduct randomized controlled trials because they are the quickest way of showing efficacy. The agency also suggested using more caution when interpreting early clinical data, in part because Sarepta's subsequent trials did not reproduce the result. (Also see "[Eteplirsen Review Offers Lessons For FDA, Advocacy Groups, Industry](#)" - Pink Sheet, 21 Sep, 2016.)

Truth Rarely Pure

A disagreement over trial design and conduct often leads to a complete response letter. But Sarepta still managed an accelerated approval for what is now the first FDA-approved treatment for Duchenne.

Ruff's webinar presentation was intended in part to offer Sarepta's viewpoint on what has been an extremely controversial approval. She said looking at the facts of the product's development will illustrate a popular quote from Oscar Wilde: "the truth is rarely pure and never simple."

Ruff said there were questions about whether dystrophin production was a pathway to approval when development began. "There were many unknowns and the knowledge of the disease evolved in parallel with the drug development," she said. "I think the analogy that we often say in the company is we were driving the bus while trying to change the wheels."

Ruff also said FDA gave two options for accelerated approval: changes to six-minute walk test results as an intermediate clinical endpoint or use of dystrophin as a surrogate endpoint.

FDA said in a 2014 memo from acting Division of Neurology Products Director Billy Dunn that the six-minute walk test option likely would "fall short of adequately characterizing the effect of eteplirsen to an extent that would support standard approval." The memo also outlined a number of concerns about the agency's "ability to draw valid conclusions based on the Study 201/202 data with respect to walking performance."

And in using dystrophin as a surrogate endpoint, FDA said in the memo that it remained skeptical about the persuasiveness of source data and images and was concerned about methodological problems.

All of those issues, as well as the conduct of the clinical trials and ultimately whether efficacy had been shown, were identified as concerns in documents prepared for the advisory committee meeting on eteplirsen. (Also see "[Duchenne Muscular Dystrophy: Second Product Isn't The Charm](#)" - Pink Sheet, 15 Jan, 2016.)

The product gained approval after Center for Drug Evaluation and Research Director Janet Woodcock overruled the review division and office directors below her involved in the review. (Also see "[Exondys Approval: FDA Commissioner's Draft Decision Drew Internal Rebuke](#)" - Pink Sheet, 3 Nov, 2016.)

Still, FDA officials said staff have put aside the internal disagreements from the Exondys 51 review. (Also see "[Sarepta's Aftermath: FDA Staff Still Working Together, Califf Says](#)" - Pink Sheet, 16 Nov, 2016.)

In the wake of the approval, Woodcock and other FDA officials have said Exondys 51 should not be a model for drug development going forward. (Also see "[No More Sarepta-Like Development, FDA Officials Say](#)" - Pink Sheet, 20 Oct, 2016.) However, one investor already has said that he has received pitches from drug companies looking to capitalize on it. (Also see "[FDA's Fears Realized: Sponsors Pitching Investors 'Sarepta Model'](#)" - Pink Sheet, 25 Oct, 2016.)

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Sarepta's Aftermath: FDA Staff Still Working Together, Califf Says

- 16 Nov 2016
- Analysis

[Derrick Gingery @dgingery derrick.gingery@informa.com](mailto:derrick.gingery@informa.com)

Executive Summary

US FDA commissioner and others say they have put disagreements from controversial decision to approve Sarepta's Duchenne muscular dystrophy drug behind them.

FDA's controversial approval of [Sarepta Therapeutics Inc.](#)'s Duchenne muscular dystrophy drug *Exondys 51* elicited emotional disagreements among FDA staff, but officials maintain that they have largely been put aside.

The decision's effect on FDA morale has been a frequent question, given the internal conflict that ensued during the review. Multiple senior leaders at the agency said they did not believe the disagreements had long-term effects on the staff.

Commissioner Robert Califf said "we've had very direct discussions of feelings" with staff since the final decision was made. He reiterated that disagreements are allowed, but that the hierarchy at FDA is in place for a reason.

"These people are still working together," Califf said Nov. 4 during the BioPharma Congress, sponsored by Prevision Policy and the Friends of Cancer Research. "They're not adversaries."

FDA reviewers and managers within the Office of New Drugs raised several concerns about whether Exondys 51 (eteplirsen) had shown enough efficacy in clinical trials. Many argued an approval was not appropriate. (Also see "[Exondys 51's Development: Was Placebo-Controlled Trial Possible?](#)" - Pink Sheet, 16 Nov, 2016.)

But Center for Drug Evaluation and Research Director Janet Woodcock overruled them and decided to grant the product accelerated approval for use in Duchenne patients amenable to exon 51 skipping.

Following Woodcock's decision, the staff appealed it to Califf, who ultimately sided with Woodcock, in part because he did not want a political appointee interfering in the drug approval process and because he was not qualified to make the decision. (Also see "[Political Appointees Shouldn't Influence Approval Decisions, Califf Says](#)" - Pink Sheet, 20 Oct, 2016.)

The internal strife was evident based on the memos and other documents released when the approval was announced. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)" - Pink Sheet, 19 Sep, 2016.)

A number of officials questioned Woodcock's reasoning for overruling the review divisions. (Also see "[Woodcock's Consideration of Sarepta Financial Issues Raises Eyebrows](#)" - Pink Sheet, 19 Sep, 2016.)

There also has been close scrutiny and speculation about whether a key reviewer's departure from OND's neurology division was related to the Exondys 51 approval. (Also see "[FDA Neurology Clinical Team Leader Departure May Be Mountain Disguised As Molehill](#)" - Pink Sheet, 15 Sep, 2016.)

Staff Refocused After Controversial Decisions, Jenkins Says

OND Director John Jenkins, who was among those against approving the product, said there was a lot of "passion" about the Exondys 51 science and data. But he also said that he has accepted Woodcock's decision to approve the product.

"Janet and I continue to work together," he said after a presentation at the conference. "We've moved on. That's the way an organization has to work to get the job done. The good news is most decisions are not this controversial."

Jenkins also said that reviewers take their jobs very seriously and that after controversial decisions staff "refocus themselves on why they're there, what the mission is of the agency."

Whether the internal aftermath of the Exondys 51 decision is in fact similar to other controversial decisions like HHS' overrule of FDA's decision to make [Teva Pharmaceutical Industries Ltd.](#)'s *Plan B One-Step* emergency contraceptive available over the counter will be interesting to watch. (Also see "[HHS Overrules FDA On Plan B OTC, Sends Teva Back To Drawing Board](#)" - Pink Sheet, 7 Dec, 2011.)

FDA has indicated that the patient advocacy campaign in favor of Exondys 51's approval at times included unseemly behavior toward agency staff. It is feared that the discourse may drive staff out of the agency as well as make recruiting more difficult. (Also see "[No More Sarepta-Like Development, FDA Officials Say](#)" - Pink Sheet, 20 Oct, 2016.)

Indeed, CDER has hundreds of positions that need to be filled on the executive and rank-and-file levels. (Also see "[Merck R&D Exec Jumps To US FDA As Office Of New Drugs Deputy Director](#)" - Pink Sheet, 8 Nov, 2016.)

Focus On Hearing All Opinions

That may be part of the reason why FDA officials, in describing how it handled the decision internally, focused on agency processes for handling scientific disagreement.

"We want people to speak up when they disagree because you know they could be right," Jenkins said. "When I'm making a decision, I want to hear the perspectives of all the staff because the lonely voice who speaks up very timidly from the back of the room may be right and the thundering herd is wrong."

Richard Pazdur, acting director of FDA's Oncology Center of Excellence, said during the conference that early involvement by senior leadership is important in resolving differences.

"Ultimately I cannot sign off on an application and approve or not approve an application based on something that I don't believe in," he said. "At the end of the day ultimately we as an agency have to sit down and say the following: is the American public ultimately better with this drug or without it?"

Pazdur said he wants his staff to "take a look at the entire field."

"I think the key is communication and sitting down with the review staff and saying what can we do?" he said. "What are your issues versus what is the existing facts at the present time."

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FDA Calls on Pharma Companies to Join Manufacturing Inspection Program

[Posted 15 November 2016](#) By [Zachary Brennan](#)

The US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) on Tuesday announced the launch of the 2017 CDER Office of Pharmaceutical Quality (OPQ) Staff Experiential Learning Site Visit Program, which is meant to help OPQ staff learn more about industry's drug development and manufacturing processes.

The program, which aims to bring groups of OPQ staff to observe operations of commercial manufacturing, pilot plants and pharmaceutical testing over a one- to two-day period, is designed to offer firsthand learning opportunities to improve staffers' understanding of the pharmaceutical industry and its operations, as well as of the challenges that impact drug development.

Focus of Inspections

OPQ has identified a number of areas of particular interest to its staff, including:

- Drug products and active pharmaceutical ingredients
- Solutions, suspensions, emulsions, and semisolids

- Sustained, modified and immediate release formulations
- Drug-device combination products, particularly inhalation, transdermal, iontophoretic, and implant formulations
- Biotech products
- Design, development, manufacturing, and controls
- Engineering controls for aseptic formulations
- Unique delivery technologies
- Hot melt extrusion processes
- Soft-gel encapsulation processes
- Lyophilization processes
- Blow-Fill-Seal and isolators
- Spray-drying processes
- Process analytical technology and real time release testing emerging technologies
- Continuous manufacturing
- 3D printing
- Nanotechnology

Selection of potential facilities for the program will be based on these priorities, FDA says, as well as the facility's current regulatory status with FDA, and based on consultation with FDA district offices.

All travel expenses associated with this program will be the responsibility of OPQ, so selection of the sites that can participate will be based on the availability of funds and resources, and OPQ says it will not provide financial compensation to the sites as part of this program.

The program will allow participating sites to benefit by having an opportunity to showcase their technologies and manufacturing processes.

Volunteers

Companies interested in offering a site visit or learning more about this site visit program should respond by submitting a proposal to Janet Wilson at CDEROPQSiteVisits@fda.hhs.gov.

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FDA Warns Japanese API Maker Over Data Integrity Issues

[Posted 15 November 2016](#) By [Michael Mezher](#)

The US Food and Drug Administration (FDA) on Tuesday released a warning letter sent to Japanese active pharmaceutical ingredient (API) maker Sekisui Medical Co., Ltd. for a series of data integrity issues at the company's Iwate, Japan site.

Data Integrity

Data integrity issues have been a growing concern for regulators in recent years. In 2016, both [FDA](#) and the [European Medicines Agency \(EMA\)](#) released new draft guidance for industry detailing their expectations for data integrity.

Philips, Howard

From: Temple, Robert
Sent: Wednesday, December 14, 2016 11:35 AM
To: Diggs, Felicia; Bastings, Eric
Cc: Unger, Ellis; Dunn, Billy
Subject: RE: 2016-6347- Burgess Drisapersen

Seems OK, but I'm not sure what the duration issue is.

(b) (4)

look at it more in the next two days.

From: Diggs, Felicia
Sent: Wednesday, December 14, 2016 8:40 AM
To: Bastings, Eric
Cc: Unger, Ellis; Temple, Robert; Dunn, Billy
Subject: RE: 2016-6347- Burgess Drisapersen

Good morning,

The Office of Legislation drafted a response to this inquiry. I don't think they were satisfied with only referencing the guidance. I made some revisions to their draft based on previously cleared language. Please see the attached letter and let me know if you have any edits or if you clear no later than COB Friday if possible.

<< File: 2016-6347 Burgess Drisapersen Incoming.pdf >> << File: 2016-6347 Burgess (Priority) Drisapersen.doc >>

Thank you,

Felicia M. Diggs

Consumer Safety Officer

Center for Drug Evaluation & Research
Office of Executive Programs
U.S. Food and Drug Administration
Tel: 240-402-4932
Felicia.diggs@fda.hhs.gov

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From: Bastings, Eric
Sent: Thursday, November 03, 2016 5:38 PM
To: Diggs, Felicia
Cc: Unger, Ellis; Temple, Robert; Dunn, Billy
Subject: RE: 2016-6347- Burgess Drisapersen

Felicia,

It seems the new question relates to trial duration.

You can refer the staffer to the DMD guidance

(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM450229.pdf>), which states that "Drugs that will be chronically administered in dystrophinopathies should be shown to be effective for a period of at least 3 months. For drugs expected to slow functional decline, study length necessarily is affected by rate of progression in addition to predicted drug efficacy. Although studies of 1 year's duration have been conducted in DMD, the duration of studies should be based on scientifically justifiable sample size calculations that include, when appropriate, the predicted rate of functional decline in the placebo group, the anticipated effect size, the variability around these estimates, and the desired statistical power. Efficacy studies of 18 to 24 months' duration may substantially increase statistical power, while only modestly increasing overall development time."

Eric

From: Diggs, Felicia
Sent: Thursday, November 03, 2016 2:59 PM
To: Dunn, Billy; Bastings, Eric
Cc: Unger, Ellis; Temple, Robert
Subject: 2016-6347- Burgess Drisapersen

In the interim of the previous inquiry, we have another inquiry from Congressman Burgess (R-TX) office on behalf of a constituent for the approval process for drisapersen. Please advise on how you would like to respond.

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Philips, Howard

From: Diggs, Felicia
Sent: Wednesday, December 14, 2016 8:40 AM
To: Bastings, Eric
Cc: Unger, Ellis; Temple, Robert; Dunn, Billy
Subject: RE: 2016-6347- Burgess Drisapersen

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Sent: Thursday, November 03, 2016 5:38 PM
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Cc: Unger, Ellis; Temple, Robert; Dunn, Billy
Subject: RE: 2016-6347- Burgess Drisapersen

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Sent: Thursday, November 03, 2016 2:59 PM
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Cc: Unger, Ellis; Temple, Robert
Subject: 2016-6347- Burgess Drisapersen

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Felicia M. Diggs

Consumer Safety Officer

Center for Drug Evaluation & Research
Office of Executive Programs
U.S. Food and Drug Administration
Tel: 240-402-4932
Felicia.diggs@fda.hhs.gov



From: [Alexander, Nicholas](#)
To: [Lexer, Susan](#)
Cc: [Meister, Karen G](#); [Skube, Jonathan](#)
Subject: RE: Drisapersen Question
Date: Friday, October 28, 2016 10:23:32 AM
Attachments: [image001.png](#)
[image003.png](#)
[image005.png](#)

Thanks Susan! Hope you have a magical weekend!!

-- Nick

Nick Alexander, J.D.
Office of Legislation
U.S. Food and Drug Administration
301 796 8893 direct
240 595 4175 mobile

From: Lexer, Susan
Sent: Friday, October 28, 2016 10:23 AM
To: Alexander, Nicholas
Cc: Meister, Karen G; Skube, Jonathan
Subject: Re: Drisapersen Question

Yes. I'll connect with Robert.

Susan

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

From: Alexander, Nicholas
Sent: Thursday, October 27, 2016 3:11 PM
To: Lexer, Susan
Cc: Meister, Karen G
Subject: FW: Drisapersen Question

Are you handling this issue with Sarah out?

-- Nick

Nick Alexander, J.D.
Office of Legislation
U.S. Food and Drug Administration
301 796 8893 direct
240 595 4175 mobile

From: Butora, Robert [<mailto:Robert.Butora@mail.house.gov>]
Sent: Thursday, October 27, 2016 11:01 AM
To: Alexander, Nicholas
Subject: Drisapersen Question

Good morning Nick,

This morning I had a conversation with a constituent regarding Duchene muscular dystrophy drug drisapersen (BioMarin product) which did the FDA advisory council did not vote to approve in November 2015. She expressed quite a bit of frustration over the approval of Sarepta's product while other applicants did not receive similar leniency.

The constituent mentioned a conversation that she had with Dr. Woodcock regarding the evaluation period duration. Dr. Woodcock said that efficacy is evaluated over a 48 week period, however BioMarin allegedly had data to show that the drug was effective at 96 weeks. I was wondering if you have any information that could provide clarity into FDA's evaluation process.

I'm not making any recommendations to my boss on this, just want to understand the process a bit better.

Let me know if you can help or if there is someone else I could reach out to.

Thanks,

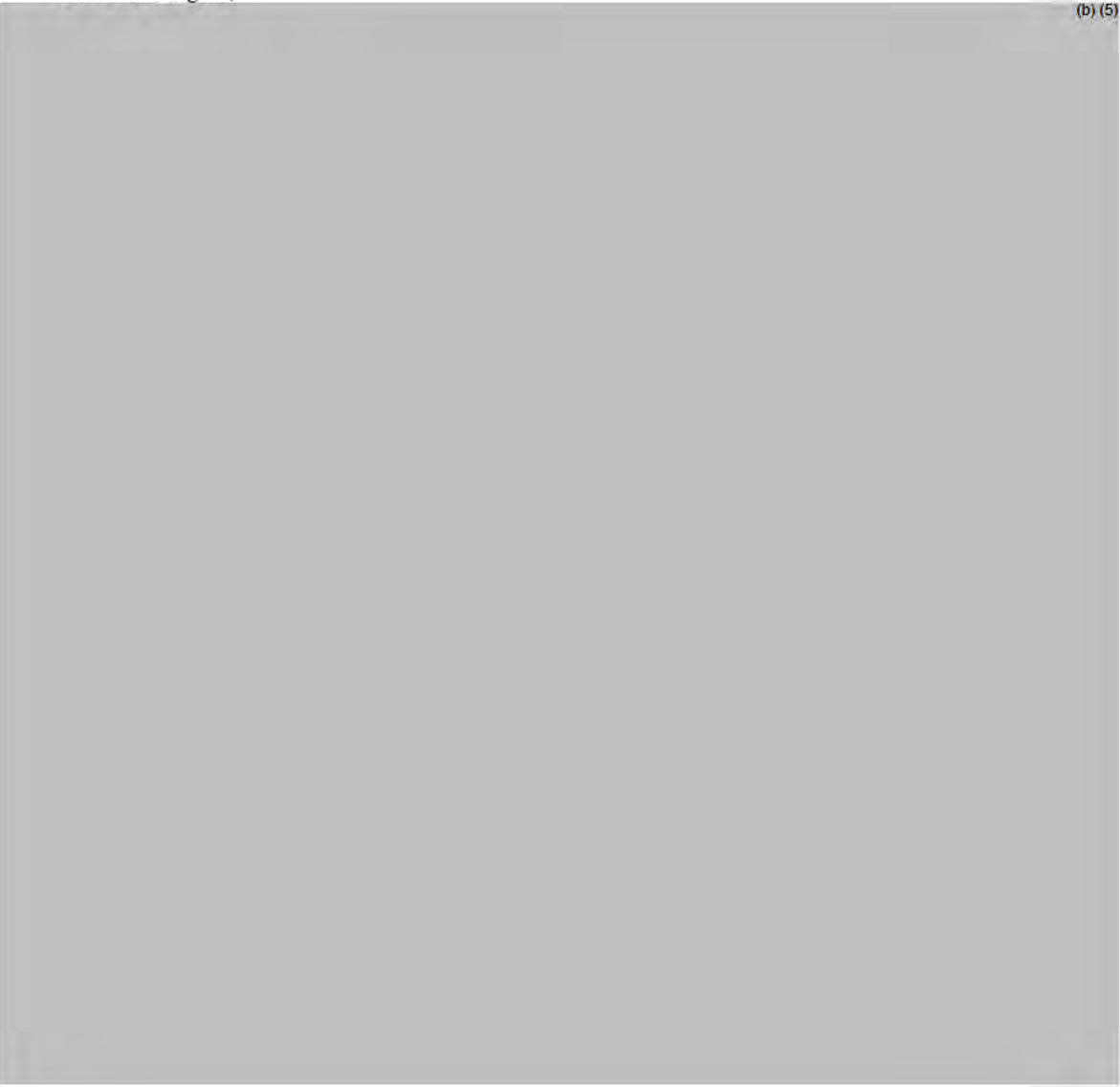
Robert Butora | Health Legislative Assistant
Congressman Michael C. Burgess, M.D. (TX-26)
2336 Rayburn HOB | Washington, DC 20515
(202) 225-7772 | Robert.Butora@mail.house.gov



The Honorable Michael C. Burgess
U.S. House of Representatives
Washington, D.C. 20515-4326

Dear Dr. Burgess,

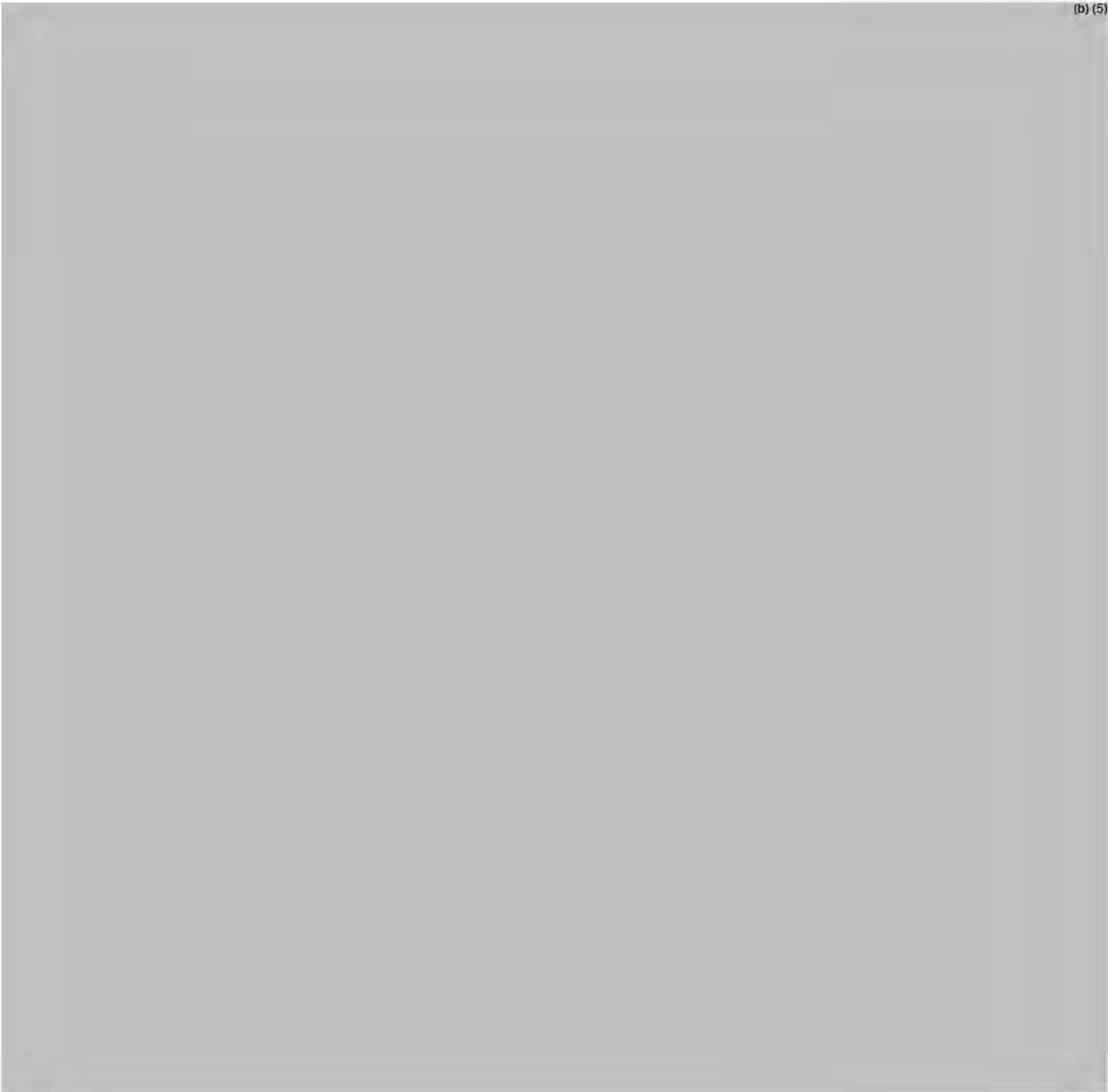
(b) (5)



(b) (5)



(b) (5)



[Redacted]

(b) (5)

Philips, Howard

From: Temple, Robert
Sent: Thursday, December 15, 2016 11:06 AM
To: Diggs, Felicia; Unger, Ellis
Cc: Dunn, Billy; Bastings, Eric
Subject: Re: 2016-6347- Burgess Drisapersen

It should probably also refer to limitations on our ability to discuss non-public aspects of the review.
Sent from my BlackBerry 10 smartphone.

From: Diggs, Felicia
Sent: Wednesday, December 14, 2016 3:24 PM
To: Unger, Ellis
Cc: Temple, Robert; Dunn, Billy; Bastings, Eric
Subject: RE: 2016-6347- Burgess Drisapersen

Good point and catch. I added the following to page two second paragraph. Feel free to edit as necessary.



(b) (5)

Felicia M. Diggs

Consumer Safety Officer

Center for Drug Evaluation & Research
Office of Executive Programs
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Tel: 240-402-4932
Felicia.diggs@fda.hhs.gov



From: Unger, Ellis
Sent: Wednesday, December 14, 2016 1:56 PM
To: Diggs, Felicia
Cc: Temple, Robert; Dunn, Billy; Bastings, Eric
Subject: RE: 2016-6347- Burgess Drisapersen

Assuming that the letter is supposed to address the constituent's concerns expressed in the email from Robert Butora to Nicholas Alexander, there is no text in the letter to address this:

"She expressed quite a bit of frustration over the approval of Sarepta's product while other applicants did not receive similar leniency."

Where is the response to that?

From: Diggs, Felicia
Sent: Wednesday, December 14, 2016 8:40 AM
To: Bastings, Eric
Cc: Unger, Ellis; Temple, Robert; Dunn, Billy
Subject: RE: 2016-6347- Burgess Drisapersen

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Thank you,

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Sent: Thursday, November 03, 2016 5:38 PM
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Subject: RE: 2016-6347- Burgess Drisapersen

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Eric

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Subject: 2016-6347- Burgess Drisapersen

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Temple, Robert

From: Unger, Ellis
Sent: Thursday, December 22, 2016 12:06 PM
To: Temple, Robert; Lowy, Naomi; Borio, Luciana; Jenkins, John K; Stein, Peter
Subject: FW: FDA response to eteplirsen article in Annals of Neurology
Attachments: Unger_et_al-2016-Annals_of_Neurology.pdf; Mendell-2016-Annals_of_Neurology.pdf

[See pdfs. Especially Mendell's!](#)

From: Bergmann, Kenneth
Sent: Thursday, December 22, 2016 8:48 AM
To: CDER-OND-120-MEDOF; CDER-OND-120-CSO; Unger, Ellis
Subject: FDA response to eteplirsen article in Annals of Neurology

Good morning, all

For those of us still following the eteplirsen story, the attached letters electronically published this week by Annals of Neurology are of interest.

It brings to mind something William James, my favorite philosopher, noted, "A difference which makes no difference is no difference at all."

I also think that as we continue to critically evaluate measures of patient experience in clinical trials it is worthwhile to remember another observation of his:

"If merely 'feeling good' could decide, drunkenness would be the supremely valid human experience."

Cheers to that, and Happy Holidays!

Ken

Kenneth J. Bergmann, MD, FAAN
Medical Officer
Division of Neurology Products, OND, CDER
Building 22, Room 4143

Letters to the Editor

[Eteplirsen improves function and partially restores dystrophin](#)

Jerry R. Mendell

Accepted manuscript online: 20 DEC 2016 11:02AM EST | DOI: 10.1002/ana.24843

[Regarding eteplirsen for the treatment of Duchenne muscular dystrophy](#)

Ellis F. Unger and Robert M. Califf

Accepted manuscript online: 20 DEC 2016 11:02AM EST | DOI: 10.1002/ana.24842

Regarding eteplirsen for the treatment of Duchenne muscular dystrophy



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an ‘Accepted Article’, doi: 10.1002/ana.24842

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

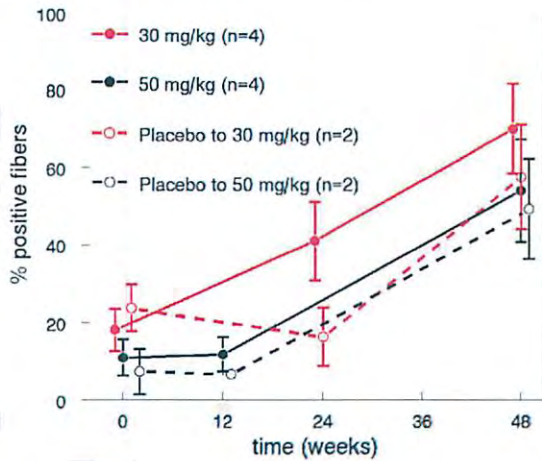
“Although the technician had been blinded to treatment group, access to the treatment code was not protected with the kinds of safeguards and firewalls that one would ordinarily put in place for an adequate and well controlled trial. The immunohistochemistry images were only faintly stained, and had 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.

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.

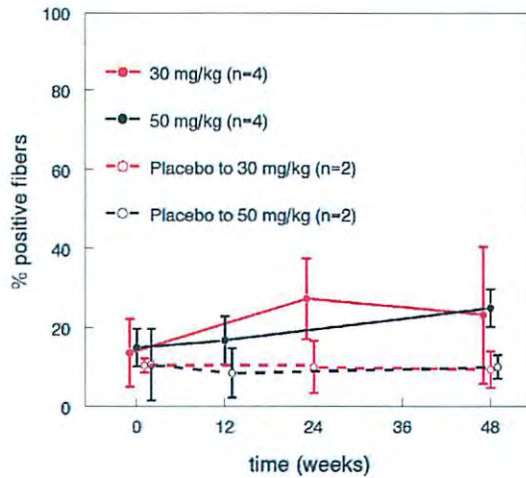
The applicant undertook a blinded re-analysis of the images on the server as FDA suggested. Unfortunately, the re-analyses failed to show a significant increase in dystrophin-positive fiber counts in eteplirsen treated patients (Figure 3). Note also that for patients who switched from placebo to eteplirsen 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.

Original reading at Nationwide Children's Hospital



Blinded re-read by 3 pathologists



The original results were shown in Table 2 of the paper as percent positive fibers; absolute change from baseline, reprinted below:

A Cohort (n)	Week 12 Mean Change from BL, SE (p-value) *	Week 24 Mean Change from BL, SE (p-value) *	Week 48 Mean Change from BL, SE (p-value) †
All Eteplirsén (8)	NA	NA	47.3, 3.89 (≤ 0.001)
Eteplirsén 30mg/kg (4)	ND	22.9, 2.90 (≤ 0.002)	51.7, 3.54 (≤ 0.001)
Eteplirsén 50 mg/kg (4)	0.8, 3.55 (NS)	ND	42.9, 6.72 (≤ 0.008)
Placebo/Delayed Eteplirsén (4) †	-4.0, 2.92	-4.0, 2.92	37.7, 6.30 (≤ 0.009) †
Eteplirsén 30 mg/kg (2)	ND	-7.48, 1.00	33.6, 5.23
Eteplirsén 50 mg/kg (2)	-0.6, 5.16	ND	41.8, 13.30

Based on data received by FDA, the revised and markedly different results from the blinded re-read of 3 pathologists are shown using the same format:

	Week 12 Mean Change from BL (SE)	Week 24 Mean Change from BL (SE)	Week 48 Mean Change from BL (SE)
All Eteplirsén (8)	NA	NA	9.8, 2.38
Eteplirsén 30 mg/kg (4)		13.7, 2.04	9.6, 4.54
Eteplirsén 50 mg/kg (4)	1.8, 3.57	ND	10, 2.41
Placebo - delayed Eteplirsén (4)		-1.2, 1.69	-0.8, 1.96
Eteplirsén 30 mg/kg (2)	ND	-0.4, 3.4	-1, 2.02
Eteplirsén 50 mg/kg (2)	-2.1, 2.05	ND	-0.6, 4.34

Note that the absolute change from baseline originally reported was approximately 50% for all eteplirsen patients, whereas the percent change reported on independent re-analysis is approximately 10%. Many time points and treatment groups were examined here; given that there was no attempt to control the type-I error rate, we did not compute nominal p -values for these results. Importantly, the independent re-analysis did not confirm the results reported in the paper and is much less supportive of the stated conclusions.

Moreover, based on our comparison of the immunohistochemistry images in Figure 3 of the paper and the raw images of all photomicrographs collected from each patient biopsy received in the New Drug Application, the images in the publication appear markedly enhanced and thereby deceptive; certainly, the images in the publication are in no way “representative,” as claimed by the authors.

Finally, we found technical problems with the supportive Western blot analyses reported in the paper. We have yet to post the details of our review on the internet; therefore, we cannot provide any specific comments with respect to the Western blot analyses at this time.

We believe that correcting these findings is important because they have been cited in a manner that overestimates the effect of eteplirsen on dystrophin. Furthermore, as human translational science advances and the time lag between discovery and human clinical trials shortens, we are seeing more critical evidence for new therapies emanating from academic laboratories. Accordingly, the numerous methodological shortcomings should be noted to assist others who may be involved in producing evidence of a quality needed for regulatory submissions.

In summary, the dystrophin-positive muscle fiber counting, as originally performed by the authors, was incorrect. In a blinded re-analysis by 3 readers, the original counts were shown to be markedly inflated, and these incorrect counts provided the basis for the conclusions of the study. In light of the above, we do not believe that the paper in its current form meets the high standards of *Annals of Neurology*.

Sincerely,

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

Robert M. Califf, M.D.
Commissioner
US Food and Drug Administration



Eteplirsen improves function and partially restores dystrophin

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www.NationwideChildrens.org

Jerry R. Mendell, M.D.
Curran-Peters Chair in Research
Professor of Pediatrics and Neurology
Director, Center for Gene Therapy
The Research Institute at
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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 response to the Letter to the Editor authored by Ellis F. Unger, MD, and Robert M. Califf, MD, representatives of the US Food and Drug Administration (FDA). They described feeling compelled to write their letter in an attempt to correct the "dystrophin-positive muscle fiber counting" we reported in the paper "Eteplirsen for the treatment of Duchenne muscular dystrophy," by Jerry R. Mendell, et al., published in the *Annals of Neurology* (*Ann Neurol* 2013; 74:637-647). They "urged that the paper be corrected or retracted" because of unreliable data that were erroneous and misleading. We take issue with their conclusions and stand behind our findings as explained in this rebuttal letter.

First, it is important to point out that the FDA representatives acknowledged that the dystrophin positive fiber analysis in the Mendell 2013 paper was done blindly, by an expert pathologist with the assistance of an experienced staff member trained to routinely assess DMD and Becker muscular dystrophy (BMD) samples. In addition, in the evaluation of specimens, the assessment of dystrophin positive fibers was done without knowledge of trial assignment as to the cohorts: placebo/controlled, 50 mg/kg eteplirsen, and 30 mg/kg eteplirsen. Certainly the blinded analyses done by our group negate any potential accusation that the team at Nationwide Children's Hospital (NCH) intentionally or knowingly misrepresented quantification of dystrophin positive fibers in the biopsy tissue post eteplirsen (Exondys51) treatment.

Secondly, the FDA representatives claim that the repeat analysis of the data, requested by the FDA, reflects the true assessment of the percentage of dystrophin positive fibers present following eteplirsen. Is that conclusion justified given that the recount occurred after a change in the protocol describing the criteria for inclusion of "positive fibers"? In the recount, 3 independent pathologists reported the results using the newly established criteria that excluded any muscle fibers with partial dystrophin staining (borderline positivity), and fibers with membrane staining that touched the borders of the image. The criteria requested by the FDA for the recount were far more stringent but ignored the fact that partial dystrophin fiber positivity is common and in our opinion a more accurate method to quantify dystrophin staining in a study that seeks to accept a milder disease outcome resulting in a BMD phenotype. In fact, the exon skipping hypothesis for this study stated: "Eteplirsen is proposed as a product with the potential

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/ana.24843

to change a DMD phenotype to the milder BMD phenotype" and this is exactly what we have achieved. In a video presentation at the American Society for Gene and Cell Therapy in 2015 and in the FDA advisory meeting for eteplirsen, we presented a fully ambulatory, nearly 16-year-old eteplirsen-treated patient, who all experts in muscle disease would agree represented a BMD phenotype.

It is also important to point out that the FDA has dwelled on differences in percent dystrophin positive fiber counts that they found in our tissue sections using their newly established criteria. While the difference in percentage is not surprising based on the use of new criteria for fiber positivity, looking side-by-side at the counts found by the FDA-imposed method vs the original Mendell 2013 method provides a better perspective on the comparative findings. In Mendell 2013 at week 24, the 30 mg/kg dose resulted in a 22.9% (range 15.9–29.0%) increase in dystrophin-positive fibers from pre-treatment ($p \leq 0.002$) compared to the placebo group. At week 48, both the 30 and 50 mg/kg cohorts showed significant increases ($p \leq 0.001$) in the percentage of dystrophin-positive fibers (mean 47.3%, range 29.8–60.3%). The 4 patients in the placebo/delayed treatment cohort taking 30 mg/kg ($n = 2$) and 50 mg/kg ($n = 2$) of eteplirsen also showed significant increases ($p \leq 0.008$, mean 37.7%, range 28.4–55.1%).

The independent pathologists performing the recount using the more conservative scoring protocol confirmed the increase in dystrophin positive fibers in the treated samples, with a mean of 16.27% increase in the number of dystrophin-positive fibers ($p \leq 0.001$), and a 15 fold increase between the pre-treatment and post-treatment samples. Interestingly, the fold increase of percent dystrophin positive fibers was higher following the rescoring by the independent pathologists, compared to the values originally reported by Mendell et al, 2013, due to the fact that the independent pathologists using the new criteria counted fewer dystrophin-positive fibers in the pre-treatment samples than the original pathologist. While the overall numbers of dystrophin positive fibers, derived from the revised, more conservative protocol were lower than the values originally obtained, the finding that the treated patients had 16.2% dystrophin positive fibers confirmed unequivocally that eteplirsen can restore dystrophin to levels that have been associated with milder phenotypes as in BMD.

In the final analysis looking at the comprehensive picture of the data from the entire 4 year eteplirsen study (dystrophin and functional outcomes) it is clear that exon skipping: 1) reduced the rate of decline in the distance walked on the 6MWT; and 2) prolonged ambulation. In our view, this functional improvement in the rate of decline can only be explained as a result of dystrophin expression, and we do not feel that the data have been misrepresented in any way. In prolonging ambulation we made a deadly disease milder and prolonging ambulation improves the quality of life providing independence in activities of daily living for DMD boys.

The claim by Unger and Califf that the change in the levels of dystrophin may not be sufficient to change the phenotype is at odds with our outcome data, and flies in the face of the experience of expert muscle clinicians who agree that the amount of dystrophin needed to change function is not known. Similarly, the emphasis by Unger and Califf on western blot data is misplaced, because we do not know how this correlates with muscle strength. For example, partially elevated levels of dystrophin expression in just a minority of fibers may potentially produce clinically useful results. Certainly, our clinical outcomes suggest that this is the case for dystrophin.

In summary, we disagree with the implication by Unger and Califf that the data from our study were unreliable, erroneous, or misleading. We stand by our findings and believe that eteplirsen increased dystrophin expression and changed the natural history of DMD.

Sincerely,



Jerry R. Mendell, MD
Curran-Peters Chair of Pediatric Research
Professor of Pediatrics and Neurology
Nationwide Children's Hospital and
The Ohio State University
Director Center for Gene Therapy
Research Institute at Nationwide Children's Hospital
Columbus, OH 43205

Accepted Article

Philips, Howard

From: Unger, Ellis
Sent: Thursday, March 16, 2017 4:11 PM
To: Temple, Robert
Subject: FW: Study of SRP-4045 and SRP-4053 in DMD Patients (ESSENCE) - NCT02500381

FYI – I see you weren't on the list.

From: Woodcock, Janet
Sent: Thursday, March 16, 2017 4:10 PM
To: Nelson, Robert 'Skip'
Cc: Unger, Ellis; Stein, Peter; Dunn, Billy; Bastings, Eric; Breder, Christopher D; Kozauer, Nicholas; Ware, Jacqueline H; Choy, Fannie (Yuet); Soreth, Janice M; McCune, Susan
Subject: RE: Study of SRP-4045 and SRP-4053 in DMD Patients (ESSENCE) - NCT02500381

Thanks for letting me know. The community has raised this issue to me about other trials that are ongoing in DMD. jw

From: Nelson, Robert 'Skip'
Sent: Thursday, March 16, 2017 1:37 PM
To: Woodcock, Janet
Cc: Unger, Ellis; Stein, Peter; Dunn, Billy; Bastings, Eric; Breder, Christopher D; Kozauer, Nicholas; Ware, Jacqueline H; Choy, Fannie (Yuet); Soreth, Janice M; McCune, Susan
Subject: Study of SRP-4045 and SRP-4053 in DMD Patients (ESSENCE) - NCT02500381

Dear Janet,

OPT has received a referral of the protocol “A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy” for federal panel review under 21 CFR 50.54. The referral is from the UCLA Institutional Review Board, asking whether the placement of central venous catheters for study drug administration would be acceptable. As you know, an infusion port could potentially be in place for up to two years, placing the children randomized to placebo at risk absent a prospect of direct benefit from the study drug. The process for handling such a referral is provided in FDA guidance at <https://www.fda.gov/RegulatoryInformation/Guidances/ucm127541.htm>. The Pediatric Advisory Committee (with the Pediatric Ethics Subcommittee) is chartered to review such referrals and to make recommendations that are incorporated into a memorandum from OPT to the FDA Commissioner, who then makes the determination about whether the intervention is allowable under 21 CFR 50, subpart D. The burden of setting up the meeting, including the development of background document(s), falls on OPT and the pediatric ethics program. Of course, we will coordinate closely with the Division of Neurology Products to assure a successful meeting.

FDA has been criticized in the past for a slow response to such referrals. To correct this impression, we already started planning for the meeting when I had heard informally that such a referral was forthcoming. Accordingly, we have reserved the WO Great Room on Thursday May 18 for the meeting, and have already polled our PAC membership on their availability, including appropriate SGE experts from the CDER neurology AC. The DMD patient advocacy community already knows about the referral (but not the date as yet) through the principle investigator at UCLA. I will be working with them, the referring IRB, and the sponsor Sarepta, to assure a productive discussion of the issues at the meeting. As this process is just getting started (the referral arrived last night), there are many details to be worked out.

As this process unfolds, I would welcome the opportunity to brief you and other CDER leadership in further detail. In the meantime, I am happy to answer any questions or concerns. Thanks.

Skip

Robert “Skip” Nelson, M.D., Ph.D.

Deputy Director and Senior Pediatric Ethicist

Office of Pediatric Therapeutics (OPT)

Office of Special Medical Programs (OSMP)

Office of the Commissioner (OC)

U.S. Food and Drug Administration

Tel: 301-796-8665; Mobile: (240) 328-7146; Fax: (301) 847-8619

robert.nelson@fda.hhs.gov

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



Philips, Howard

From: Unger, Ellis
Sent: Wednesday, April 05, 2017 1:12 PM
To: Temple, Robert
Subject: Re: WSJ working on lengthy story on eteplirsen

Thanks! I am not going to let them quote me.

Norman Stockbridge and Julie Beitz are here with me at this meeting. Norm says "of course you knew." Julie said that the involvement was extraordinary and she was surprised. Sandy Walsh was also very surprised.

From: Temple, Robert
Sent: Wednesday, April 5, 2017 12:33 PM
To: Unger, Ellis
Subject: RE: WSJ working on lengthy story on eteplirsen

Well, there are a lot of questions. I think we did know that the parents/patients and the sponsors were in very close touch, but as you say, the review team did not weigh the patient reports very heavily, as they were not supported by the (minimal) controlled trial data, and even the putatively supportive external control was not that impressive when you looked at people close to not walking. Note also that the approval decision was not based on the credibility of the patient reports (or at least as I recall, Janet never argued that these individual reports supported the meaningfulness of the small increase in dystrophin. The AC did not support approval but it did seem that some members probably were influenced by the patient/mother reported individual results. As a general rule, of course, we are not persuaded by individual results that are not clearly impossible in the untreated group (tumor shrinkage, elimination of metastases). Maybe ability to walk in someone who was clearly documented (before the study) as not being able walk could meet that test. Even for [REDACTED] (b) (4)

Before endorsing the quote I would look at what the AC members actually said, esp the ones who supported approval on either clinical or surrogate grounds to see if there are any signs of influence of the patients' reports. Whatever your conclusion you should look at what they actually said. And rember (if I recall it correctly) Janet did not express any influence of those reports.

From: Unger, Ellis
Sent: Wednesday, April 05, 2017 12:08 AM
To: Unger, Ellis
Subject: FW: WSJ working on lengthy story on eteplirsen

I'm also interested in your thoughts on the below.

From: Unger, Ellis
Sent: Wednesday, April 05, 2017 12:03 AM
To: Walsh, Sandy
Subject: WSJ working on lengthy story on eteplirsen

Sandy,

Susan Pullium called me today and left a voice message. She said she had one question, wouldn't quote my answer, etc., and so I returned her call this evening and we talked for some time. The angle of her story seems to be how the company worked extensively with the 12 patients and their families, using them as delegates to help get eteplirsen approved. She had talked with some of the parents, and presumably with Frank Sasinowski. She noted that interactions between the company and the families

were far reaching. Parents were talking with Chris Garabedian (the former CEO of Sarepta) by phone on almost a weekly basis. The company, and specifically Frank Sasinowski, worked extensively with the boys and their parents, crafting a 50-page document for FDA, and putting together other documents and the presentations for the advisory committee meeting. She believes that the company was coaching these boys and their families for years - the entire time they were participating in the study.

She wanted to know if I was aware of this. She was looking for a reaction, and she got one, because she described a level of company involvement that I'd never contemplated. Maybe I had just been naïve, but when she told me all of this, it seemed like news to me and I became quite upset.

So the answer to her question was "no, I wasn't aware." She wanted to know if this knowledge would have affected the review team (I said "no" – they didn't want to approve the drug in the first place) and the AC members (I couldn't say). I told her she could try to contact the AC members, as their contact information is public. I told her she could try to contact members of the review team who had left FDA.

In terms of the way the review played out, she seemed genuinely supportive of the actions I took – fighting for what was right, including my public disagreement with my supervisor.

She wanted a quote, of course, and I told her I'd think about it.

During our discussion, she wrote this, and then emailed to me. I told her I'd think about whether I'd be comfortable with it:

"I wasn't aware of the extent of the company's involvement in interacting with the parents and I'm not sure the advisory committee was aware either. In retrospect, it could have been important."

Truthfully, I doubt that the members of the AC were aware of the company's extensive involvement here.

What do you think of all of this? Would it be unwise to be quoted?

Thanks for your thoughts!

Ellis

From: Walsh, Sandy
Sent: Wednesday, March 08, 2017 3:48 PM
To: Unger, Ellis
Subject: RE: FYI only - WSJ working on lengthy story on eteplirsen

I suspect she might send us a list of questions to address, but we are not planning to do any interviews.

From: Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Date: March 8, 2017 at 3:44:33 PM EST
To: Walsh, Sandy <Sandy.Walsh@fda.hhs.gov>
Subject: RE: FYI only - WSJ working on lengthy story on eteplirsen

Ok, thanks. It sounds like it will come out without any input from here...

From: Walsh, Sandy
Sent: Wednesday, March 08, 2017 3:26 PM
To: Unger, Ellis
Subject: RE: FYI only - WSJ working on lengthy story on eteplirsen

She said it won't come out for a couple of weeks.

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



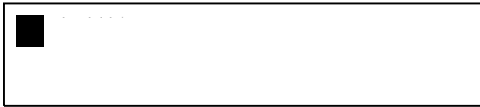
From: Walsh, Sandy
Sent: Wednesday, March 08, 2017 12:57 PM
To: Unger, Ellis
Subject: RE: FYI only - WSJ working on lengthy story on eteplirsen

Not yet, I just emailed her to ask if she's willing to share a status update. Will let you know what I can find out.

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



From: Unger, Ellis
Sent: Wednesday, March 08, 2017 12:52 PM
To: Walsh, Sandy
Subject: RE: FYI only - WSJ working on lengthy story on eteplirsen

Any news on this?

From: Walsh, Sandy
Sent: Wednesday, March 01, 2017 1:10 PM

To: Unger, Ellis
Subject: RE: FYI only - WSJ working on lengthy story on eteplirsen

She seems to be, much better than others.

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



From: Unger, Ellis
Sent: Wednesday, March 01, 2017 1:10 PM
To: Walsh, Sandy
Subject: Re: FYI only - WSJ working on lengthy story on eteplirsen

Thanks! Not that it matters much, but do you know if she is a responsible, competent writer?

From: Walsh, Sandy
Sent: Wednesday, March 1, 2017 11:59 AM
To: Unger, Ellis
Subject: FYI only - WSJ working on lengthy story on eteplirsen

Hi Ellis,

I wanted to make you aware that reporter Susan Pulliam from the Wall Street Journal is doing extensive, deep research on the eteplirsen decision to write a lengthy feature (she said front page). From what I understand she is talking to many people involved, including the company, patients, researchers, etc. She is deeply and carefully going through the FDA's documents, including meeting minutes with Sarepta from years past, emails and memos, the drug review package and appeal documents. She did request an interview with both you and Janet, but as with all other interview requests on eteplirsen, we referred her back to the detailed documents that have been posted. I hope to learn more about her story and the timing soon. I'll keep you posted, I just wanted to let you know she is working on this and we expect her to send a bunch of questions our way at some point.

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



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:

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.

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: 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

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Sent: Sunday, May 22, 2016 2:12 PM
To: Unger, Ellis; Jenkins, John K; Dunn, Billy; Temple, Robert
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high. The proposed message to Serapta 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?

eteplirsen



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TAGS: Clinical Trials | Pediatrics | Rare Diseases

Sarepta Trial Protocol Changes May Ignite Debate On Placebo Design

15 May 2017 | ANALYSIS



by Sue Sutter

@PinkSheetSutter

sue.sutter@informa.com

Executive Summary

US FDA's external advisors will meet May 18 to consider allowing use of central venous access lines in a study of two Duchenne muscular dystrophy drugs. Agency briefing documents show decision-making on placebo-controlled trial design was informed by problems in the clinical development of Exondys 51 (eteplirsen).





US FDA advisory committee deliberations over the potential allowance of central venous access lines in a **Sarepta Therapeutics Inc.** Duchenne muscular dystrophy drug trial could have broader implications for use of placebo-controlled trials and alternative study designs in rare disease populations.

In briefing documents released ahead of a May 18 meeting, FDA poses only one voting question for its Pediatric Advisory Committee and Pediatric Ethics Subcommittee: whether there are circumstances in which an in-dwelling central venous access device should be allowed in Sarepta's ESSENCE trial.

The agency presents a second, non-voting question on the circumstances under which such a central access device should be used. (See box.)

However, the narrow focus of the two questions belies the broader discussion in FDA's briefing documents on the rationale for requiring Sarepta to conduct a placebo-controlled trial – rationale that was based, in part, on the development and regulatory challenges Sarepta and FDA faced with the company's approved DMD drug *Exondys 51* (eteplirsen).

The briefing document's discussion of the pros and cons of alternative study designs in which use of central lines in

Advisory Committee Discussion Question

If version 6 (amendment 5) of the ESSENCE clinical trial (dated April 3, 2017), amended to include the use of an in-dwelling central venous access device, is allowed to proceed, please discuss the following issues:

pediatric patients would be considered ethically acceptable is sure to be an avenue of further exploration by the advisory committee.

UCLA IRB Referral For FDA Review

ESSENCE is a double-blind, placebo-controlled trial evaluating two compounds, SRP-4045 and SRP-4053, in DMD patients with out-of-frame deletion mutations amenable to skipping exon 45 and 53, respectively. Patients who complete the initial 96-week placebo-controlled portion of the study will be eligible to enroll in an open-label extension, during which all participants will receive active study drug. (Also see "Eteplirsen Revisited? FDA Panel To Weigh Protocol Changes For Two Sarepta Drugs" - Pink Sheet, 24 Apr, 2017.)

FDA's Division of Neurology Products cited ethical concerns in recommending against allowing use of central venous catheters for infusion in placebo-treated patients. Consequently, to maintain the study blind, the current protocol uses only a peripheral intravenous line for weekly infusions.

The University of California at Los Angeles' Institutional Review Board requested a change in the protocol to allow for the option of central venous catheter, also known as a portacath. The request was based on the problems experienced by subjects enrolled at the UCLA site, including difficulty placing peripheral intravenous lines and multiple attempts at accessing veins that resulted stress and discomfort.

The UCLA investigator proposed making the portacath an option for study subjects that require three or more attempts at venipuncture access at two consecutive visits, or five or more attempts at a single visit.

Sarepta has revised the protocol to allow for "venous access methods such as midline catheter, central line or portacath" for study treatment administration at the discretion of the site investigator.

(a) Should the choice and timing of placement of a clinically-appropriate central venous access device be left to the discretion of the study site investigator?

(b) Should the protocol include criteria for deciding when an individual study participant has difficulties with peripheral intravenous access (DIVA) such that use of a central venous access device may be appropriate?

(c) If the protocol should include such criteria, what type of criteria ought to be specified (e.g., number of failed attempts at establishing peripheral intravenous access, number of visits where there was difficulty establishing peripheral intravenous access, use of alternative visualization technologies)?

(d) How should the burden of undergoing multiple failed attempts at establishing peripheral intravenous access be taken into account (e.g., anticipatory anxiety, post-traumatic stress)?

Pediatric Study Protections

From FDA's briefing document:

"21 CFR 50, subpart D, the additional safeguards for children in FDA-regulated clinical investigations, restricts IRB approval to interventions and procedures that either present minimal risk (21 CFR 50.51) or a minor increase over minimal risk absent any prospect of direct clinical benefit (21 CFR 50.53), or that provide a sufficient prospect of direct benefit to justify the risks, the balance of which is comparable to the available alternatives (21 CFR 50.52)."

Following a review of the proposed protocol change by the FDA's advisory committees, newly confirmed FDA Commissioner Scott Gottlieb must determine whether the amendment satisfies the additional safeguards for children in FDA-regulated clinical studies and is allowed to move forward. (*See box*)

Although use of a central venous catheter for administration of investigational drug may be approvable under 21 CFR 50.52 because patients have a prospect of direct benefit, "children receiving placebo do not have a prospect of direct benefit, and thus the risks to this group must not exceed a minor increase of minimal risk (21 CFR 50.53) for the IRB to be able to approve the intervention absent" a referral to FDA, the agency's briefing document states.

Pros And Cons Of IV Access Methods

The briefing document reviews the features, advantages and disadvantages of several types of pediatric IV access methods for use in DMD patients, including peripherally inserted central venous catheters (PICC lines), tunneled central venous catheters (CVCs), and totally implantable venous access ports or portacaths.

Portacaths can be maintained for an extended period of time but are more invasive and require general anesthesia for placement and removal. PICCs can be used for up to several months and do not require general anesthesia for placement, but are associated with higher complication rates than implanted ports. CVC also have higher complication rates than PICCs or in-dwelling ports, FDA said.

The agency has previously determined in a placebo-controlled pediatric trial of a monoclonal antibody that midline catheters were approvable as a minor increase over minimal risk. "Midline catheters have a lower risk of infection [than] PICC lines, do not require sedation for placement, and migration of catheter tips is less of a concern," the agency said.

However, "given the anticipated length of study treatment in ESSENCE and lower reported rates of infection, a venous access port may be a better option for DMD patients, since other forms of central venous access and midline catheters may require re-insertion during the course of the study."

Eteplirsen Development Pitfalls To Avoid

Consideration of whether central venous access methods should be permitted in ESSENCE includes other factors, including the rationale for a placebo-controlled trial design, the briefing document state. The agency notes it has been highly flexible in interpreting the statutory requirements for efficacy in the context of rare diseases, and it discusses alternatives to the traditional placebo-controlled trial design in the setting of DMD.

"Elimination of the placebo arm and/or blinding to treatment assignment so that it was known which boys were on placebo would allow the use of a PICC line, CVC or venous access port under 21 CFR 50.52 for those boys receiving active product," the documents state. "Other than a placebo control, the other options for the study of SRP-4045 and SRP-4053 include: an external (historical) control; an active-comparator control; a dose-ranging control; and no treatment control."

In highlighting the limitations with each of these trial designs, the agency harkens back to the missteps in the development program for eteplirsen. Center for Drug Evaluation and Research Director Janet Woodcock granted eteplirsen accelerated approval in September 2016 despite strong opposition from reviewers and other senior staff who questioned the adequacy of the efficacy evidence. (Also see "Sarepta's Eteplirsen Approved After Contentious Internal FDA Debate" - Pink Sheet, 19 Sep, 2016.)

In the eteplirsen studies, "use of an external control was problematic, because it was difficult to ensure that patients used for comparison had similar characteristics, similar disease severity and had received similar treatments." – FDA's briefing document

Use of a nonconcurrent external or historical control design increases the chance of selection bias because the population chosen for comparison may not be representative of the study treatment group, FDA said. "For studies submitted to support approval of eteplirsen, use of an external control was problematic, because it was difficult to ensure that patients used for comparison had similar characteristics, similar disease severity and had received similar treatments." (Also see "Duchenne Muscular Dystrophy: Second Product Isn't The Charm" - Pink Sheet, 15 Jan, 2016.)

The briefing document also reiterates a concern frequently voiced by FDA reviewers: that study subjects may be more motivated to complete functional outcomes, such as the six-minute walk test, when they know they are on active drug.

There is no active treatment against which a comparison of SRP-4045 and SRP-4053 "would be appropriate," the document states, noting that all subjects enrolled in ESSENCE are required to be on corticosteroids.

Using a different dose or regimen of the study treatment as a concurrent control also can be problematic because if the doses chosen are too high, too low or too close together, efficacy will not be established because all doses will appear equivalent.

"For eteplirsen, no difference in the dose-response for the amount of dystrophin produced between a 30 mg/kg and 50 mg/kg weekly dose was seen in the conducted studies at Week 180, which suggests that this approach may not be successful for other exons," the agency said.

During the eteplirsen review, FDA staff repeatedly raised concerns that Sarepta had failed to explore a high enough dose. The company must conduct a randomized, placebo-controlled trial of the approved eteplirsen dose and one that provides significantly higher exposure level as a confirmatory, postmarketing study. (Also see "Eteplirsen Review Offers Lessons For FDA, Advocacy Groups, Industry" - Pink Sheet, 21 Sep, 2016.)

Awaiting Validation Of Dystrophin As A Reliable Surrogate

The briefing document suggests that using no treatment as a concurrent control presents the risk of bias in functional outcome assessments given the lack of randomization and blinding.

“Until the use of dystrophin levels has been established as a validated surrogate biomarker for meaningful clinical changes in motor function (such as 6MWT), it is not clear how the bias introduced by the lack of blinding and randomization would be reduced to the point of being able to draw meaningful conclusion from short-term clinical trials (ie, $\leq$ two years in duration).”

However, the agency sees hope for more streamlined development programs in other DMD populations if and when dystrophin is validated as a biomarker in a “strong study design” such as the ESSENCE trial. “Once dystrophin has been established as a surrogate marker, such studies may not require randomization to different treatment arms or blinding of treatment assignment.”

Preventing Dropouts

Trial compliance issues also are likely to be a topic of advisory committee discussion.

The briefing document notes that Sarepta, in originally proposing a venous access port option for the ESSENCE protocol, asserted that not allowing such a measure could undermine the study’s feasibility because patients who can no longer maintain peripheral venous access would have to drop out.

Sarepta told FDA that in its DMD clinical trial experience, more than half of study participants had a port placed for infusions, and approximately 40% of these ports were due to loss of peripheral access during the course of study.

Sarepta CEO and President Edward Kaye similarly highlighted these concerns during the company’s recent quarterly earnings call.

“One of the problems we had is that the FDA had made us put in a provision that the use of essential intravenous ports could not be allowed,” Kaye said of the ESSENCE trial. “The families and the patients objected to this because it was really a hardship for them and it was adding an enormous amount of stress on the boys having to try to find intravenous access in some of these boys every week.”

Allowing the use of ports would be advantageous because Sarepta “will have much better compliance during the trial,” Kaye said. The advisory committee review “is actually a really good thing for us, and we’re very pleased that the FDA Pediatric Advisory Committee took this question up.”

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Sarepta's ESSENCE Trial Gets FDA Panel Nod For Protocol Changes

18 May 2017 | NEWS



by Sue Sutter

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Executive Summary

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The US FDA's external advisors gave a thumbs up to allowing use of in-dwelling ports in a **Sarepta Therapeutics Inc.** Duchenne muscular dystrophy study, endorsing the trial's placebo-controlled design in the process.

At a May 18 meeting, the Pediatric Advisory Committee and Pediatric Ethics Subcommittee unanimously concluded there are circumstances in which an in-dwelling central venous access device should be allowed for patients in the ESSENCE trial.

The ultimate decision on whether the ESSENCE protocol should be amended rests with newly installed FDA Commissioner Scott Gottlieb.

ESSENCE is a 96-week, double-blind, placebo-controlled study of two compounds, SRP-4045 and SRP-4053, in DMD patients with out-of-frame deletion mutations amenable to skipping exon 45 and 53, respectively. The current protocol allows only for use of a peripheral intravenous line for weekly infusions.

Sarepta, at the request of a study site institutional review board (IRB), has proposed amending the protocol to allow additional types of venous access methods. The amendment is intended to address difficulties in gaining peripheral intravenous access in DMD patients that has resulted in some boys enduring numerous painful and stressful needle sticks for every weekly infusion. (*See box.*)

"I believe if you're going to be requiring 96 weeks of weekly infusions, the standard of care is the offer of an in-dwelling venous access device, and so to withhold that offer from patients and families I think is cruel and unusual punishment," Steven Joffe, a pediatric medical ethicist at the University of Pennsylvania, said in explaining his vote.

Sarah Hoehn, a pediatrician at University of Kansas, said she voted yes "from the palliative care perspective, which is minimizing suffering and [maintaining] quality of life and respecting the families that they know best in terms of what their child needs."

"For a rare disease that is progressive and with a ... medication that does not have any other alternatives ... this is a no brainer," said Wael Sayej, a pediatric gastroenterologist at the University of Connecticut.

No Restrictions On Device Or Timing

Committee members said the choice of whether to use a central venous access device should be left to the discretion of the study site investigator, in consultation with the family, patient and surgeon. While panelists favored an in-dwelling port, also known as a portacath, they believed the protocol should allow for the possible use of other types of devices.

They also declined to attach specific criteria to which patients should receive ports or when. While the optimal time for insertion would be at the baseline muscle biopsy, which like port insertion also requires general anesthesia, they left the door open for insertion at a later time period, such as when study subjects begin to experience difficulties with peripheral venous access.

FDA's Office of Pediatric Therapeutics will take the panelists' input into consideration in drafting a recommendation that will be forwarded to newly installed FDA Commissioner Scott Gottlieb, who must make the final determination as to whether the amendment satisfies the additional safeguards for children in FDA-regulated clinical studies and is allowed to move forward. (Also see "Sarepta Trial Protocol Changes May Ignite Debate On Placebo Design" - Pink Sheet, 15 May, 2017.)

Investigator, Patient And Family Testimony

The ESSENCE study protocol amendment came before the agency's advisory committees through the infrequently used IRB referral process. (Also see "Eteplirsen Revisited? FDA Panel To Weigh Protocol Changes For Two Sarepta Drugs" - Pink Sheet, 24 Apr, 2017.)

When FDA reviewed the original protocol in 2015, the study plan allowed for use of a venous access port at the investigator's discretion. However, the agency concluded that implantation of a port in a patient randomized to the placebo arm exceeded a

Sarepta's Proposed Protocol Amendment

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minor increase over minimal risk, offered no prospect of direct benefit and, therefore, was not approvable under federal regulations governing safeguards for children.

However, the University of California at Los Angeles' Medical Institutional Review Board requested a protocol change based upon problems experienced by all five subjects enrolled in ESSENCE at the UCLA site.

Advisory Committee Vote

Are there circumstances in which an in-dwelling central venous access device should be allowed in the ESSENCE clinical trial? Y - 14, N - 0

UCLA investigator and neurologist Perry Shieh presented the committee with what he said was an alternative view of the risk/benefit analysis for use of ports in ESSENCE. He noted that the study's 96-week, double-blind period is followed by a 96-week, open-label period in which all study participants, including those originally randomized to placebo, will receive one of Sarepta's investigational agents.

"If you want to talk about the prospect of benefit of this new investigational product, it's perceived that the opportunity to participate even in the open-label extension is an important one," Shieh said.

In addition, the risks of the port lie mostly with the surgical procedure, he said. "We're talking about a fixed amount of risk with different, varying levels of benefit."

The panel heard from DMD patient Nicholas Bullers and his family, who raised the original complaint about the ESSENCE protocol to the UCLA IRB. The family showed a video of Nicholas screaming as a nurse tried at length to find a vein in his arm during one of his weekly infusions.

The committees also heard heart-rending testimony from other patients and families involved in the ESSENCE study, as well as those who participated in studies for Sarepta's approved exon 51-skipping drug *Exondys 51* (eteplirsen), about the difficulties they experienced with peripheral venous access and the resulting anguish from multiple needle sticks.

IRB Worried About Stress, Dropouts

James McGough, chair of the UCLA IRB, said that only after patients in ESSENCE started receiving infusions did it become apparent to the board that "multiple difficult sticks in these really at-risk children who are difficult to get blood from really was a burden that was perhaps not fully considered when we initially discussed it."

The IRB was concerned about the potential for weekly trauma and undue psychological risks over the course of the study, and the potential risk of iatrogenic post-traumatic stress disorder, which is a particular concern in DMD patients who will require increased medical care over their lifetimes.

“The risk for drop out or early termination is, I think, a real one.” – UCLA's McGough

Study dropout concerns also factored into the IRB's decision to refer the matter for FDA review.

“The risk for drop out or early termination is, I think, a real one,” McGough said. “Ninety-six weeks is a long time. And, of course, if participants drop out that's going to undermine the validity of the whole study, and then all the risk that everyone has shared in really could become a moot point if there's a lot of dropouts.”

Satisfied With Placebo Design

Early in the meeting, some advisory committee members questioned the need for a placebo control and the two-year duration of the double-blind period.

Shieh explained that this design was deemed necessary because the primary outcome is a functional assessment, the six-minute walk test, that can be influenced by knowledge of treatment assignment.

In response to committee members' questions about the possible use of dystrophin production as a primary endpoint, Robert “Skip” Nelson, deputy director and senior pediatric ethicist in FDA's Office of Pediatric Therapeutics, explained that dystrophin production as a biomarker for clinical benefit in DMD has not yet been sufficiently validated. “Dystrophin production is a promising, but not proven, biomarker,” Nelson said.

Eteplirsen, Sarepta's exon 51-skipping drug, received accelerated approval in September after Center for Drug Evaluation and Research Director Janet Woodcock concluded the small increase in dystrophin seen in trials was reasonably likely to predict clinical benefit. However, this decision proved highly controversial within FDA, and Sarepta must confirm the clinical benefit in postmarketing studies. (Also see “Sarepta's Eteplirsen Approved After Contentious Internal FDA Debate” - Pink Sheet, 19 Sep, 2016.)

Learnings from the eteplirsen experience heavily influenced the design of ESSENCE, which Sarepta said is the first long-term, placebo-controlled study in DMD.

“I fully accepted and endorse the need for a placebo-controlled trial.” – U-Penn's Joffe

“The reason for the lengthy placebo-controlled period is based on our experience with eteplirsen in which especially on the six-minute walk test as a clinical outcome, it took time for dystrophin to be made and then for that to translate into a clinical effect,” said Genevieve Laforet, Sarepta's medical director for the ESSENCE study. “If you're looking at a clinical endpoint like a six-minute walk test, we know from existing data that it's going to take two years.”

By the meeting's end, several panelists said they not only understood why the two-year, double-blind, placebo control was recommended by FDA, they also supported the design.

"I tried to argue my way into the reason behind this being a placebo-controlled trial to come up with some way we could do it without using placebo to obviate the need for a central line in the placebo group, and I can't," said Michael White, a pediatric cardiologist at Ochsner Health System. "I think you presented good enough data to support the idea that this can only be done as a

placebo-controlled trial."

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resistant pathogens that could pose a serious threat to public health. The bill has been referred to the House Ways and Means Committee.

Shimkus said more incentives are needed because the government is asking drug companies to develop and be prepared to deploy treatments only based on the chance they may be needed.

"That's kind of the business debate," he said. "In this case they have to be able to respond quickly and prepare something and have something on the shelf that we hope we never have to use."

The Research to Accelerate Cures and Equity (RACE) for Children Act, [HR 1231](#), a bill that would mandate pediatric studies in oncology based on the drug's molecular target, also garnered some attention during the mark-up, but was not offered as an amendment.

There still appears to be stakeholder pressure to include it, however. The American Academy of Pediatrics said it was not happy the user fee bill did not include it.

"The bill passed today misses critical opportunities to ensure that all drugs used in children are studied in children, to advance appropriate and safe medical devices available for children, and to strengthen FDA's pediatric expertise," AAP President Fernando Stein said in a statement.

The Senate version of the user fee bill calls for guidance on pediatric studies for molecularly targeted cancer drugs, but does not mandate them. It also requires earlier planning of pediatric trials. (Also see "[Pediatric Study Timelines Could Change Under Senate PDUFA Bill](#)" - Pink Sheet, 8 May, 2017.)

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News

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Executive Summary

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But industry has said the agency could have done more with the guidances (*see box*). (Also see "[Off-Label Wish List: Industry Groups Want US FDA's Guidances To Do More](#)" - Pink Sheet, 8 Mar, 2017.) New FDA Commissioner Scott Gottlieb also has said the agency should allow more off-label discussion. (Also see "[Gottlieb Q&A: Off-Label Communications And Right-To-Try](#)" - Pink Sheet, 2 May, 2017.)

Because the issue is controversial, it could slow the user fee bill if changes were attached, which may be why the off-label focused bills were not included among the four amendments the subcommittee added.

The prescription drug, generic drug, medical device and biosimilar user fee programs will expire Oct. 1 if not renewed. Leaders in the House and Senate want the user fee bill completed and sent to the White House by the end of July to avoid forcing FDA to notify employees they could be laid off if the package is not enacted.

Off-label issues could emerge again if the House conducts a hearing on drug pricing, as has been promised in the Senate. (Also see "[User Fee Bill Caught In Comey Firing Tidal Wave](#)" - Pink Sheet, 10 May, 2017.)

So far, though, both chambers have mostly focused on speeding generic approvals as the key to reducing Rx prices. (*See sidebar for related story.*)

Off-Label Bills Seek To End Judicial Policymaking

Griffith's bill, [HR 1703](#), states that a drug's intended use shall not be determined by reference to "actual or constructive knowledge of the manufacturer or sponsor" that the product "will be used in a manner that varies from the use approved for marketing," or to scientific exchange of sound data or studies, according to the bill text.

Griffith said during the mark-up that manufacturers need to be able to talk about data not included in the label when appropriate.

"The judiciary branch has become the defacto policy makers due to our inaction," he said. "I would argue that federal judges and their clerks have a less nuanced understanding and appreciation for the FDA approval process than does this committee. Congress needs to step up to the plate and responsibly set the rules of the road before it's too late."

Rep. Brett Guthrie, R-Ky., discussed a bill, [HR 2026](#), which states that "health care economic information or scientific information provided to a payor, formulary committee, or other similar entity ... shall not be considered false or misleading or any other form of misbranding" if based on "competent and reliable scientific evidence" and relates to an investigational new drug or investigational use of an approved drug, according to the bill text.

The bill states that to receive the exemption, the use must have been submitted for approval in an application supplement or the studies must have been completed and intended to be submitted in a supplement for approval of the use.

Walden praised that bill as well, saying that Congress should move forward with the changes.

Antibiotics, Pediatric Cancer Bills Still Could Be Attached

Rep. John Shimkus, R-Ill., said he was hopeful to gain support for incentives to develop new antibiotics that treat highly resistant infections when the bill reaches the full Energy and Commerce Committee.

Shimkus is a co-sponsor of the Reinvigorating Antibiotic and Diagnostic Innovation Act, [HR 1840](#), which would allow tax credits for 50% of clinical testing expenses for some infectious disease products, including those intended to fight

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Manufacturer Communications: Industry Seeks Single Evidentiary Standard

- 18 May 2017
- Analysis

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Executive Summary

'Competent and reliable scientific evidence' standard for payer communications also should apply to medical product communications that are consistent with labeling, manufacturers say in comments on US FDA draft guidance documents.

Biopharma companies want FDA to apply a single evidentiary standard to two types of drug manufacturer communications.

In comments on two agency draft guidances, industry groups and individual companies urge FDA to harmonize its evidentiary standards for medical product communications that are consistent with approved labeling, and communications with payers and formulary committees.

The "scientifically appropriate and statistically sound" standard is a new one "not otherwise defined by statute, in case law or in other regulatory constructs." – PhRMA

In the two guidances issued in mid-January, FDA proposed "highly related but slightly divergent standards" for each type of communication without articulating a good reason for doing so, [AbbVie Inc.'s comments](#) state.

Industry commenters urge FDA to take the statutory standard of "competent and reliable scientific evidence" applicable to payer communications and apply it to medical product communications consistent with labeling.

Manufacturers also seek greater harmonization in the scope of communications covered by the two guidance documents and FDA reassurance that scientific exchange will not be considered drug promotion under the medical product communications guidance.

'Competent and Reliable Scientific Evidence' ...

The payer guidance describes what types of healthcare economic information (HCEI) manufacturers may share with payers, formularies and related entities for approved drugs under Section 114 of the FDA Modernization Act of 1997 and the 21st Century Cures Act, which was signed into law in December. (Also see "[Industry Communications With Payors: US FDA Okays Info On Investigational Drugs](#)" - Pink Sheet, 19 Jan, 2017.)

The guidance also discusses the types of information that manufacturers may share with payers about investigational drugs, although it does not address communications about unapproved uses of approved drugs. (*See sidebar for story.*)

Under the statute, HCEI shall not be considered false or misleading if it is "related to" to an approved indication and is based on "competent and reliable scientific evidence" (CARSE).

FDA considers HCEI to be based on CARSE if the information "has been developed using generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results," the draft guidance states.

In determining whether the evidence meets generally accepted scientific standards, FDA will consider the merits of current good research practices for substantiation developed by authoritative bodies. "When evaluating HCEI based on indirect treatment comparisons in the absence of data from head-to-head controlled clinical trials, FDA may refer to guidelines issued by external expert bodies regarding current rigorous methodologies and best practices for such comparisons," the guidance states.

... Vs. 'Scientifically Appropriate And Statistically Sound'

Temple, Robert

From: Unger, Ellis
Sent: Thursday, May 18, 2017 11:17 AM
To: Temple, Robert; Lowy, Naomi; Locicero, Colleen L; Bastings, Eric; Dunn, Billy; Kozauer, Nicholas
Subject: FW: story is out: How the FDA Approved a \$300,000-a-Year Drug Its Own Experts Didn't Believe Worked

FYI

From: Walsh, Sandy
Sent: Thursday, May 18, 2017 10:50 AM
To: Unger, Ellis
Subject: RE: story is out: How the FDA Approved a \$300,000-a-Year Drug Its Own Experts Didn't Believe Worked

How the FDA Approved a \$300,000-a-Year Drug Its Own Experts Didn't Believe Worked

After trial data for a new medicine proved inconclusive, Sarepta Therapeutics joined with the parents of sick boys to persuade officials it helped

By Susan Pulliam and Brody Mullins

Jennifer McNary, a stay-at-home mother, was desperate to find a medicine that might spare her two sons an early death from a rare form of muscular dystrophy.

Chris Garabedian, the chief executive of a pharmaceutical firm, was desperate to find a profitable drug that would reverse his company's slow fall.

They met in June 2012 at a conference on Duchenne muscular dystrophy and joined forces, often behind the scenes and with little public disclosure, in a yearslong mission to push the government to approve a drug to treat DMD, as it is known.

At the time, it wasn't at all clear the firm's drug worked. Faced with government skepticism, a consultant to Mr. Garabedian's company helped Ms. McNary and other parents prepare slickly packaged testimony to convince the Food and Drug Administration that the drug was helping their sick children, according to parents, company managers and the consultant.



Jennifer McNary and her sons Max, left, and Austin during the fall of 2015 in Pembroke, Mass. Photo: Kayana Szymczak

The company, [Sarepta Therapeutics](#) Inc., leveraged the emotional appeal of the parents' stories. Without that, the drug—eteplirsen—likely wouldn't have been approved, said stock analysts, investors and people close to the matter.

An FDA advisory committee voted 7-6 last year to oppose the drug's approval, a position later overruled. The Wall Street Journal found that a majority didn't know how Sarepta's consultant had guided the patients' families.

"More might have voted no if they were aware," said Dr. Bruce Ovbiagele, a committee member, when he learned the role the company consultant played in helping parents prepare for FDA hearings.

Relationships between companies and advocacy groups are important to know about, said Dr. G. Caleb Alexander, co-director of the Johns Hopkins Center for Drug Safety and Effectiveness, who served as chairman of the FDA's advisory committee. "The advisory committee received little information about how that played out in the development of eteplirsen."

Companies that need Washington have turned to new, often untraceable tools—including hidden involvement with grass-roots organizations—to lobby decision makers and help sway public opinion. Many of these emerging tactics fall outside the government's longstanding definition of lobbying and remain masked to both officials and the public, making it hard to know how companies are interacting with the people charged with running the country.

Eteplirsen's drug application coincided with a shift at the FDA to give a larger role to patient families and advocacy groups. The change helped propel the drug-campaign effort by Sarepta and parents.

“The FDA’s regulatory decision-making on medical products is science-based and involves the careful evaluation of risks and benefits for the drug at issue and is informed by science, medicine, policy and judgment,” an agency spokeswoman said.

This account of the drug’s FDA application is based on interviews with parents, company officials, investors and current and former FDA officials.

When Ms. McNary first talked with Mr. Garabedian in 2012, his company was approaching the one-year mark in a clinical trial of eteplirsen.

DMD, a genetic disorder that targets boys, is usually diagnosed around kindergarten. It saps muscle strength and by adolescence leaves many of its victims in wheelchairs. Boys with DMD lack the protein dystrophin, which is critical to muscle function. In time, their hearts and respiratory systems stop working. Few survive past their 20s.

Researchers believed eteplirsen could help patients produce enough of the missing protein to slow DMD’s progression.

“This drug works,” Ms. McNary said, introducing herself to Mr. Garabedian at the DMD conference. Her youngest son, Max, 10 years old at the time, was one of a dozen boys enrolled in the eteplirsen drug trial at the Nationwide Children’s Hospital in Columbus, Ohio. After four months on the drug, she said, Max could open a milk carton and needed a wheelchair less often.

Ms. McNary turned out to be the cheerleader Mr. Garabedian needed. His company had just been warned by the [Nasdaq Stock Market](#) that its share listing might be dropped from the exchange for trading below \$1.

Mr. Garabedian told the Journal his company was having trouble raising money after it had spent \$30 million on eteplirsen in the 18 months since he had joined as CEO.



Doses of the drug eteplirsen to treat Duchenne muscular dystrophy. Photo: Adam Glanzman for The Wall Street Journal

Before eteplirsen would be available to the 1,000 or more sick boys who might benefit in the U.S.—and before the company could charge patients more than \$300,000 a year for the treatment—the drug needed FDA approval.

Looking back, Catherine Collins, whose son has DMD, said, “Sarepta used the parents to push their regulatory agenda,” she said. “We were willing participants, but they were trading on our desperation.”

Edward Kaye, Sarepta’s chief executive since 2015, said the company was “able to make a true partnership” with DMD patient groups, helping parents give the FDA firsthand observations of how the drug had worked for their sons.

Former FDA Commissioner Robert Califf, who stepped down in January, said the Sarepta case was “an example where things should have been done better... There should be disclosure of the source of documents and presentations, and who was involved.”

Hopeful shortcut

Mr. Garabedian and Dr. Kaye, the company’s chief medical officer at the time, revealed at the 2012 conference early data from the drug trial that suggested eteplirsen was working.

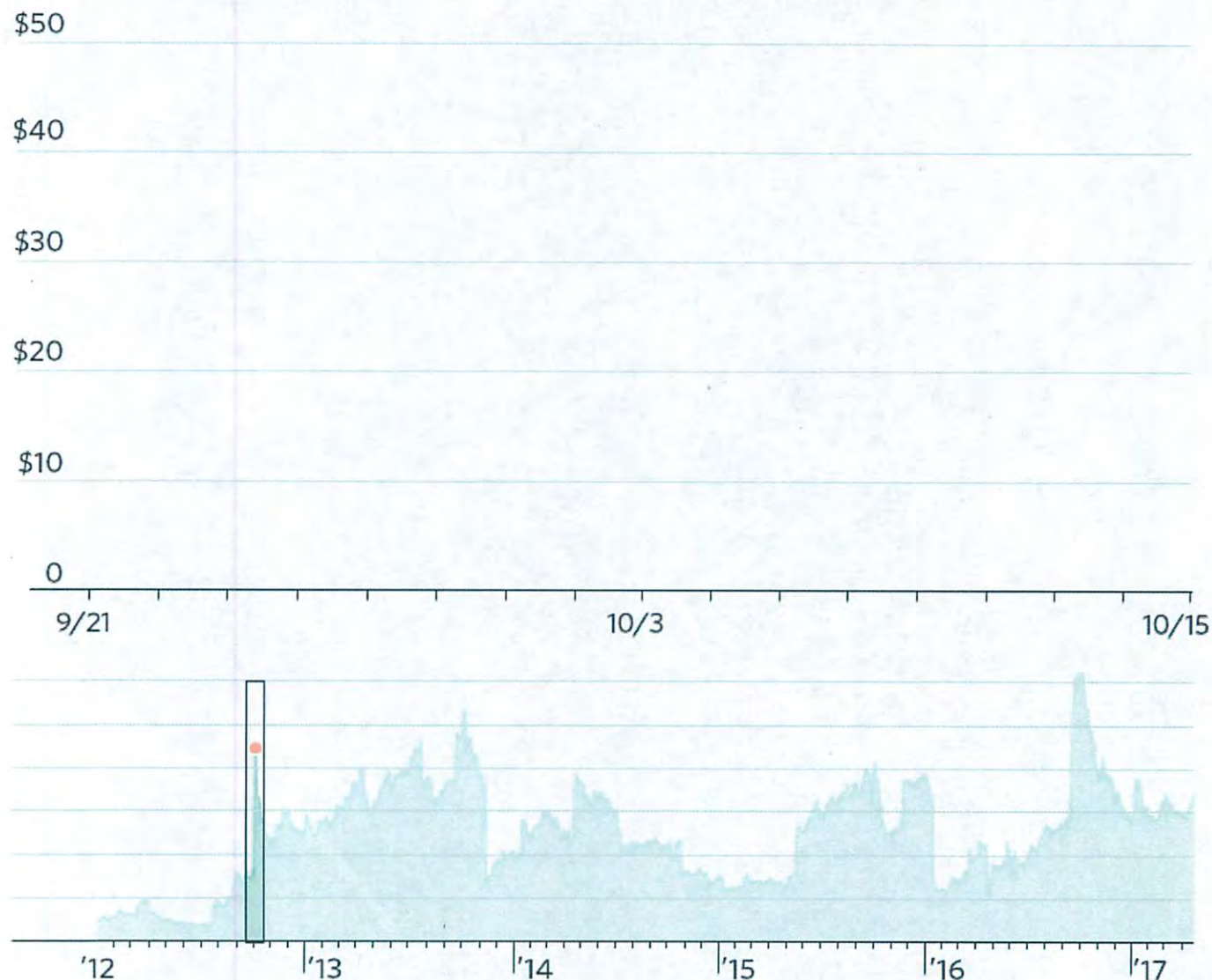
With the stock trading below \$1, Mr. Garabedian didn’t have the luxury of waiting to spread encouraging news. Trial researchers were measuring levels of the protein dystrophin in the patients, all boys, and how far they could walk in six minutes.

Dr. Kaye said it appeared the drug helped lift dystrophin levels. Even better, 10 of the 12 boys in the trial walked, on average, more than 50 feet farther during the timed walk, he said; two boys became unable to walk.

Two weeks after the conference, the company made a 1-for-6 stock split, which raised its share price and allowed it to keep its Nasdaq listing. It also changed its name to Sarepta from AVI BioPharma Inc.

Oct. 3, 2012

Sarepta shares reach nearly \$45 after the company issues positive drug trial results.



The company in a July 24 news release said the boys showed “significant clinical benefit” after 36 weeks of treatment. Shares jumped past \$8. Another positive news release at the 48-week mark pushed the stock close to \$45.

Even with the promising news, Mr. Garabedian’s company had concerns about whether it could raise enough money to support third- and fourth-phase drug trials, which must show drugs work effectively and safely. Parents, meanwhile, were clamoring for a treatment.

One shortcut was accelerated approval—that’s when the FDA gives permission to dispense a drug before proving a clinical benefit. It allows patients a quicker chance at treatment for maladies that have none, such as DMD. Sarepta’s application would rely on trial data showing that eteplirsen would be “reasonably likely” to produce a clinical benefit, rather than proving it was effective.

That fall, Mr. Garabedian met Christine McSherry, a former nurse of Pembroke, Mass., whose son, Jett, now 21, had been diagnosed with DMD on his fifth birthday. Ms. McSherry said she was so upset at the news she briefly considered killing herself and her son. Instead, she became an advocate for treatment. She began speaking regularly with Mr. Garabedian and other Sarepta managers to learn about the FDA's regulatory machinery.



Christine McSherry helps her son, Jett, who suffers from Duchenne muscular dystrophy, at their home in Pembroke, Mass. Photo: Adam Glanzman for The Wall Street Journal

Ms. McSherry and Ms. McNary, who was living in Vermont, had met at a camp for boys with DMD in 2011. Ms. McSherry's son didn't qualify for the eteplirsen trial because he could no longer walk. Ms. McNary's

oldest son, Austin, couldn't participate for the same reason. Her son Max joined the drug trial and seemed to improve.

On Sept. 12, Ms. McNary's husband at the time tweeted, "Dropped max at school this morning just max no wheelchair." Volume in Sarepta stock soared as investors took note of social-media posts by parents. On Oct. 31, Ms. McNary's husband posted a video of Max walking in a Halloween parade. Shares jumped 10% the next day.

"A big reason investors got more interested in this than they would have in other situations was you had these mothers saying the drug was helping their son," said investment manager Brad Loncar, who bought company shares.

Hidden Influence



- [The Rise and Fall of a K Street Renegade](#)

In February 2013, Ms. McSherry and Ms. McNary met with FDA officials and other patient advocates. A 2012 law encouraged the FDA to be flexible when considering applications for therapies to treat such life-threatening diseases as DMD. Ms. McNary brought a petition with more than 170,000 signatures asking the FDA to expedite approval.

That day, the two mothers met Janet Woodcock, the FDA's director of the Center for Drug Evaluation and Research. Dr. Woodcock told them to call her office anytime.

"Janet had the attitude that if the public called on her, she would take a meeting if she could," Ms. McSherry said. She and Ms. McNary met with Dr. Woodcock and two other top FDA officials in April 2013. Ms. McNary talked about how the drug was helping Max and showed a video of him walking. Ms. McSherry said the FDA told the women to collect more videos, and that even showing how a child could better comb his hair was important.

In August, Sarepta put out a release trumpeting an academic paper on the results of its eteplirsen trial. The paper, published in a neurology journal, said weekly treatments showed a statistically significant increase in dystrophin

By fall 2013, however, the Sarepta campaign suffered a setback. A competitor, [GlaxoSmithKline](#) PLC, had completed three trials of a DMD drug that, similarly to eteplirsen, also sought to raise levels of the protein dystrophin. Results of the trials, involving 290 patients, weren't persuasive.

“Any effect on dystrophin appears to be small as to be unlikely to have resulted in clinical benefit,” the FDA said later in agency documents.

The FDA met with Sarepta to tell the company that GlaxoSmithKline's study raised doubts about eteplirsen, Sarepta recounted in a Nov. 12, 2013, news release. Share prices fell 64% from the previous day to \$13.

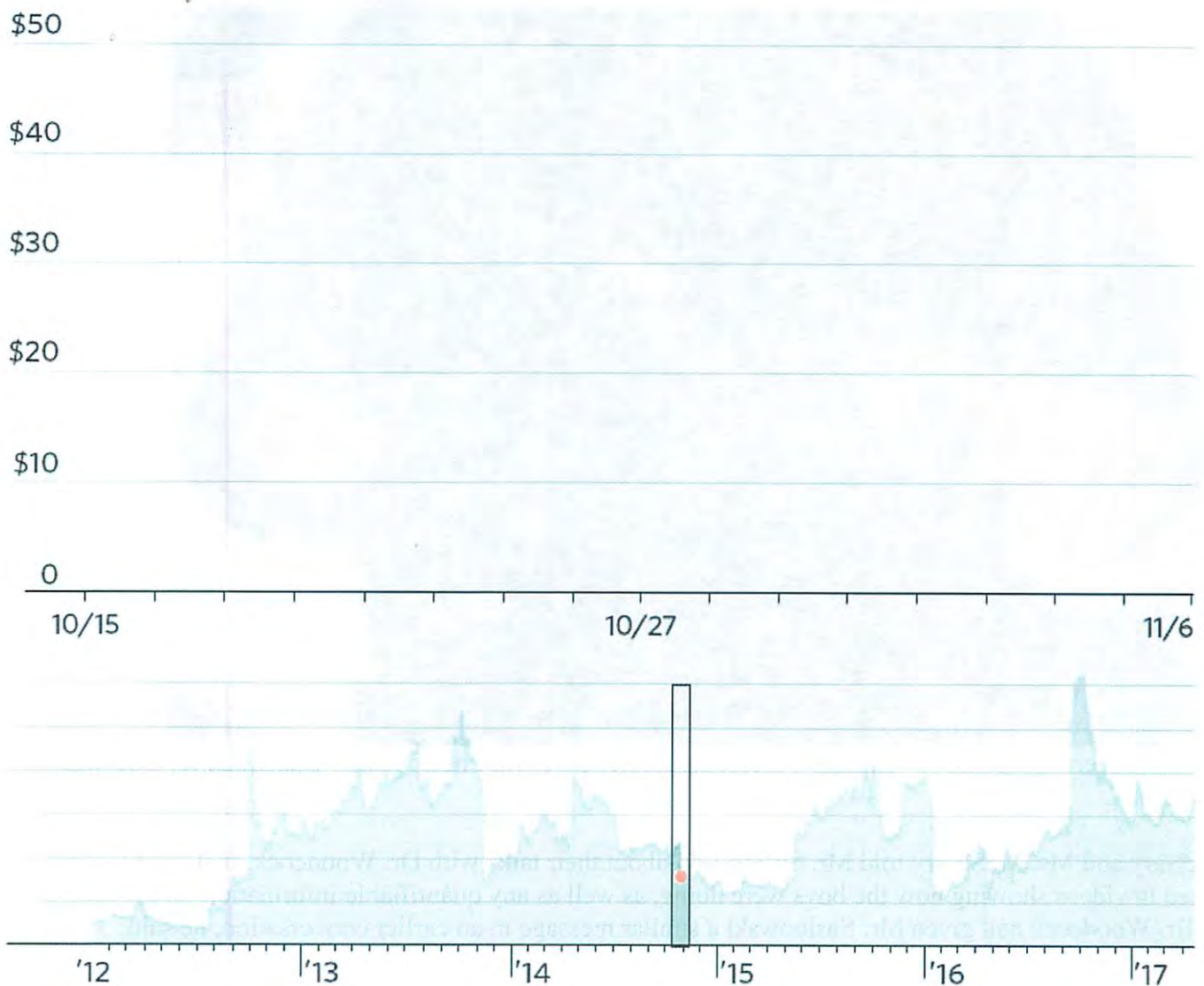
Eyewitness evidence

In May 2014, Frank Sasinowski recognized Max McNary in the cafeteria of the Nationwide Children's Hospital from his family's social-media posts, and he introduced himself to Ms. McNary. Mr. Sasinowski, a former FDA lawyer, was hired by Sarepta to help get government approval for eteplirsen.

Ms. McNary had already proven herself an effective advocate, garnering several news stories in print and on TV about how eteplirsen was helping her son Max. Mr. Sasinowski gave her his card and said they should stay in touch.

[Oct. 27, 2014](#)

An FDA review of Sarepta's years long drug trial concludes the company's data is "uninterpretable," "unreliable" and "misleading." After the company's news release, its stock price falls more than 30%.



He was at the hospital because the FDA had asked for a review of Sarepta’s trial results. The FDA later said the data was “uninterpretable,” “unreliable” and “misleading,” according to FDA documents. The findings hadn’t been made public. Sarepta said in an Oct. 27, 2014, news release the FDA had found “marked disparities” in the data. The stock price fell more than 30% from the previous day’s closing.

Three more researchers who re-examined the trial data found that eteplirsen produced only a nominal increase in dystrophin in some patients, the FDA said, not the “significant” increase Sarepta had earlier indicated. Additionally, the 2013 article in the neurology journal, and the Sarepta news release that buoyed investors, had “raised wildly unrealistic expectations” among patient families, according to FDA documents.

FDA officials met with Sarepta in the fall of 2014 about its findings and suggested the company add three months of data from 12 to 24 new patients.

Mr. Sasinowski, Ms. McNary and Ms. McSherry were working on a new plan, to show how the boys were improving from the point of view of families and caregivers.

Mr. Sasinowski said he told Sarepta officials, “ ‘You are going to have to trust me,’ and they did.”



Christine McSherry prepares to administer medicine for her son, Jett. Photo: Adam Glanzman for The Wall Street Journal

Ms. McNary and Ms. McSherry told Mr. Sasinowski about their talks with Dr. Woodcock, that the FDA was interested in videos showing how the boys were doing, as well as any quantifiable information on the drug's effect. Dr. Woodcock had given Mr. Sasinowski a similar message in an earlier conversation, he said.

"You could sense the movement of the waters," said Mr. Sasinowski, a consultant, who helps clients navigate the FDA to get drugs approved. The agency, he said, was open to hearing the "patient experience." Videos and stories, he said, would be woven into "something that looked akin to a study report."

Ms. McSherry's son, Jett, got permission to begin eteplirsen treatments in November 2014. At the time, she said, he was having difficulty breathing. Two months later, he was sleeping better and stopped snoring. She said she had concluded that the FDA was too focused on the six-minute walk.

The company began three new trials involving 110 new patients. In June 2015, Sarepta filed its formal drug application, using data from its trials.

Mr. Sasinowski, meanwhile, had been working with the two mothers for months on a parallel set of measurements that the women had gathered. He and an assistant helped them draft a 50-page FDA-friendly document, with bar charts, graphs and tables to show how the boys on eteplirsen fell less and spent less time in wheelchairs.

Mr. Sasinowski said he helped the parents make their report "as close to being acceptable by rigorous reviewers as possible."

In July 2015, Ms. McSherry and Ms. McNary made a two-hour closed-door presentation to FDA officials, including a video of boys who described how eteplirsen had increased their strength. They passed out copies of their report.

Mr. Sasinowski said in an interview he recalled telling FDA officials at the meeting he was working with both parents and the company.

Parents asked the FDA and the company if they could present their findings to the agency's advisory committee, which comprises outside experts. The FDA agreed, and the company gave them a portion of its allocated time at the April 25, 2016 committee hearing.

There was a conflict between the parents' stories of improvement and the FDA's interpretation of the trial. Trial data showed the performance of boys taking the drug had declined in the walk test, the FDA said.

[Interactive: A Roller-Coaster Ride to FDA Approval](#)

Ms. McNary, in contrast, told the panel: “Last week, 14 1/2 year-old Max got out of bed. He got dressed. He put on his shoes and his backpack, and he walked out to the school bus unassisted.”

The advisory committee voted 7-to-6 against accelerated approval, concluding the trial results didn’t provide substantial evidence the drug was effective.

Dr. Ellis Unger, director of the Office of Drug Evaluation, said in a July 15, 2016, memo that the FDA review team had unanimously rejected approval of eteplirsen, agency records show.

On July 14, 2016, Dr. Woodcock, who seldom interceded in drug-approval decisions, overruled both the advisory committee and the FDA review team. In a memo, she said she believed eteplirsen was “reasonably likely to predict clinical benefit.” She declined through a spokeswoman to comment further on her decision.

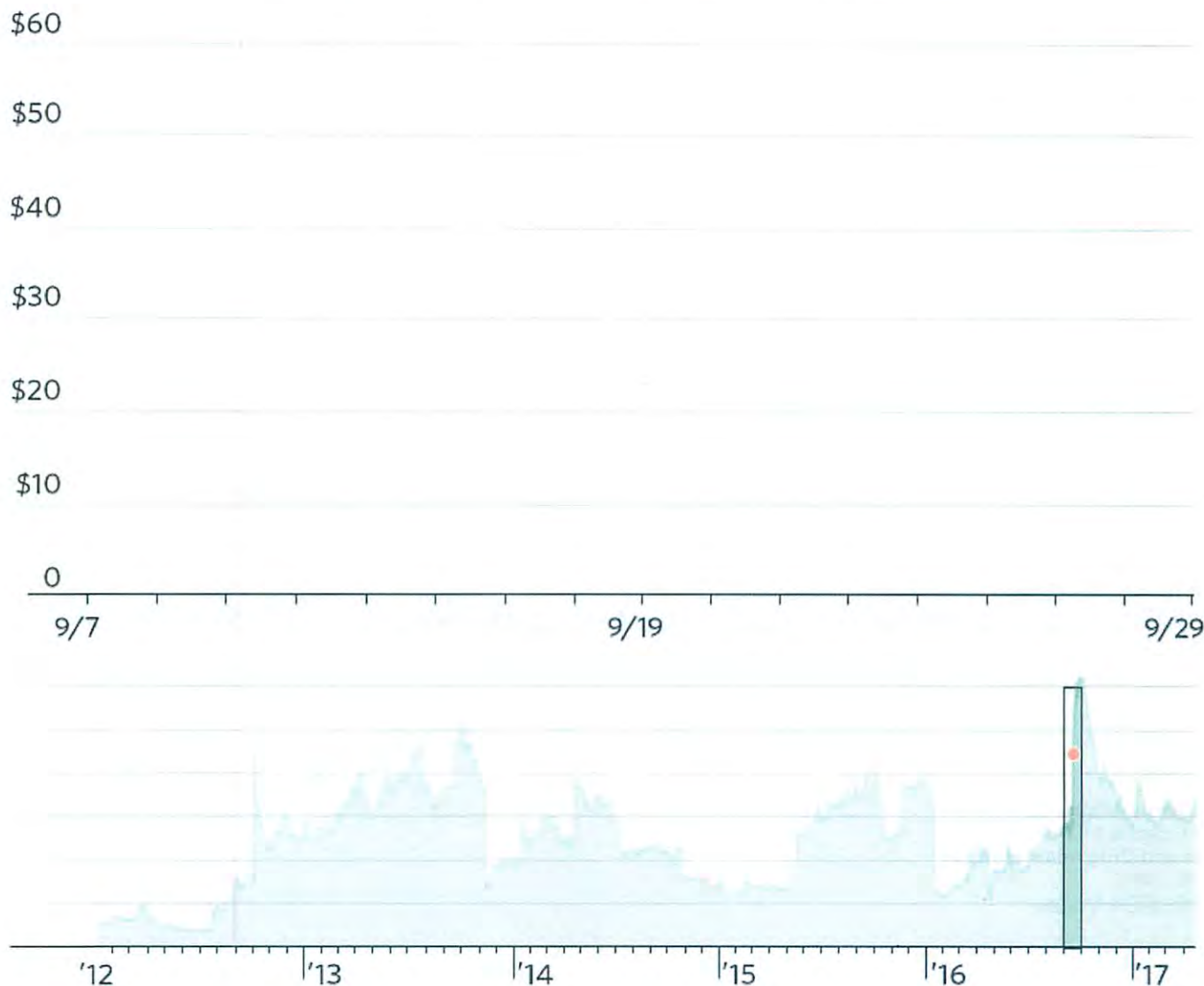
Dr. Unger appealed to an FDA committee that reviews such disputes. He wrote in his appeal that eteplirsen was a “scientifically elegant placebo,” giving “false hope in exchange for hardship and risk.”

He said it would appear to the public that “unprecedented lobbying efforts” had earned eteplirsen its accelerated approval.

The head of the FDA committee said she agreed with Dr. Unger’s conclusion that the data didn’t show the drug was “reasonably likely” to provide a clinical benefit, according to agency documents. The dispute was sent to Dr. Califf, the FDA commissioner at the time. He deferred to Dr. Woodcock’s “judgment and authority,” an agency memo said.

[Sept. 19, 2016](#)

FDA approves use of eteplirsen. In the following days, Sarepta shares more than double to \$60.



On Sept. 19, Ms. McSherry was helping Jett get ready for school when her cellphone buzzed. Her daughter, who was getting the same text messages, yelled from upstairs: “You did it!”

The FDA had approved eteplirsen. Ms. McSherry drove to Mr. Garabedian’s house in Boston. “We had a big hug and tears,” she said. Within days, company shares more than doubled to \$60.

In December, Congress passed a law intended to expedite the FDA's approval process for new drugs and allowing companies to provide patient input and other information to bolster clinical data.

Sarepta shares have dropped back to \$35. Some insurance companies refuse to cover the drug. A label on the medicine—renamed Exondys 51—says a clinical benefit of the drug “has not been established.”

Write to Susan Pulliam at susan.pulliam@wsj.com and Brody Mullins at brody.mullins@wsj.com

Top photo illustration: Jessica Kuronen/The Wall Street Journal; Photo credits: Adam Glanzman for The Wall Street Journal (3); Associated Press; Getty Images

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



From: Walsh, Sandy
Sent: Thursday, May 18, 2017 10:47 AM
To: Unger, Ellis
Subject: story is out: How the FDA Approved a \$300,000-a-Year Drug Its Own Experts Didn't Believe Worked
Importance: High

Story in WSJ just posted

[**How the FDA Approved a \\$300,000-a-Year Drug Its Own Experts Didn't Believe Worked**](#)

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: Bell, Tammie Jo (CDER)
Sent: Thursday, June 22, 2017 8:27 AM
To: Temple, Robert; Stein, Peter; CDER OND IO (Mailbox)
Cc: CDER INTL EXEC
Subject: [REDACTED] (b) (4)
Attachments: [REDACTED] (b) (4)

Follow Up Flag: Follow up
Due By: Friday, June 23, 2017 4:00 PM
Flag Status: Flagged

Good morning Gentlemen,

[REDACTED] (b) (4)

Thanks, and best regards,
Tammie

From: Andy Hua [<mailto:andy.hua@hc-sc.gc.ca>]
Sent: Wednesday, June 21, 2017 9:25 PM
To: Bell, Tammie Jo (CDER)
Cc: Nancy Shadeed
Subject: [REDACTED] (b) (4)

Hi Tammie,

Hope all is well and [REDACTED] (b) (4) I'm back from Chicago. Nice city but traffic is terrible.

[REDACTED] (b) (4)

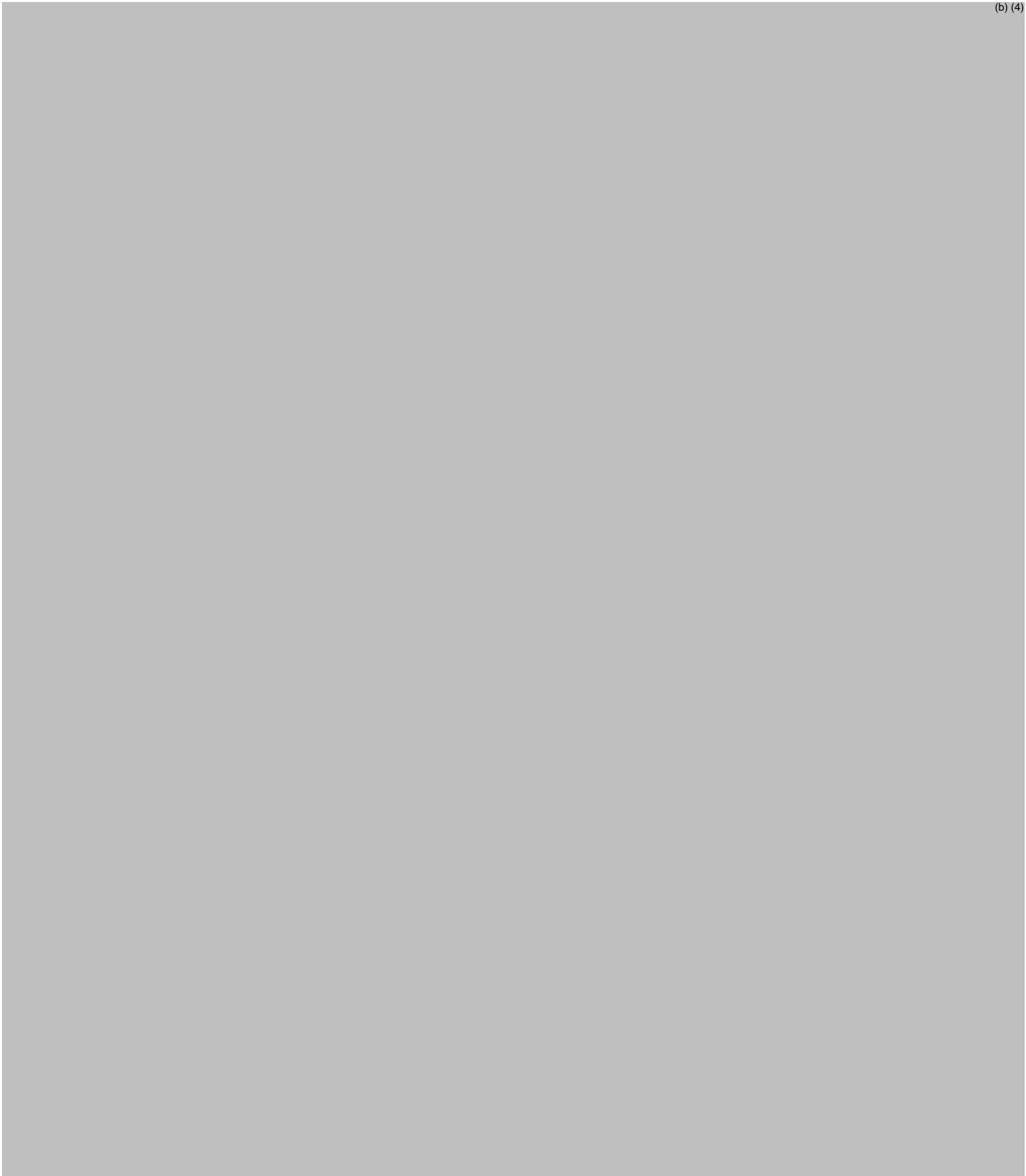
Cheers
Andy

Senior Policy Advisor | Conseiller principal en politiques
International Programs | programmes internationaux
Therapeutic Products Directorate | Direction des produits thérapeutiques
Health Products and Food Branch | Direction générale des produits de santé et des aliments
Health Canada | Santé Canada
Tel: 613-716-8781 (new)
email: andy.hua@hc-sc.gc.ca

----- Forwarded by Andy Hua/HC-SC/GC/CA on 2017-06-21 09:06 PM -----

From: Carole Legare/HC-SC/GC/CA
To: Andy Hua/HC-SC/GC/CA@HWC
Cc: Nancy Shadeed/HC-SC/GC/CA@HWC
Date: 2017-06-21 05:49 PM
Subject: [REDACTED] (b) (4)

[REDACTED] (b) (4)





Philips, Howard

From: Bell, Tammie Jo (CDER)
Sent: Monday, June 26, 2017 2:27 PM
To: Temple, Robert; Stein, Peter; CDER OND IO (Mailbox)
Cc: CDER INTL EXEC; Unger, Ellis; Dunn, Billy
Subject: [REDACTED] (b) (4)

(b) (4)

Best regards,
Tammie

From: Temple, Robert
Sent: Monday, June 26, 2017 2:24 PM
To: Bell, Tammie Jo (CDER); Stein, Peter; CDER OND IO (Mailbox)
Cc: CDER INTL EXEC; Unger, Ellis; Dunn, Billy
Subject: [REDACTED] (b) (4)

(b) (4)

From: Bell, Tammie Jo (CDER)
Sent: Thursday, June 22, 2017 8:27 AM
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Cc: CDER INTL EXEC
Subject: [REDACTED] (b) (4)

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(b) (4)

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Sent: Wednesday, June 21, 2017 9:25 PM
To: Bell, Tammie Jo (CDER)
Cc: Nancy Shadeed
Subject: [REDACTED] (b) (4)

Hi Tammie,

Hope all is well [REDACTED] (b) (4). I'm back from Chicago. Nice city but traffic is terrible.

Cheers
Andy

Senior Policy Advisor | Conseiller principal en politiques
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From: Carole Legare/HC-SC/GC/CA
To: Andy Hua/HC-SC/GC/CA@HWC
Cc: Nancy Shadeed/HC-SC/GC/CA@HWC
Date: 2017-06-21 05:49 PM
Subject: Re: [REDACTED] (b) (4)

(b) (4)

Philips, Howard

From: Blount, Aprile
Sent: Monday, July 17, 2017 6:06 PM
To: Bernstein, Jessica; Stein, Peter
Cc: Temple, Robert
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers
Attachments: OCOMM approval statement DNP TempleEdits.docx

Bob made some additional changes (highlighted) and some comments to the last page.

From: Blount, Aprile
Sent: Monday, July 17, 2017 4:43 PM
To: Bernstein, Jessica; Stein, Peter
Cc: Temple, Robert
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers

Hi Jessica,
Here are Bob's edits.

From: Unger, Ellis
Sent: Friday, July 14, 2017 5:39 PM
To: Bernstein, Jessica; Stein, Peter
Cc: Vail, Victor H; Temple, Robert; Blount, Aprile
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers

Jessica,

Dr. Temple has some edits on the letter to Ms. McNary; he'll get them typed up and have them to you early next week.

We both looked at the proposed web posting on FDA approval. I made a few edits, we are concerned that the overall content is so superficial that it will not provide much value. I've attached my track changes version, as well as a scan of Dr. Temple's comments.

Ellis

From: Bernstein, Jessica
Sent: Friday, July 14, 2017 3:17 PM
To: Unger, Ellis; Stein, Peter
Cc: Vail, Victor H
Subject: FW: Exondys 51 (Eteplirsen) approval and insurers

Good Afternoon Dr. Unger and Dr. Stein,

CDER received an inquiry Ms. Jean McNary about Exondys 51 and difficulties some patients are having with insurance coverage. Can you please review the attached draft response and let me know whether it is cleared by ODE I/OND and if changes are needed? Once we get the copy cleared for this letter, we may use essentially the same copy for a more general letter to patients and families.

I am also attaching for your review, draft copy that OCOMM prepared for a Web page, FDA Approval: What It Means.

Thank you,
Jessica

Jessica Bernstein, MPH
Writer-Editor
Division of Executive Operations
Office of Executive Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(240) 402-0524
jessica.bernstein@fda.hhs.gov

FDA Approval: What it Means

(b) (5)



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

Philips, Howard

From: Temple, Robert
Sent: Tuesday, July 18, 2017 10:36 AM
To: Stein, Peter; Blount, Aprile; Bernstein, Jessica
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers

Agree. All good suggestions.

From: Stein, Peter
Sent: Tuesday, July 18, 2017 7:05 AM
To: Blount, Aprile; Bernstein, Jessica
Cc: Temple, Robert
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers

I am OK with this – but I don't think it is quite responsive to the letter's issue. The letter is pointing out that some insurance companies have not reimbursed for use of the medication in patients with DMD. She notes that this is because companies have viewed the drug as "investigational" – and indicates that she believes that FDA's *intention* was to provide full *access* to all patients with DMD, regardless of age (as per labeling). She is asking that we make a statement that they can use for insurance companies – essentially that our intent was to provide full access – or specifically, she is asking that we have a DMD community meeting, and indicate that we intended for all DMD patients to have access to the drug.

I don't think she is unclear as to what AA is – she indicates as much in the first and second paragraphs (or is interested in other accelerated pathways) – she is frustrated by the access issue.

My suggestion here is to be clear that our role is in the scientific evaluation of drug applications – and approving them consistent with our regulations and statues – we allow drugs, through our approval, to be marketed (made available), we do not assure access. In this case, the drug was approved under AA (which she knows), which means that it is approved on the basis of an endpoint that is "reasonably likely" but not fully demonstrated to predict clinical benefit – which is why we required a confirmatory trial when Exondys-51 was approved. We can comment that we do not have authority over reimbursement decisions (which she also knows....) by insurers. We can say that our decision allows the *availability* of Exondys-51 for use in all patients for whom it was approved – and that we understand that approval may not be the same thing as access.

Peter

From: Blount, Aprile
Sent: Monday, July 17, 2017 6:06 PM
To: Bernstein, Jessica; Stein, Peter
Cc: Temple, Robert
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers

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Cc: Temple, Robert
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers

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Cc: Vail, Victor H
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Jessica

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Writer-Editor
Division of Executive Operations
Office of Executive Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(240) 402-0524
jessica.bernstein@fda.hhs.gov

Temple, Robert

From: Bernstein, Jessica
Sent: Tuesday, July 25, 2017 8:53 AM
To: Stein, Peter; Temple, Robert; Unger, Ellis
Cc: Vail, Victor H; Blount, Aprile
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers
Attachments: Exondys 51 McNary Letter Temple Stein 072117.docx; Exondys 51 McNary Letter Temple Stein Unger 072117.docx

Good Morning Dr. Stein, Dr. Temple, and Dr. Unger,

Thank you all for your comments and edits. I revised the letter, accepted Dr. Temple's changes, and added copy (shown with tracked changes) based on the comments. Please let me know if you have additional edits/comments, and whether the letter is cleared by ODE 1 and OND.

For the web page, I am circling back with OCOMM to revisit the purpose of the page. I will convey your concerns about the copy being superficial to OCOMM's attention, particularly in the context of what is already posted on the public website about accelerated approval, fast track, breakthrough therapy, and priority review. I added material as you requested, but it looks quite similar to what is already online.

Jessica

From: Unger, Ellis
Sent: Friday, July 14, 2017 5:39 PM
To: Bernstein, Jessica; Stein, Peter
Cc: Vail, Victor H; Temple, Robert; Blount, Aprile
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers

Jessica,

Dr. Temple has some edits on the letter to Ms. McNary; he'll get them typed up and have them to you early next week.

We both looked at the proposed web posting on FDA approval. I made a few edits, we are concerned that the overall content is so superficial that it will not provide much value. I've attached my track changes version, as well as a scan of Dr. Temple's comments.

Ellis

From: Bernstein, Jessica
Sent: Friday, July 14, 2017 3:17 PM
To: Unger, Ellis; Stein, Peter
Cc: Vail, Victor H
Subject: FW: Exondys 51 (Eteplirsen) approval and insurers

Good Afternoon Dr. Unger and Dr. Stein,

CDER received an inquiry Ms. Jean McNary about Exondys 51 and difficulties some patients are having with insurance coverage. Can you please review the attached draft response and let me know whether it is cleared by ODE I/OND and if changes are needed? Once we get the copy cleared for this letter, we may use essentially the same copy for a more general letter to patients and families.

I am also attaching for your review, draft copy that OCOMM prepared for a Web page, FDA Approval: What It Means.

Thank you,
Jessica

Jessica Bernstein, MPH
Writer-Editor
Division of Executive Operations
Office of Executive Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(240) 402-0524
jessica.bernstein@fda.hhs.gov

July xx, 2017

(b) (5)



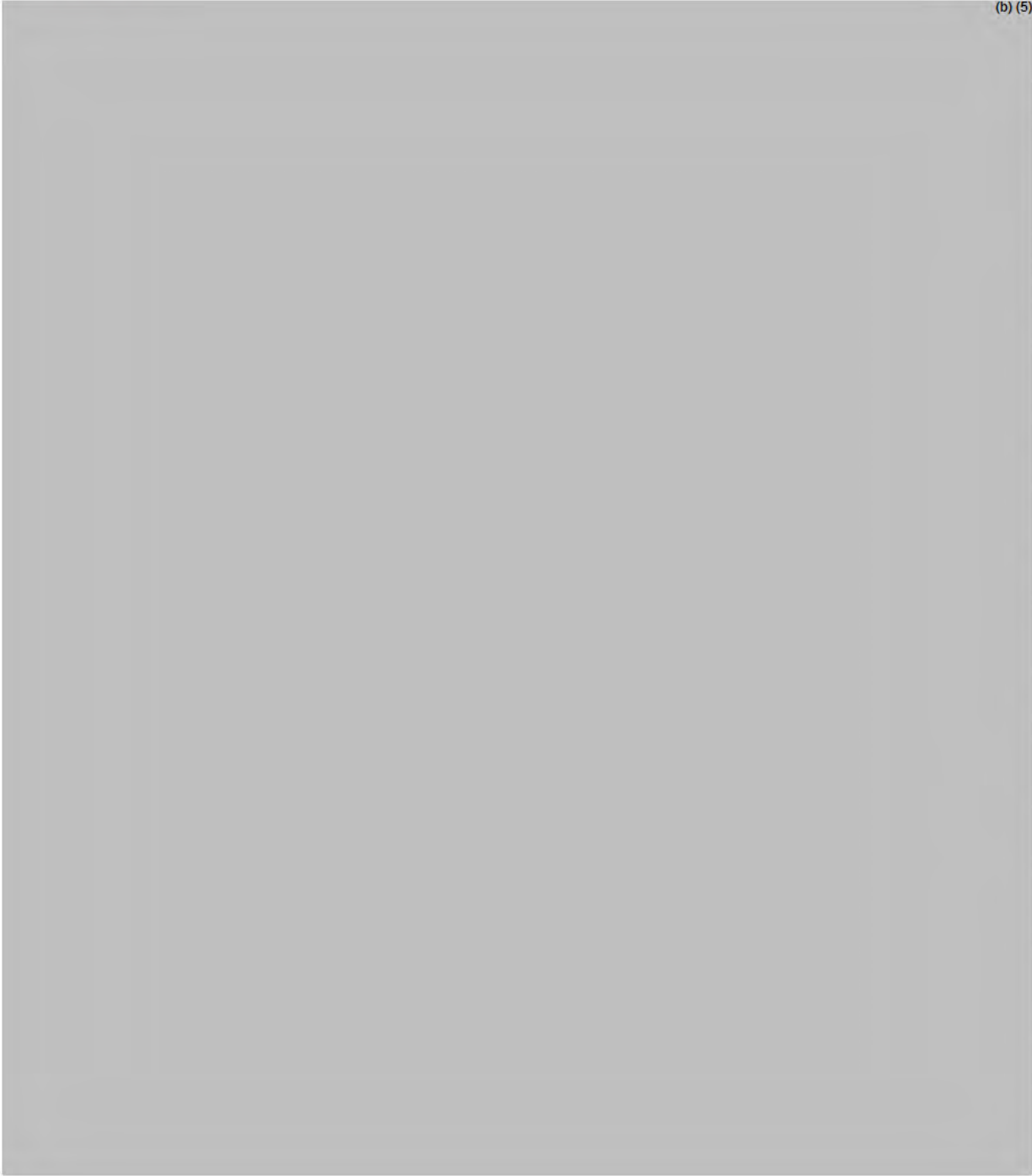


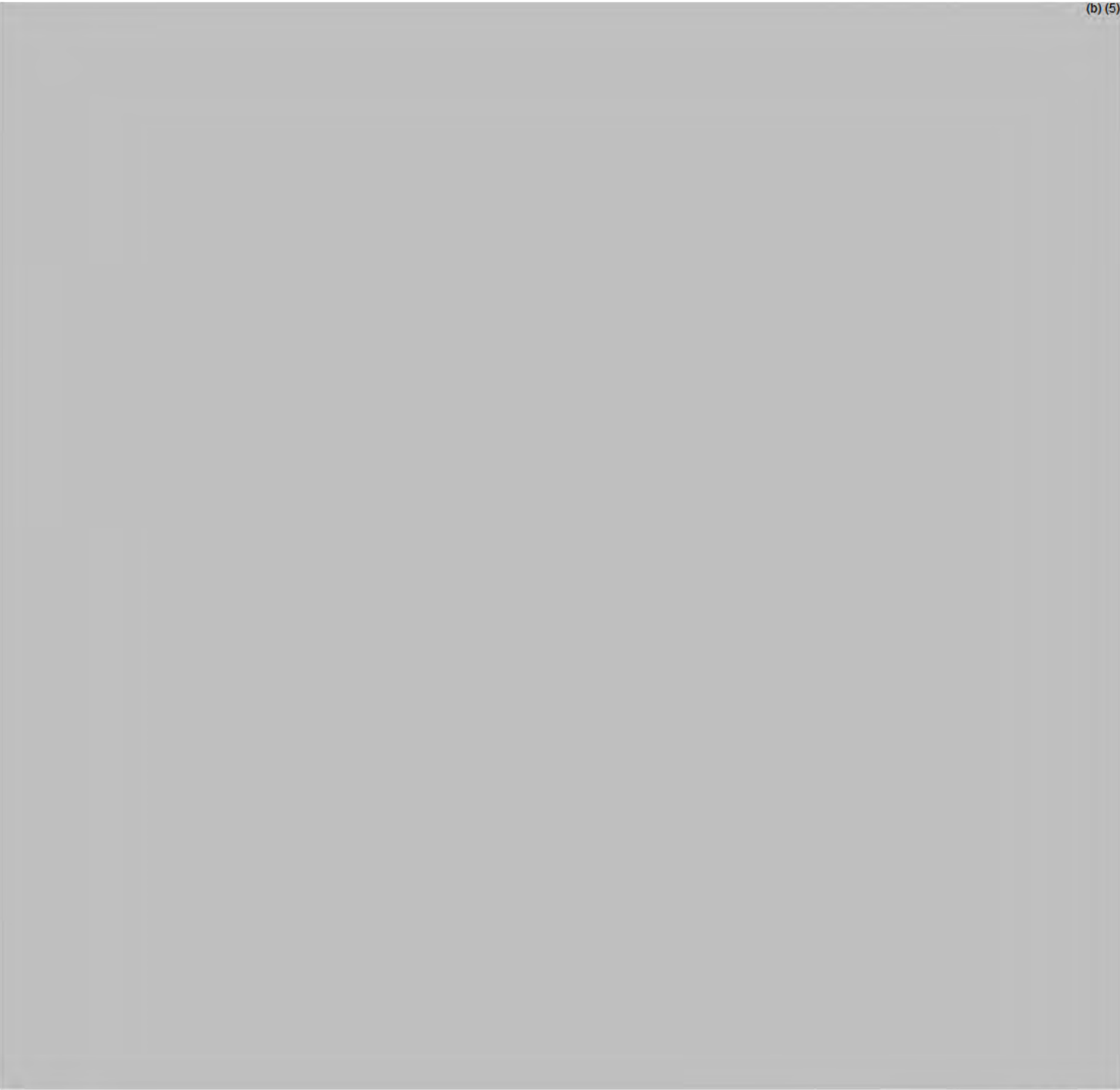
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July xx, 2017

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Philips, Howard

From: Bernstein, Jessica
Sent: Tuesday, July 25, 2017 8:53 AM
To: Stein, Peter; Temple, Robert; Unger, Ellis
Cc: Vail, Victor H; Blount, Aprile
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers
Attachments: Exondys 51 McNary Letter Temple Stein 072117.docx; Exondys 51 McNary Letter Temple Stein Unger 072117.docx

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Sent: Friday, July 14, 2017 5:39 PM
To: Bernstein, Jessica; Stein, Peter
Cc: Vail, Victor H; Temple, Robert; Blount, Aprile
Subject: RE: Exondys 51 (Eteplirsen) approval and insurers

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Sent: Friday, July 14, 2017 3:17 PM
To: Unger, Ellis; Stein, Peter
Cc: Vail, Victor H
Subject: FW: Exondys 51 (Eteplirsen) approval and insurers

Good Afternoon Dr. Unger and Dr. Stein,

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I am also attaching for your review, draft copy that OCOMM prepared for a Web page, FDA Approval: What It Means.

Thank you,
Jessica

Jessica Bernstein, MPH
Writer-Editor
Division of Executive Operations
Office of Executive Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(240) 402-0524
jessica.bernstein@fda.hhs.gov

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 5:06 PM
To: DeMarco, Devota R
Subject: RM

From: Beitz, Julie G
Sent: Friday, July 07, 2017 12:04 PM
To: Moscicki, Richard; Roman, Dragos
Subject: RE: graph for our phone call at 5 PM

We should involve our pharm tox folks in DGIEP to address this question. Perhaps also include Karen Davis Bruno...

Julie

From: Moscicki, Richard
Sent: Friday, July 07, 2017 11:35 AM
To: Beitz, Julie G; Roman, Dragos
Subject: FW: graph for our phone call at 5 PM

Hi, Francis Collins called me yesterday to discuss his latest findings in Progeria and seek advice. He is working with Sarepta using a morpholino to reduce production of progerin. (b) (4)

[REDACTED]

[REDACTED] Thought the division should give this a thought. Rich.

From: Collins, Francis (NIH/OD) [E] [<mailto:collinsf@od.nih.gov>]
Sent: Thursday, July 06, 2017 1:44 PM
To: Moscicki, Richard
Subject: graph for our phone call at 5 PM

Hi Rich,

See attached graph, which I will explain when we speak.

Thanks, Francis

Philips, Howard

From: Guidos, Robert
Sent: Friday, June 23, 2017 4:43 PM
To: Stein, Peter; Moscicki, Richard; Woodcock, Janet
Subject: FDA Urged To Broaden Use Of Flexible Approval Standard In Wake Of Sarepta DMD Drug Approval

Follow Up Flag: Follow up
Flag Status: Flagged

Inside Health Policy

DAILY NEWS

FDA Urged To Broaden Use Of Flexible Approval Standard In Wake Of Sarepta DMD Drug Approval

June 23, 2017

CHICAGO -- A representative from pharmaceutical company Sarepta -- manufacturer of the controversial Duchenne muscular dystrophy drug Exondys 51 -- touted FDA's use of regulatory flexibility to approve Exondys 51, saying the approach has been frequently used for oncology drugs and could be a boon for the rare disease space. But one legal expert urged caution, saying FDA needs to ensure the validity of the science as it heads into implementing the 21st Century Cures Act, which will facilitate a more flexible approval approach. The issue came up during a panel discussion at the DIA annual conference this week.

FDA granted accelerated approval to Exondys 51 in September 2016, months after an advisory committee voted to not approve the drug ([see related story](#)). The approval sparked backlash from public health advocates who argued FDA showed too much flexibility when it approved the drug based on little scientific evidence that it was beneficial for patients. However, at the June 21 DIA panel, Sarepta's Shamim Ruff, senior vice president of regulatory affairs and quality, said "there are a lot of misconceptions out there" around the approval adding that "A lot of people seem to think that we got approval based on a 12-patient NDA ... it was a little more extensive than that."

Ruff explained that Sarepta provided data from two phase I studies and two phase II studies. The phase II studies consisted of what was "initially a randomized placebo controlled study. A 28-week study where 24 weeks had a randomized placebo control," Ruff said.

"We didn't know enough about the disease or the drug to know that we needed a longer study and now we know it can take up to two years before you can see a difference," she added.

The company's single-arm study provided individual patient data from the natural history studies and then, in addition to the 13 patients who were amenable to exon 51 skipping, data was provided from "a large number of patients who were anti-exon amenable, so again it wasn't just a tiny dataset," Ruff said. Sarepta also provided safety data from 114 patients "primarily from the phase I and phase II studies but also a number of ongoing clinical studies using eteplirsen," she said.

Ruff said the accelerated approval was "based on the totality of evidence" with dystrophin as a surrogate endpoint reasonably likely to predict benefit.

"And the support from reasonably likely comes from long-term experience ... both chemical and clinical data supported that low-level increase in dystrophin is reasonably likely to predict benefit," Ruff said. "And the patient voice that was very critical to this. The patients provided us with what their needs were and what they believed was

clinically meaningful. They provided information of a risk tolerance and it was clear that as far as the patients were concerned, small functional improvements or delay to loss in ambulation were clinically meaningful and this was certainly taken into consideration.”

Sarepta knew that there was a regulatory framework for flexibility for rare disease therapies, Ruff said. However, the FDA division the company worked with to get Exondys 51 approved “had never exercised this flexibility. They had been more used to the larger indications so had never worked really in the rare disease arena and they certainly were not used to accelerated approvals until very recently that was really the purview of the office of oncology drugs,” she said.

Ruff argued that flexibility is needed in the rare disease space.

“I worked in oncology for about 16 or 17 years prior to joining the rare disease arena, and I actually saw a lot of flexibility. To me, flexibility equals clinical judgment. I think it’s easy to interpret data from a large, or two large, randomized placebo controlled studies but when you get into the rare disease arena with targeted drugs, there needs to be clinical judgment ... Certainly in oncology there was always a lot of regulatory flexibility. The subpart H approval, or accelerated approval, was used pretty extensively ... FDA for oncology will often approve drugs on a single-arm study based on response rates. So it’s a paradigm that’s being used within FDA quite a bit,” she said.

Alexander Varond, associate at Goodwin Proctor, said FDA has for a long time used an accelerated approval pathway, also known as subpart H, and been flexible in its approval standards when there is an urgent need for a drug. And laws, such as the 2012 FDA Safety and Innovation Act (FDASIA), have only helped to codify “what FDA was already doing.” He also argues the pathway has not been heavily utilized but that may change with the implementation of the 21st Century Cures Act.

“The conversation has shifted and there’s greater discussion on subpart H, but there’s also this reluctance. And that reluctance is important because oftentimes the science isn’t adequate to support the use of some unvalidated surrogate endpoints. There needs to be a discussion here. There needs to be an active consideration of does this drug warrant a subpart H approval ... As FDASIA goes through and we see implementation of 21st Century Cures, subpart H is going to be used more,” Varond said.

Christine McSherry, executive director of the Jett Foundation, also argued that FDA should develop more standardized questions focused on benefit and risk for its advisory committee meetings.

According to McSherry, FDA’s current approach can lead to members voting no on a drug even if they think it is effective. She pointed to the April advisory committee’s vote to not approve the drug, which she said was based on an oddly worded question from FDA that did not address the real benefit of Exondys 51.

The final question posed to the committee asked: “Do the clinical results of the single historically-controlled study, study 201/202, provide substantial evidence, that is evidence from adequate and well-controlled studies or evidence from a single highly persuasive adequate and well-controlled study that is accompanied by independent findings that substantiate efficacy, that eteplirsen is effective for the treatment of DMD?”

McSherry argued that the wording of the question focused too much on whether the study was “well controlled” and not enough on the risk-benefit profile of the drug.

“[N]othing in this question, nor the other voting questions, actually reflected the risk-benefit profile of eteplirsen nor did it for the safety and efficacy. These questions had no bearing on the efficacy or safety. And what was really disturbing is that we felt like the division had done a really good job at dismantling the idea that this study was adequate and well-controlled, but what they couldn’t disagree with was the study’s safety and efficacy ... I think one of the things that we learned about that is it would be better if FDA standardized questions across the board and really answered the question not of the well-controlled studies but let’s talk about safety and efficacy of a drug. And we believe that if that had been in the questions, the panel wouldn’t have been forced to answer in a negative way,” McSherry said.

McSherry also posited that patient-reported outcomes (PROs) will be vital for companies developing rare disease therapies.

“I think that the implementation of patient-reported outcomes is an upcoming catalyst ... if it’s done correctly it can really soar the field to where its needs to be,” McSherry said.

The DMD patient advocate argued that PROs can shorten clinical trial timelines, lower costs and give FDA the data it needs to “support these messier type trials,” McSherry said.

“Because [the trials are] not always going to be clean cut. There’s going to be messy trials but there’s going to be efficacy in there and we have to be able to pull it out. So I think that the development of PROs is going to be very important over the next five years. And I would love to see agency be supportive of that,” she said.

PROs are already being used in oncology, Ruff added.

“It’s being used considerably in oncology and certainly you can get full approval based on feeling better. There are two things that you need to do for regulatory approval: feel better or live longer in the oncology arena,” she said.

Ruff also pointed to FDA’s Oncology Center of Excellence as an example of something that could be used in the rare disease space. “I know rare diseases are many different diseases but so is oncology. It’s hundred of different diseases,” she said.

McSherry told the group that FDA’s drug center director Janet Woodcock had “actually mentioned that to us. That would be her dream ... I think that’s the way she would like to move things,” McSherry said -- *Beth Wang*

(bwang@iwppnews.com)

Philips, Howard

From: Shreeve, Chris
Sent: Friday, June 02, 2017 1:46 PM
To: Moscicki, Richard; Guidos, Robert
Cc: Bolek, Michelle
Subject: FW: Inside Health Policy

For awareness.. This is from *Inside Health Policy*

From: Shreeve, Chris
Sent: Friday, June 02, 2017 1:41 PM
To: Bolek, Michelle
Cc: Rawlings, Kimberly
Subject: Inside Health Policy

Not sure if you saw this:

Despite FDA chief counsel saying Sarepta-like issues to grow in importance . . .

FDA Sued For Withholding DMD Drug Documents It Said Lack Urgent Public Interest

June 02, 2017

FDA is being sued by a journalist for refusing to hand over documents surrounding the approval of Sarepta Therapeutics' Duchenne muscular dystrophy drug, Exondys 51, and FDA's justification for withholding the information – that there is no “urgency to inform the public” – comes just weeks after the agency's chief counsel publicly said FDA will increasingly face issues similar to those surrounding the controversial DMD drug approval. The journalist argues the documents will inform ongoing policy discussions, including implementation of 21st Century Cures.

The plaintiff, Charles Seife, journalism professor at New York University and former writer for *Science Magazine*, argues that FDA violated the Freedom of Information Act by not expediting his FOIA request, originally filed in December, and that FDA's failure to release any documents to date constitutes a constructive denial of the FOIA request. Seife is suing to force FDA to “conduct an immediate, complete and thorough search for all responsive records;” immediately provide him with the requested records; and enjoin FDA from both withholding the records requested and from assessing fees, according to the complaint filed May 25 in the federal district court for the Southern District of New York.

“In connection with his reporting on this continuing controversy, Seife seeks six discrete and easily searchable categories of information related to the approval of eteplirsen. This information is needed to answer urgent questions about the efficacy of Exondys 51 and the validity of the approval process. It will shed light on the hotly debated issue of whether the FDA approved an entirely ineffective drug based on faulty clinical trials and undue industry influence, or whether an effective drug is being unjustly excluded from reimbursement in many prescription drug plans,” the complaint states.

Seife argues that the documents he seeks are relevant given industry's calls to speed up the approval process. The Exondys decision may have “essentially signaled the FDA's removal of any need to establish clinical efficacy,” Seife argues.

Release of information around the Sarepta decision will also inform implementation of 21st Century Cures, Seife argues. He notes that the Cures law calls for FDA to increase its reliance on patient testimonials.

“Disclosure of the facts surrounding approval of Exondys 51 may improve the implementation of the 21st Century Cures Act, a law enacted in December 2016 that requires the FDA to issue new regulations for the use of ‘patient testimonials’ in the drug approval process. An increased reliance on ‘patient testimonials’ in the drug approval process cuts against the current rigorous standards requiring a drug's manufacturer to provide substantial evidence of safety

and efficacy derived from adequate and well-controlled studies. Investigative journalism demonstrating how the use of patient testimonials influenced FDA officials in the case of Exondys 51 can help to properly shape the new regulations to best serve the public interest," the lawsuit states.

The plaintiff also argues that the information he is seeking will "allow the public to judge whether the standards for accelerated approval--and the use of surrogate endpoints--are adequate to ensure that the agency properly gauges the effectiveness of a drug."

FDA argues that Seife's request does not merit expedited review because it doesn't demonstrate an "urgency to inform the public." The agency points to the fact Seife filed his FOIA request in December, three months after the Sarepta decision, to argue that the issue is no longer considered a "breaking news story of general interest."

However, FDA Chief Counsel Elizabeth Dickinson recently argued that the issues surrounding the Exondys 51 approval will increasingly affect FDA's decisions. "Although the route to approval for Exondys 51 was unusual, the scientific and regulatory issues with which FDA experts were grappling are likely to become increasingly common as the agency considers product applications that are characterized by limited data sets for orphan and other small populations, data derived from trials with novel design and other sources, and more robust information regarding patient preferences and risk assessments," Dickinson said at the Food & Drug Law Institute annual conference.

The plaintiff's FOIA seeks information on what he alleges were irregularities in the clinical studies used to support approval of Exondys 51. Seife claims that the irregularities raise concerns that Sarepta may have intentionally misled FDA to push the agency toward approving the drug. Seife is seeking under FOIA the clinical study reports; protocols and protocol amendments; statistical analysis plans and plan amendments; and documents of regulatory communication regarding the studies.

"[I]t appears that there were several significant changes not just to the protocol but to the endpoints of the trial after the study was underway, including extending the trial from 24 to 28 weeks, eliminating a key secondary efficacy endpoint, and generating a new secondary endpoint. Further, a dramatic mismatch between two methods of measuring the concentration of dystrophin (along with an equally striking mismatch between the study sponsors' readings of the values versus blinded pathologists' readings), the failure to have a pre-specified statistical analysis plan, and the proposed use of historical controls in a 'statistically uninterpretable' manner all raise serious questions about the quality and integrity of Sarepta's generation and communication of study outcomes," Seife's FOIA states. Seife argues that irregularities in Sarepta's studies prompted FDA officials to request the study be retracted from publication, and so he is also seeking any correspondence from then-Commissioner Robert Califf or Ellis Unger, director of Office of Drug Evaluation-I, and the editors or publishers of the journal which published the study.

The journalist also is digging for information on possible connections between Richard Moscicki, deputy center director for science operations in FDA's drug center, and Sarepta. "Through this investigation Seife was able to identify information relevant to his reporting, including information relevant to understanding the influence exerted by industry members over Dr. Woodcock and her deputy Dr. Richard Moscicki, who had previously worked with the CEO of Sarepta and did not recuse himself from the approval process," the lawsuit states.

Seife is requesting any documents mentioning possible or actual recusal by Moscicki from any of his duties reviewing Exondys 51; and any correspondence from Moscicki that mention or are addressed to Sarepta President and CEO Ed Kaye; any Sarepta employee; any employee of BioMartin, which received a complete response letter to its DMD drug back in January 2016; or that mentions Genzyme, which also was developing a DMD drug back in 2010 but later abandoned the program.

Seife is also requesting the chronology of the Sarepta decision submitted to FDA's Scientific Dispute Resolution Board, and all emails containing key search terms related to Exondys 51, which were sent to drug center chief Janet Woodcock; Moscicki, former commissioners Califf and Margaret Hamburg; and Robert Temple, deputy director for clinical science in the drug center and acting deputy director of the office of drug evaluation I. -- *Nicholas*

Florko (nflorko@iwpnews.com)

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Chris Shreeve

Director, Office of Communications/CDER

240-402-5772 (work)

240-801-2725 (mobile)

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 10:57 AM
To: DeMarco, Devota R
Subject: RM FW: Thanks

From: LaVange, Lisa
Sent: Thursday, May 25, 2017 5:56 PM
To: 'Abby Bronson'; Chen, Yeh-Fong; Goldsmith, Jonathan
Cc: Franson, Timothy; Annie Kennedy; Pat Furlong; Moscicki, Richard
Subject: RE: Thanks

Hi Abby,

I intended to follow-up with another suggestion, so thanks for your email! We debriefed Rich on our meeting the day after, and he suggested that you consider holding some sort of public meeting to discuss master protocols and platform trials for DMD. We recently participated in a public meeting to discuss a master protocol for antibacterials to treat resistant pathogens, and it gave several sponsors with drugs in development a chance to hear FDA's endorsement of such a collaboration. Dr. Woodcock would probably agree to attend and show her enthusiasm, as would several others of us. Something to think about. If you are interested, I can provide more information about the other meeting for you.

Thanks,
Lisa

From: Abby Bronson [<mailto:Abby@parentprojectmd.org>]
Sent: Thursday, May 25, 2017 4:48 PM
To: LaVange, Lisa; Chen, Yeh-Fong; Goldsmith, Jonathan
Cc: Franson, Timothy; Annie Kennedy; Pat Furlong
Subject: Thanks

Dear Lisa, Jonathan and Yeh-Fong:

Thank you so much for the time you took to meet with us on Monday. It was a very thought-provoking meeting and we learned a lot, if nothing else that there is much for us to think about. I think internally we will be doing some thinking and coming back to you shortly with some next steps. But I didn't want too much time to pass before I reached out. Your energy and passion to help our community was clear. On behalf of everyone at PPMD, thanks. I look forward to speaking with you again soon.

Kind regards,
Abby

Abby Bronson
SVP, Research Strategy
Parent Project Muscular Dystrophy
Washington, DC
202-440-3497

EndDuchenne.org

Philips, Howard

From: Guidos, Robert
Sent: Monday, May 22, 2017 4:27 PM
To: JW Direct Reports & Deputies
Subject: A Thorny Thicket of Potential Conflicts for New FDA Chief

CQ MAGAZINE – Features May 22, 2017

A Thorny Thicket of Potential Conflicts for New FDA Chief

Gottlieb's Plan to Deal With Conflicts



Board of Directors: Resigned and divested; will recuse for two years if he receives a final contingency payment from the company.

NEA

Partner: Resigned and divested; will recuse for one year. NEA has 104 health companies in its investment portfolio, and Gottlieb personally worked for two of them and had a financial interest in four more.

T.R. WINSTON & COMPANY

Managing Director: Resigned from the boutique investment banking firm and two of its client companies, and has divested. Will recuse from decisions affecting the firm's clients for one year.

StrikeBio

Board of Directors: Will recuse for one year from March resignation; he has divested.

AEI

Resident Fellow

NYU School of Medicine
OF LUNDMAN MEDICAL CENTER
Assistant Professor

slm

Policy Board

IBDO

Senior Health Care Adviser



Board of Directors

Resigned from all five; will recuse for one year.



Global Business

Product Investment Board Member:

Resigned; will recuse from decisions until receiving payment for work with the board, then for one year following.



TOLERO
PHARMACEUTICALS

Board of Directors: Resigned and divested; will recuse for one year.

Glytec

Board of Directors: Resigned and divested; will recuse for one year.

encore

Consultant for Vertex Pharmaceuticals: Ceased involvement in August 2016; will recuse for one year.



Gradalis

Board of Directors: Will recuse for one year from his March resignation; he has divested.



Consultant: Project ended in December and will remain dormant; will recuse from BMS-related decisions for one year.

CombiMatrix

Board of Directors: Will recuse for one year from his December resignation.

By: Andrew Stiller, CQ Roll Call

The new commissioner of the Food and Drug Administration, Scott Gottlieb, has deep knowledge of the industries he oversees. That's partly because he has unprecedented professional and financial ties to some of those companies from his career as an industry adviser. The companies that Gottlieb has worked for, advised or invested in encompass nearly every aspect of the FDA's broad mission.

Though he has promised to take steps to avoid conflicts of interest, Gottlieb will routinely confront potential ethical dilemmas. Further complicating matters are new policies the FDA is developing that will increase the influence of patient groups and change how clinical trials are conducted, which could offer opportunities for companies to influence the review process.

Among companies Gottlieb has recently worked for are big drugmakers like GlaxoSmithKline, Daichi Sankyo and Bristol-Myers Squibb, who between them have several applications pending at the FDA and more in the development pipeline. And he's linked to smaller companies focusing on a single drug or treatments to address different cancers.

Some of the companies are involved in issues facing broad FDA policy changes, such as diagnostic tests that are developed in labs or software with health care uses. He also has ties to the medical device industry, the restaurant industry and the e-cigarette industry.

Gottlieb told senators during his confirmation hearing in April that he would regularly consult with ethics officials and adhere to safeguards to help him avoid conflicts, as previous FDA commissioners have done.

"I understand how important impartiality of this agency is, so that people can continue to have trust in the decisions that FDA makes," Gottlieb said at his confirmation hearing in April before the Senate Health, Education, Labor and Pensions Committee. "This is exceedingly important to me. I want to earn and keep the public's trust."

The FDA says that since his confirmation, Gottlieb has resigned from all companies he agreed to leave and completed the necessary divestment of his financial interests.

"Dr. Gottlieb takes the federal ethics obligations seriously. He has met with ethics officials and is following through on all of the commitments he made during the confirmation process," said an FDA spokesperson.

When Republicans look at Gottlieb's résumé and connections, instead of conflicts they see an experienced professional who knows the FDA well.

But Democrats remain concerned about his web of industry ties. He could still influence decisions involving companies affiliated with his former investment firms but that he didn't specifically advise, or companies he had links to from years before.

"Dr. Gottlieb will be allowed to weigh in on matters involving other companies in which he was previously invested," Sen. **Patty Murray** of Washington, the HELP Committee's top Democrat, said in April when the panel sent his nomination to the Senate floor.

"His complicated relationships with a venture capital firm and an investment bank raise many questions, and he will not be recused from matters involving a number of their clients," Murray said.

Potential Land Mines

Gottlieb's labyrinth of connections could cause him to face questions about both actions he takes and those he avoids. If he does weigh in to favor companies he was involved in or handicap their competitors, he could be accused of conflicts of interest. But recusing himself from some situations could hamstring him from being involved in decisions that could benefit from leadership by the agency head.

Gottlieb served on a product investment board for GlaxoSmithKline, a drugmaker that specializes in treatments for HIV, respiratory conditions and vaccines. It's one of the private-sector companies in the early stages of development for a vaccine against the Zika virus. The company also collaborated with the National Institutes of Health on an Ebola vaccine.

Both vaccines are in the early stages of research that can take years before FDA decisions are made. But in the event of an emergency, if the early human testing shows promise, the FDA might allow more widespread use of a vaccine.

Gottlieb, however, might have to recuse himself from such a determination.

"It seems possible — if not likely — that they [GlaxoSmithKline] would be involved in a response to the next disease outbreak," Murray said in written questions to Gottlieb. "Wouldn't the American people be better served in a time of crisis by an FDA Commissioner who was not recused from matters related to such a large number of companies and whose focus was guaranteed to be on the crisis and not on the sidelines?"

Gottlieb responded, "It is routine in those circumstances for other senior agency officials to be involved in the matter and I have every confidence that if I am recused my team at FDA will ensure that Congress' laws will be properly implemented and the FDA's mission fulfilled."

As a managing director at T.R. Winston & Company, a boutique investing firm, Gottlieb worked with 10 companies affected by the FDA. In some cases, he was simply an investor, but he served as a board member or executive for several. He had a similar relationship with health-related companies as a partner at New Enterprise Associates, a leading venture capital firm.

But there are dozens of other health and pharmaceutical interests that both New Enterprise and T.R. Winston were involved with. Gottlieb has not promised to recuse himself from decisions involving some of those companies.

Gottlieb could avoid accusations of favoritism by refusing to weigh in on specific product approvals. Commissioners often do not weigh in on drug approvals anyway, and he can assign subordinates to handle meetings or issues that might have the appearance of a conflict.

But some individual drug-approval decisions could pose a quandary.

In March, he resigned from Tivorsan Pharmaceuticals, where he was a board member and for a time acting chief executive. In 2016, Gottlieb's investment firm, T.R. Winston, helped Tivorsan raise \$1.8 million to finance its research into treatment for a condition called Duchenne muscular dystrophy. The fatal disease primarily impacts young boys. There is no cure — only a couple of treatments that slightly slow its progression. The FDA granted Tivorsan's drug, Biglycan, an "orphan drug" designation in August, which means the company will be exempt from FDA review fees if it submits an application, and it will enjoy tax credits during its first phase of human drug testing this year.

To be sure, it may be years before Biglycan has an application ready for FDA review. However, things can sometimes move fast with drugs that are tested in small clinical trials to treat an underserved population. And the very first drug to be approved for Duchenne — a drug for slowing muscle deterioration called Exondys 51 — marked one of those instances when a commissioner did have to weigh in on an approval.

Last year, FDA reviewers who were considering the application of that drug found there wasn't enough evidence to prove the drug worked. But they were overruled by the head of the drug review division. The approval decision was appealed to Robert Califf, the FDA commissioner at the time, who declined to weigh in.

By staying out of it, Califf effectively upheld the drug's controversial approval. If Gottlieb were in a similar situation, he could be dogged by accusations that his lack of action amounted to a favor for his former company.

As the FDA develops policies that will impact broad classes of industries, there could be other questions about Gottlieb's role.

Over the last few years, the FDA has flirted with the regulation of diagnostic tests that are developed in labs. While the FDA says it has the authority to regulate the lab-developed tests, it has chosen not to use it. The labs themselves are regulated and certified by the Centers for Medicare and Medicaid Services.

When the FDA in 2014 released a draft proposal for regulating the tests, it was met with jeers by some lawmakers and scientists. After the election of President Donald Trump, the FDA announced it would postpone a decision on the lab-test regulations, leaving it to the new administration.

Top lawmakers on the committees that oversee the FDA want to do something to give the lab-test makers certainty about the regulatory landscape and hope to pass legislation to do that. The FDA often has significant leeway to develop certain policies, and Gottlieb would be in a position to ensure that new lab-test regulations are industry-friendly.

But Gottlieb could easily be accused of a conflict of interest. He has recently served on the board of American Pathology Partners, which operates three labs specializing in tests for diseases like the human papilloma virus and different cancers. GlaxoSmithKline also has an interest in the lab-test regulations. While the company does not make the lab tests itself, sometimes the use of its product is guided by the test results. In 2015 comments to the FDA on the draft proposal, GSK wrote that the FDA regulations could "impact the attractiveness and health of the diagnostic test market and thus patient access to our innovative medicines."

Gottlieb seems to accept the industry's preference that the FDA take a hands-off approach on the lab-developed tests, or LDTs, and that the system shouldn't stray far from the status quo. In a column last year in *Forbes*, he argued that the tests themselves were only as good as the labs and technicians running them. He suggested that if the FDA regulated lab tests, it would be too close to regulating the practice of medicine, instead of just the safety and efficacy of the devices.

Combustible Connection

Gottlieb also appears sympathetic to the industry's viewpoint on regulations of e-cigarettes and other alternative nicotine products. A year ago, the FDA finalized long-awaited rules for e-cigarettes. It essentially brought the unregulated products under the same level of oversight as traditional cigarettes, which the FDA has regulated since 2010.

Unsurprisingly, the e-cigarette industry and some members of Congress felt that the FDA went too far with the regulations and sought to water them down. The primary argument against the regulation of e-cigarettes is that they are a less harmful alternative to the

combustible products. While e-cigarettes cannot be marketed as smoking cessation products, about one-third of smokers seeking to quit try e-cigarettes for that purpose. If the FDA regulations add restrictions for the e-cigarette industry, fewer people might switch to those products.

Gottlieb has the power to work with Congress to ease the regulatory burden on e-cigarettes and he appears open to the industry's argument. That's hard to separate from the fact that he previously worked for Kure, a chain of upscale lounges selling vaporizing hardware and liquid nicotine. He resigned from the company in May 2016, the same month FDA finalized its e-cigarette rules.

"There should be reduced-harm products available to consumers to transition them off of combustible cigarettes," he said at his confirmation hearing. He acknowledged there is a potential for e-cigarettes to be harmful, especially products with flavors attractive to kids or nonsmokers. He suggested the FDA could help promote the less harmful products over problematic ones, and said he would support the FDA's tobacco experts as they work on the policies.

"There is a line here somewhere. And I don't know where that line gets drawn. I think that that line needs to get drawn by people who are expert in evaluating that science and I want to support them," he said.

Matthew Myers, president of the Campaign for Tobacco-Free Kids, is worried by that answer, especially since Kure sells nicotine with flavors like "Shamrock Shake" and "Sweet Hearts."

"He did not make a solid commitment in support of FDA's current regulations," Myers says. "Whether one is a believer in harm reduction or not, it is essential that the commissioner of the Food and Drug Administration believes that the right path there is appropriate regulation requiring sound science."

'Real World' Evidence

Some changes Gottlieb will oversee are so widespread it may be impossible to avoid the appearance of a conflict. In the 21st Century Cures Act, Congress last year charged the FDA with developing policies to incorporate so-called "real world evidence" into its product reviews. That evidence includes data from things like electronic health records or insurance claims.

The typical FDA-approved product undergoes several rounds of testing in humans before going on the market, and this won't change anytime soon. But as companies seek approvals for new uses of older products, they might be able to use evidence from such "real world" sources to make their claims. It has the potential to save companies time and money they would otherwise spend on clinical trials. The use of such information could also guide the FDA's policy about products already being used outside of their approved scope, a practice known as off-label usage.

Insurance claims data is one promising example of real-world evidence FDA might tap. One of the largest sources of claims data is the Centers for Medicare and Medicaid Services, where Gottlieb served between two previous stints at the FDA, including in the No. 2 job.

Michael Gaba, a partner at the law firm Polsinelli PC who advises industry clients on FDA and CMS policies, expects Gottlieb to look at CMS as a way to leverage claims data and speed the approval of new uses of drugs.

"The level of the sophistication of data systems is such that Medicare claims can help inform the extent to which a product is being used off label," Gaba says. "And presuming we can then track the outcomes, that could help inform FDA decisions around enabling off-label promotion."

This kind of change would likely benefit almost every drug company, not just those Gottlieb is tied to.

Bristol-Myers Squibb, where Gottlieb served as a consultant, offers an example.

The company is researching new uses for seven drugs already on the market. In addition to attracting new patients, winning approval for additional uses can win drug companies longer exclusive rights to the drugs and delay generic competition. The company is currently engaged in patent lawsuits to fend off generic competition and the approval of new uses could help in that fight.

To consumer advocates, using evidence that's potentially weaker than traditional clinical trials could be harmful. Consumers might not be able to tell which uses went through rigorous testing and which didn't.

"That would undermine the drug approval process for additional uses of an already approved drug, and that could create a dangerous double standard," says Michael Carome of Public Citizen's health research group.

Under Gottlieb's leadership, the FDA will decide how much weight to give to real-world evidence in its review decisions. Consumer advocates who think the FDA is already too industry-friendly see the potential for Gottlieb to continue that trend.

The concerns about Gottlieb also may be about his philosophical outlook. His views tend to align with the industry he'll be regulating, which, for a Republican political appointee, is not a shock.

Former FDA officials, including the last two commissioners, endorsed Gottlieb's nomination. Joshua Sharfstein, a former acting FDA commissioner and an FDA deputy during the Obama administration, was optimistic about Gottlieb's nomination.

"What he's said about respecting the decision-making process at the agency is very positive. It's hard to predict in advance, but I think he sent the right signals about how he would approach things," Sharfstein says.

Sharfstein describes an extensive process at the agency that guides how the commissioner gets involved in decisions and which meetings end up on a commissioner's schedule. He noted that many policies are developed at lower levels before the commissioner weighs in to choose between options or mitigate a disagreement between divisions.

"For most policy issues, that's true," he says. "I think it's also true that the commissioner can have an agenda, and convene people around that agenda."

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 1:52 PM
To: DeMarco, Devota R
Subject: RM FW: WSJ story today: How the FDA Approved a \$300,000-a-Year Drug Its Own Experts Didn't Believe Worked

Importance: High

Follow Up Flag: Follow up
Flag Status: Completed

From: Walsh, Sandy
Sent: Thursday, May 18, 2017 11:18 AM
To: Woodcock, Janet; Moscicki, Richard
Cc: Shreeve, Chris; Bolek, Michelle; Rawlings, Kimberly; Shaham, Lauren
Subject: WSJ story today: How the FDA Approved a \$300,000-a-Year Drug Its Own Experts Didn't Believe Worked
Importance: High

Hi Janet and Rich,

The WSJ story from Susan Pulliam on eteplirsen posted this morning:

[How the FDA Approved a \\$300,000-a-Year Drug Its Own Experts Didn't Believe Worked](#)

May 18, 2017

How the FDA Approved a \$300,000-a-Year Drug Its Own Experts Didn't Believe Worked

After trial data for a new medicine proved inconclusive, Sarepta Therapeutics joined with the parents of sick boys to persuade officials it helped

By Susan Pulliam and Brody Mullins

Jennifer McNary, a stay-at-home mother, was desperate to find a medicine that might spare her two sons an early death from a rare form of muscular dystrophy.

Chris Garabedian, the chief executive of a pharmaceutical firm, was desperate to find a profitable drug that would reverse his company's slow fall.

They met in June 2012 at a conference on Duchenne muscular dystrophy and joined forces, often behind the scenes and with little public disclosure, in a yearslong mission to push the government to approve a drug to treat DMD, as it is known.

At the time, it wasn't at all clear the firm's drug worked. Faced with government skepticism, a consultant to Mr. Garabedian's company helped Ms. McNary and other parents prepare slickly packaged testimony to convince the Food and Drug Administration that the drug was helping their sick children, according to parents, company managers and the consultant.



Jennifer McNary and her sons Max, left, and Austin during the fall of 2015 in Pembroke, Mass. Photo: Kayana Szymczak

The company, [Sarepta Therapeutics Inc.](#), leveraged the emotional appeal of the parents' stories. Without that, the drug—eteplirsen—likely wouldn't have been approved, said stock analysts, investors and people close to the matter.

An FDA advisory committee voted 7-6 last year to oppose the drug's approval, a position later overruled. The Wall Street Journal found that a majority didn't know how Sarepta's consultant had guided the patients' families.

“More might have voted no if they were aware,” said Dr. Bruce Ovbiagele, a committee member, when he learned the role the company consultant played in helping parents prepare for FDA hearings.

Relationships between companies and advocacy groups are important to know about, said Dr. G. Caleb Alexander, co-director of the Johns Hopkins Center for Drug Safety and Effectiveness, who served as chairman of the FDA’s advisory committee. “The advisory committee received little information about how that played out in the development of eteplirsen.”

Companies that need Washington have turned to new, often untraceable tools—including hidden involvement with grass-roots organizations—to lobby decision makers and help sway public opinion. Many of these emerging tactics fall outside the government’s longstanding definition of lobbying and remain masked to both officials and the public, making it hard to know how companies are interacting with the people charged with running the country.

Eteplirsen’s drug application coincided with a shift at the FDA to give a larger role to patient families and advocacy groups. The change helped propel the drug-campaign effort by Sarepta and parents.

“The FDA’s regulatory decision-making on medical products is science-based and involves the careful evaluation of risks and benefits for the drug at issue and is informed by science, medicine, policy and judgment,” an agency spokeswoman said.

This account of the drug’s FDA application is based on interviews with parents, company officials, investors and current and former FDA officials.

When Ms. McNary first talked with Mr. Garabedian in 2012, his company was approaching the one-year mark in a clinical trial of eteplirsen.

DMD, a genetic disorder that targets boys, is usually diagnosed around kindergarten. It saps muscle strength and by adolescence leaves many of its victims in wheelchairs. Boys with DMD lack the protein dystrophin, which is critical to muscle function. In time, their hearts and respiratory systems stop working. Few survive past their 20s.

Researchers believed eteplirsen could help patients produce enough of the missing protein to slow DMD’s progression.

“This drug works,” Ms. McNary said, introducing herself to Mr. Garabedian at the DMD conference. Her youngest son, Max, 10 years old at the time, was one of a dozen boys enrolled in the eteplirsen drug trial at the Nationwide Children’s Hospital in Columbus, Ohio. After four months on the drug, she said, Max could open a milk carton and needed a wheelchair less often.

Ms. McNary turned out to be the cheerleader Mr. Garabedian needed. His company had just been warned by the Nasdaq Stock Market that its share listing might be dropped from the exchange for trading below \$1.

Mr. Garabedian told the Journal his company was having trouble raising money after it had spent \$30 million on eteplirsen in the 18 months since he had joined as CEO.



Doses of the drug eteplirsen to treat Duchenne muscular dystrophy. Photo: Adam Glanzman for The Wall Street Journal

Before eteplirsen would be available to the 1,000 or more sick boys who might benefit in the U.S.—and before the company could charge patients more than \$300,000 a year for the treatment—the drug needed FDA approval.

Looking back, Catherine Collins, whose son has DMD, said, “Sarepta used the parents to push their regulatory agenda,” she said. “We were willing participants, but they were trading on our desperation.”

Edward Kaye, Sarepta’s chief executive since 2015, said the company was “able to make a true partnership” with DMD patient groups, helping parents give the FDA firsthand observations of how the drug had worked for their sons.

Former FDA Commissioner Robert Califf, who stepped down in January, said the Sarepta case was “an example where things should have been done better... There should be disclosure of the source of documents and presentations, and who was involved.”

Hopeful shortcut

Mr. Garabedian and Dr. Kaye, the company's chief medical officer at the time, revealed at the 2012 conference early data from the drug trial that suggested eteplirsen was working.

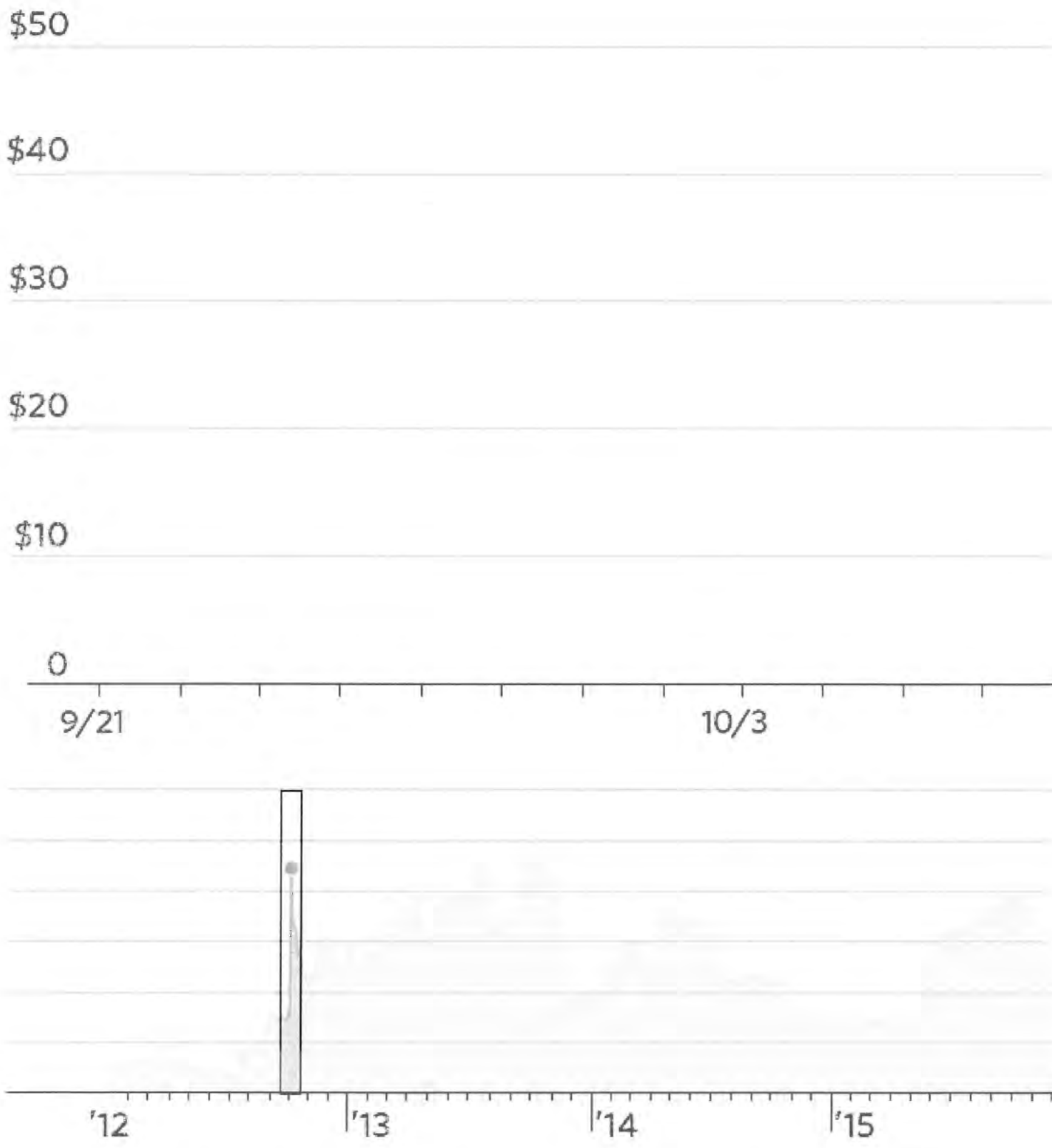
With the stock trading below \$1, Mr. Garabedian didn't have the luxury of waiting to spread encouraging news. Trial researchers were measuring levels of the protein dystrophin in the patients, all boys, and how far they could walk in six minutes.

Dr. Kaye said it appeared the drug helped lift dystrophin levels. Even better, 10 of the 12 boys in the trial walked, on average, more than 50 feet farther during the timed walk, he said; two boys became unable to walk.

Two weeks after the conference, the company made a 1-for-6 stock split, which raised its share price and allowed it to keep its Nasdaq listing. It also changed its name to Sarepta from AVI BioPharma Inc.

Oct. 3, 2012

Sarepta shares reach nearly \$45 after the company issues positive drug trial results.



The company in a July 24 news release said the boys showed “significant clinical benefit” after 36 weeks of treatment. Shares jumped past \$8. Another positive news release at the 48-week mark pushed the stock close to \$45.

Even with the promising news, Mr. Garabedian's company had concerns about whether it could raise enough money to support third- and fourth-phase drug trials, which must show drugs work effectively and safely. Parents, meanwhile, were clamoring for a treatment.

One shortcut was accelerated approval—that's when the FDA gives permission to dispense a drug before proving a clinical benefit. It allows patients a quicker chance at treatment for maladies that have none, such as DMD. Sarepta's application would rely on trial data showing that eteplirsen would be "reasonably likely" to produce a clinical benefit, rather than proving it was effective.

That fall, Mr. Garabedian met Christine McSherry, a former nurse of Pembroke, Mass., whose son, Jett, now 21, had been diagnosed with DMD on his fifth birthday. Ms. McSherry said she was so upset at the news she briefly considered killing herself and her son. Instead, she became an advocate for treatment. She began speaking regularly with Mr. Garabedian and other Sarepta managers to learn about the FDA's regulatory machinery.



Christine McSherry helps her son, Jett, who suffers from Duchenne muscular dystrophy, at their home in Pembroke, Mass. Photo: Adam Glanzman for The Wall Street Journal

Ms. McSherry and Ms. McNary, who was living in Vermont, had met at a camp for boys with DMD in 2011. Ms. McSherry's son didn't qualify for the eteplirsen trial because he could no longer walk. Ms. McNary's oldest son, Austin, couldn't participate for the same reason. Her son Max joined the drug trial and seemed to improve.

On Sept. 12, Ms. McNary's husband at the time tweeted, "Dropped max at school this morning just max no wheelchair." Volume in Sarepta stock soared as investors took note of social-media posts by parents. On Oct. 31, Ms. McNary's husband posted a video of Max walking in a Halloween parade. Shares jumped 10% the next day.

"A big reason investors got more interested in this than they would have in other situations was you had these mothers saying the drug was helping their son," said investment manager Brad Loncar, who bought company shares.

Hidden Influence



- The Rise and Fall of a K Street Renegade

In February 2013, Ms. McSherry and Ms. McNary met with FDA officials and other patient advocates. A 2012 law encouraged the FDA to be flexible when considering applications for therapies to treat such life-threatening diseases as DMD. Ms. McNary brought a petition with more than 170,000 signatures asking the FDA to expedite approval.

That day, the two mothers met Janet Woodcock, the FDA's director of the Center for Drug Evaluation and Research. Dr. Woodcock told them to call her office anytime.

“Janet had the attitude that if the public called on her, she would take a meeting if she could,” Ms. McSherry said. She and Ms. McNary met with Dr. Woodcock and two other top FDA officials in April 2013. Ms. McNary talked about how the drug was helping Max and showed a video of him walking. Ms. McSherry said the FDA told the women to collect more videos, and that even showing how a child could better comb his hair was important.

In August, Sarepta put out a release trumpeting an academic paper on the results of its eteplirsen trial. The paper, published in a neurology journal, said weekly treatments showed a statistically significant increase in dystrophin

By fall 2013, however, the Sarepta campaign suffered a setback. A competitor, GlaxoSmithKline PLC, had completed three trials of a DMD drug that, similarly to eteplirsen, also sought to raise levels of the protein dystrophin. Results of the trials, involving 290 patients, weren’t persuasive.

“Any effect on dystrophin appears to be small as to be unlikely to have resulted in clinical benefit,” the FDA said later in agency documents.

The FDA met with Sarepta to tell the company that GlaxoSmithKline’s study raised doubts about eteplirsen, Sarepta recounted in a Nov. 12, 2013, news release. Share prices fell 64% from the previous day to \$13.

Eyewitness evidence

In May 2014, Frank Sasinowski recognized Max McNary in the cafeteria of the Nationwide Children’s Hospital from his family’s social-media posts, and he introduced himself to Ms. McNary. Mr. Sasinowski, a former FDA lawyer, was hired by Sarepta to help get government approval for eteplirsen.

Ms. McNary had already proven herself an effective advocate, garnering several news stories in print and on TV about how eteplirsen was helping her son Max. Mr. Sasinowski gave her his card and said they should stay in touch.

Oct. 27, 2014

An FDA review of Sarepta’s years long drug trial concludes the company’s data is” uninterpretable,” “unreliable” and”misleading.” After the company’s news release, its stock price falls more than 30%.



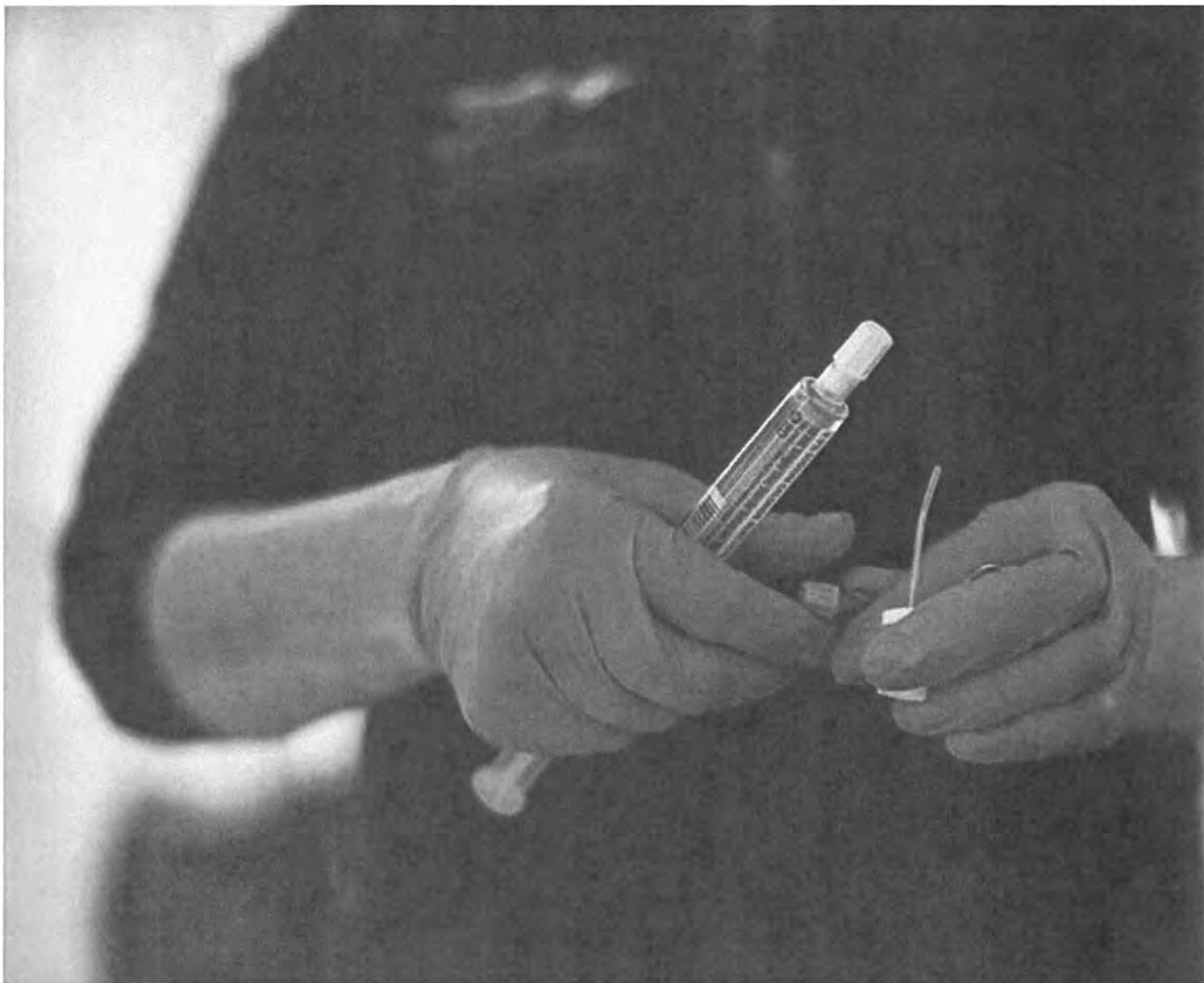
He was at the hospital because the FDA had asked for a review of Sarepta’s trial results. The FDA later said the data was “uninterpretable,” “unreliable” and “misleading,” according to FDA documents. The findings hadn’t been made public. Sarepta said in an Oct. 27, 2014, news release the FDA had found “marked disparities” in the data. The stock price fell more than 30% from the previous day’s closing.

Three more researchers who re-examined the trial data found that eteplirsen produced only a nominal increase in dystrophin in some patients, the FDA said, not the “significant” increase Sarepta had earlier indicated. Additionally, the 2013 article in the neurology journal, and the Sarepta news release that buoyed investors, had “raised wildly unrealistic expectations” among patient families, according to FDA documents.

FDA officials met with Sarepta in the fall of 2014 about its findings and suggested the company add three months of data from 12 to 24 new patients.

Mr. Sasinowski, Ms. McNary and Ms. McSherry were working on a new plan, to show how the boys were improving from the point of view of families and caregivers.

Mr. Sasinowski said he told Sarepta officials, “ ‘You are going to have to trust me,’ and they did.”



Christine McSherry prepares to administer medicine for her son, Jett. Photo: Adam Glanzman for The Wall Street Journal

Ms. McNary and Ms. McSherry told Mr. Sasinowski about their talks with Dr. Woodcock, that the FDA was interested in videos showing how the boys were doing, as well as any quantifiable information on the drug's effect. Dr. Woodcock had given Mr. Sasinowski a similar message in an earlier conversation, he said.

"You could sense the movement of the waters," said Mr. Sasinowski, a consultant, who helps clients navigate the FDA to get drugs approved. The agency, he said, was open to hearing the "patient experience." Videos and stories, he said, would be woven into "something that looked akin to a study report."

Ms. McSherry's son, Jett, got permission to begin eteplirsen treatments in November 2014. At the time, she said, he was having difficulty breathing. Two months later, he was sleeping better and stopped snoring. She said she had concluded that the FDA was too focused on the six-minute walk.

The company began three new trials involving 110 new patients. In June 2015, Sarepta filed its formal drug application, using data from its trials.

Mr. Sasinowski, meanwhile, had been working with the two mothers for months on a parallel set of measurements that the women had gathered. He and an assistant helped them draft a 50-page FDA-friendly document, with bar charts, graphs and tables to show how the boys on eteplirsen fell less and spent less time in wheelchairs.

Mr. Sasinowski said he helped the parents make their report "as close to being acceptable by rigorous reviewers as possible."

In July 2015, Ms. McSherry and Ms. McNary made a two-hour closed-door presentation to FDA officials, including a video of boys who described how eteplirsen had increased their strength. They passed out copies of their report.

Mr. Sasinowski said in an interview he recalled telling FDA officials at the meeting he was working with both parents and the company.

Parents asked the FDA and the company if they could present their findings to the agency's advisory committee, which comprises outside experts. The FDA agreed, and the company gave them a portion of its allocated time at the April 25, 2016 committee hearing.

There was a conflict between the parents' stories of improvement and the FDA's interpretation of the trial. Trial data showed the performance of boys taking the drug had declined in the walk test, the FDA said.

[Interactive: A Roller-Coaster Ride to FDA Approval](#)

Appears this way on the original

Ms. McNary, in contrast, told the panel: “Last week, 14 1/2 year-old Max got out of bed. He got dressed. He put on his shoes and his backpack, and he walked out to the school bus unassisted.”

The advisory committee voted 7-to-6 against accelerated approval, concluding the trial results didn’t provide substantial evidence the drug was effective.

Dr. Ellis Unger, director of the Office of Drug Evaluation, said in a July 15, 2016, memo that the FDA review team had unanimously rejected approval of eteplirsen, agency records show.

On July 14, 2016, Dr. Woodcock, who seldom interceded in drug-approval decisions, overruled both the advisory committee and the FDA review team. In a memo, she said she believed eteplirsen was “reasonably likely to predict clinical benefit.” She declined through a spokeswoman to comment further on her decision.

Dr. Unger appealed to an FDA committee that reviews such disputes. He wrote in his appeal that eteplirsen was a “scientifically elegant placebo,” giving “false hope in exchange for hardship and risk.”

He said it would appear to the public that “unprecedented lobbying efforts” had earned eteplirsen its accelerated approval.

The head of the FDA committee said she agreed with Dr. Unger’s conclusion that the data didn’t show the drug was “reasonably likely” to provide a clinical benefit, according to agency documents. The dispute was sent to Dr. Califf, the FDA commissioner at the time. He deferred to Dr. Woodcock’s “judgment and authority,” an agency memo said.

Sept. 19, 2016

FDA approves use of eteplirsen. In the following days, Sarepta shares more than double to \$60.



On Sept. 19, Ms. McSherry was helping Jett get ready for school when her cellphone buzzed. Her daughter, who was getting the same text messages, yelled from upstairs: “You did it!”

The FDA had approved eteplirsen. Ms. McSherry drove to Mr. Garabedian's house in Boston. "We had a big hug and tears," she said. Within days, company shares more than doubled to \$60.

In December, Congress passed a law intended to expedite the FDA's approval process for new drugs and allowing companies to provide patient input and other information to bolster clinical data.

Sarepta shares have dropped back to \$35. Some insurance companies refuse to cover the drug. A label on the medicine—renamed Exondys 51—says a clinical benefit of the drug "has not been established."

Write to Susan Pulliam at susan.pulliam@wsj.com and Brody Mullins at brody.mullins@wsj.com

From: Guidos, Robert
Sent: Friday, March 10, 2017 5:21 PM
To: JW Direct Reports & Deputies
Cc: LaVange, Lisa; Sitlani, Jay; Joy, David; Kim, Nam; Hayes, Nancy; Bernstein, Jessica; Frey, Patrick
Subject: Gottlieb Press

Two Articles from Inside Health Policy

Daily News

Trump's FDA Pick, Scott Gottlieb, Promises To Bring Reforms To FDA Review Process

March 10, 2017

President Donald Trump has delivered on his promise to shake up FDA by nominating American Enterprise Institute resident fellow and agency veteran Scott Gottlieb to serve as FDA commissioner. Trump's desire to reform what he has called FDA's "slow and burdensome" approval process aligns with Gottlieb's longtime calls to allow the agency more flexibility when reviewing drugs for rare diseases. The White House confirmed the nomination Friday afternoon.

Gottlieb has been seen as industry's favorite among the rumored top contenders for the position, but his plans to cut regulations at the agency have raised concerns among some consumer advocates.

Gottlieb, who served as FDA deputy commissioner under the George W. Bush administration, has been a staunch critic of the agency's approach toward reviewing drugs for rare diseases, and has laid out reform plans that include reorganizing FDA around diseases, basing clinical reviews around particular approaches to drug development, revamping how biomarkers are qualified and pursuing new statistical approaches ([see Inside Health Policy's previous in-depth look at what Gottlieb will mean for FDA reform](#)).

The newly tapped FDA head has also argued that speeding drug approval could lower drug prices, [a view President Donald Trump has also been outspoken about](#).

A longtime FDA observer told *IHP* that the industry will be pleased with the choice. "It means that we will be getting a Commissioner who understands the agency," the source wrote in a statement to *IHP*. "Whatever changes evolve from here, they will at least be informed changes."

Consumer advocacy group Public Citizen came out in strong opposition to Gottlieb's nomination, arguing that his ties to the pharmaceutical industry would pose problems for the agency.

"When Gottlieb served as FDA deputy commissioner, he was recused from many key meetings and decisions due to his close relationship with industry," Public Citizen wrote. "If the Senate does not reject Gottlieb, he will have to be recused from key decisions time and time again, otherwise there is no way to be sure he will put the public's health over industry profits."

The group also does not support his approaches to deregulation of FDA's drug review process. "Gottlieb has advocated dangerous deregulatory approaches to the review process for new medications. In exchange for getting medications to the market faster, Gottlieb is willing to accept a greater degree of uncertainty about safety and effectiveness at the time of approval. He also has favored looser restrictions on off-label promotion," the group wrote. -- *Beth Wang* (bwang@iwpnews.com), *Nicholas Florko* (nflorko@iwpnews.com)

Daily News

Following Trump's criticisms of FDA at joint session of Congress . . .

Gottlieb's FDA Reform Proposals Provide Possible Insight Into Upcoming Agency Efforts

March 01, 2017

President Donald Trump's allegation Tuesday (Feb. 29) that FDA's approval process impedes patient access to drugs aligns closely with criticisms levied for years by a top contender for the FDA commissioner position, Scott Gottlieb. The former FDA deputy commissioner and current resident fellow at the American Enterprise Institute has publicly criticized FDA's handling of rare diseases drug reviews, frequently calling for greater flexibility and less focus on drug efficacy. Gottlieb has also laid out grander FDA reform visions including restructuring the agency around diseases -- possibly signifying what could be in store for the agency should he be selected for the top post.

Despite Trump's insistence that FDA needs to speed up its approval process, the agency is reviewing applications at record speeds and approval rates are at a nearly 30-year high. Additionally, a large portion of applications are going through some form of expedited review, according to a recent presentation by a top FDA official. One consumer advocacy group argued Wednesday (March 1) that Trump's comments "reflect complete ignorance about the FDA's current regulatory schemes."

Trump's joint address to Congress Tuesday highlighted the story of a rare disease patient, Megan Crowley, and blamed FDA's "slow and burdensome approval process" for allegedly keeping treatments out of the hands of patients. Trump also pledged to "slash restraints" at FDA.

"[O]ur slow and burdensome approval process at the Food and Drug Administration keeps too many advances, like the one that saved Megan's life, from reaching those in need. If we slash the restraints, not just at the FDA but across our Government, then we will be blessed with far more miracles like Megan," Trump said.

However, the drug that saved Crowley's life has been cited as an example of FDA's flexibility in approving drugs, and was used by Sarepta Therapeutics to support approval of its controversial Duchenne muscular dystrophy drug, Exondys 51.

"Historically, FDA has exercised some form of regulatory flexibility in the approval of new drugs for serious and rare conditions with unmet medical needs (Sasinowski 2015)," Sarepta wrote in its briefing materials. "An example of FDA's flexibility is demonstrated in the approval of Myozyme (alglucosidase alfa) for the treatment of patients with infantile onset Pompe disease."

While Trump did not provide details on how he planned to “slash restraints,” the policy stances of Gottlieb, rumored to be a top pick for the FDA commissioner post following his appointment to the Trump transition team, may provide clarity as to what changes Trump may be eying.

Gottlieb has been a staunch critic of the agency's approach toward reviewing drugs for rare diseases.

In a December 2010 *Wall Street Journal* op-ed Gottlieb slammed FDA for not approving Pirfenidone to treat the rare disease idiopathic pulmonary fibrosis. Gottlieb alleged that the agency was “evading” the FDA Modernization Act, which gave the agency the ability to approve drugs based on surrogate endpoints and single arm trials. In response, Gottlieb urged Congress to mandate FDA approve drugs for severe conditions “on the basis of a single study, or a more lenient statistical orthodoxy than ‘two, randomized, placebo controlled trials.’”

“[T]he FDA has steadily disregarded many of the law's provisions. Longer, larger trials that require drug makers to evaluate ‘hard’ endpoints (like how long a cancer patient lives) rather than ‘surrogate’ endpoints (like a drug's ability to shrink tumors) give FDA reviewers more statistical confidence. Reviewers prefer these drawn-out trials because they insulate the FDA from critics who say that it isn't focused enough on safety. But bigger trials increase the time needed to develop a drug, keeping it out of the hands of patients,” Gottlieb wrote.

Other suggestions from Gottlieb included mandating the agency convene an advisory panel “to cultivate principles that are more permissive when it comes to very bad diseases,” and establishing a mechanism whereby patient groups could review FDA drug approval decisions.

Gottlieb doubled down on his criticisms of the agency in a March 2016 *Chicago Tribune* op-ed -- this time taking aim at FDA's approach toward drugs to treat Fabry's disease -- arguing that questions of efficacy frequently hang up FDA's approval decisions.

“Some think the FDA is risk-averse primarily out of concerns of drug safety. But when it comes to medicines that target rare diseases, it's rarely a question of safety that hangs up the FDA's decision to approve a new drug. Instead, it's almost always a question of drug efficacy,” Gottlieb wrote.

While Gottlieb maintained in a May 2016 speech that challenges for FDA still remain, it seemed that FDA's oncology center assuaged some of his earlier criticisms of the agency.

“It's important that I note at the outset that much of my past criticism of FDA's handling of these issues was lodged in relation to the agency's cancer drug approval process. And the last time that I could find myself prominently on the record, raising critical issues about FDA's handling of potential breakthrough drugs, was in a 2010 editorial titled ‘FDA is Evading the Law’ that I published in the *Wall Street Journal*. This is not to suggest that I've moved on from these topics -- or that I believe that FDA's challenges are all fully resolved. It's just that I see FDA's oncology group making great strides in recent years to adjust its regulatory process to the scope of the opportunities being enabled by scientific discoveries, advances in medicine, and drug development,” Gottlieb said.

Gottlieb went on to praise the oncology group for its flexible approach to drug approvals, namely its embrace of the breakthrough pathway.

“I believe better science and better drugs, at least as it relates to the oncology division, instigated a lot of FDA's regulatory adjustment. But also, to some degree, it was enabled by implementation of the ‘Breakthrough’ process. And I believe that no FDA division has more fully embraced these methods and the spirit of that law than FDA's cancer group,” Gottlieb said.

Gottlieb also used his March 2016 speech to lay out a four-step FDA reform plan, which he said would “build on the ‘Breakthrough’ policy framework.” The plan included:

Reorganizing FDA around diseases. “I believe it’s time we reconsider the old governmental structures at FDA that place the regulation of drugs and diagnostics in separate ‘Centers.’ There are some diagnostic systems

that are very clearly devices. But more of these tests are closely coupled to the delivery of treatments. We should think about organizing more of FDA’s review process along the lines of medical programs that recognize that many drugs are components of a medical treatment system that incorporates -- and is dependent on -- other products like a diagnostic test,” Gottlieb argued.

Basing clinical reviews around particular approaches to drug development. “[I]t’s often the case that the issues related to a particular type of platform or approach to drug development is a more prominent and challenging feature of the drug review versus the clinical issues. Yet FDA organizes its review process almost solely around the clinical aspects of a product. The problem is that not all clinical review divisions have the same degree of familiarity with different approaches to trial design, statistical analysis, and the product issues related to new platforms for pursuing biological targets. Greater expertise with these areas of the critical path might allow FDA to have more creativity in how it approaches development programs and applies concepts like Breakthrough designation,” Gottlieb explained.

Revamping how biomarkers are qualified. Gottlieb suggested developing “a more systematic and inclusive process for qualifying biomarkers and measures of disease activity that can form the basis of regulatory approvals.” More specifically, he advocated for FDA to accept biomarkers that have been accepted in clinical practice.

Pursuing new statistical approaches. These would include Bayesian analysis, coupled with a recognition that FDA’s review standard is flexible and that the agency’s single standard in Gottlieb’s view is a “false construct.”

“FDA adheres rigidly to a view that there’s a single standard for drug approval. Conceptually, that serves as an important management principle. But in practice, FDA’s statistical and policy standards fluctuate depending on the clinical circumstance. This bureaucratic adherence to a false construct (that there’s one single ‘standard,’ when in practice the agency’s data requirements and prerequisite for different levels of statistical certainty already fluctuate depending on clinical circumstance) is an obstacle to providing more uniformity around when FDA is willing to adjust its requirements, and when it’s not,” Gottlieb explains.

Gottlieb called for radical changes to FDA’s authority in a 2012 *National Affairs* article -- based once again on criticisms of the agency’s approach toward rare diseases. He argued in 2012 that FDA’s review culture was one “devoted to averting risks and protecting the public,” and laid out steps he believed would “change the FDA review culture itself.”

Gottlieb suggested passing approval decisions to a part of the agency separate from the review division, or to a group outside the agency. He argued such a change would “change the way liability is distributed.” He suggested placing this burden on the agency’s “most senior scientists.”

“It is unusual for data on risks and benefits to be so straightforward that the information firmly determines whether a drug should be approved. More often, weighing this data requires judgment; it is inherently a policy call. And having to make that policy call puts undue pressure on the scientific review process, coloring how agency reviewers ask for and evaluate data,” Gottlieb wrote.

Gottlieb argued that Congress should consider restructuring FDA’s authority, perhaps removing the agency’s authority to approve treatments. The Trump FDA contender pointed to the example of the European Medicines Agency, which evaluates but does not make approval decisions.

“This sort of approach -- one that fundamentally re-examines and recasts the FDA’s responsibilities -- would do more than current legislative proposals to speed up the FDA’s drug-approval process without undermining the agency’s ability to protect the public,” Gottlieb wrote.

However, it would appear that FDA's -- and specifically the Oncology Center's -- embrace of the breakthrough designation, may have tempered some of Gottlieb's criticisms, as he appears not to have advocated such sweeping reforms in recent years.

Gottlieb has also recently argued that speeding approval could lower drug prices -- which Trump has pegged a priority. "Making drug development more efficient can also reduce the capital to undertake these efforts, which will allow more drugs to be pursued, and can ultimately lower the costs that need to be recouped after a drug is approved. Drugs are priced, in part, off the cost of capital needed to underwrite the investment, time and risk of developing a new medicine. If these elements can be reduced, so can the cost return needed to underwrite these efforts," Gottlieb said in his May 2016 speech.

However, a recent presentation by FDA calls into question the validity of Gottlieb and Trump's criticisms. FDA is reviewing drugs faster than in recent years -- the agency's median new drug approval time was 7.8 months in 2016, which was down from 10.9 months in 2015 and 8.1 months in 2014, according to a Dec. 14 presentation from former Office of New Drugs director John Jenkins.

Companies are also increasingly utilizing FDA's expedited approval pathways. Sixty-eight percent of drugs in 2016 were approved under priority review, 37 percent received fast-track designation, and 32 percent received breakthrough-designation, according to Jenkins.

FDA's New Molecular Entity (NME) approval rate under PDUFA V is also at a record high since at least 1988, and at an all-time high for all of the prescription drug user fee cohorts. Nearly 90 percent of NMEs are approved within 18 months under PDUFA V, compared to roughly 60 percent under PDUFA IV and 55 percent under PDUFA III in the same time period. Neither of the past two user fee agreements achieved a near 90 percent NME approval rate.

However, Chad Landmon, head of Axinn Veltrop & Harkrider's FDA practice, maintained that while it probably is the case that PDUFA has sped FDA up, there are those in industry that think the agency can take actions to further speed products' entry to market. Landmon cited increased clarity through communication between the agency and sponsors as one way to possibly accelerate the process.

Public Citizen slammed Trump in a March 1 press release, arguing that Trump's comments "reflect complete ignorance about the FDA's current regulatory schemes."

"[O]ver the past three decades Congress has created, and the FDA has routinely used, several pathways for expediting the review and approval of promising new medications for treating serious or rare diseases. Indeed, since 2000, the FDA has reviewed applications for novel medications more quickly, on average, than its counterparts in Canada and Europe, and the vast majority of these new products were approved first in the U.S." Michael Carome, director of Public Citizen's Health Research Group, wrote. -- *Nicholas Florko*

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Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 1:20 PM
To: DeMarco, Devota R
Subject: RM - FW: DMD

From: Dunn, Billy
Sent: Saturday, February 25, 2017 7:54 AM
To: Moscicki, Richard
Subject: RE: DMD

Thanks, Rich. We did get a message from her but if memory serves it was complicated because she was referring to confidential information. I'll go back and look at the request and see what we can do. Appreciate the heads-up.

Billy

From: Moscicki, Richard
Sent: Thursday, February 23, 2017 2:46 PM
To: Dunn, Billy
Subject: DMD

Hi Billy, I flew in to DC very early Tuesday and Christine McSherry was on the flight and button holed me to discuss some thoughts. She said she had emailed you repetitively but hadn't heard back. She believes strongly that the postmarketing trial for eteplirsen is designed to fail. She feels clinical effect could easily be detected in advanced boys with the disease using nonambulatory measures in short times and urged us to urge sponsors to look at that. She offers some clarification in a subsequent email that I will forward to you separately. I said I would forward these thoughts to you and your team. Rich.

Philips, Howard

From: Guidos, Robert
Sent: Tuesday, January 24, 2017 11:27 PM
To: Woodcock, Janet; Throckmorton, Douglas C; Pretti, Jeffery; Mullin, Theresa; Clarke, Mary Beth; Moscicki, Richard
Subject: More on Gulfo

Follow Up Flag: Follow up
Flag Status: Flagged

From Inside Health Policy...

DAILY NEWS

Exclusive interview . . .

Trump Eyes FDA Critic Gulfo To Head Agency, Gulfo Outlines Agenda To IHP

January 24, 2017

Self-described FDA law originalist Joseph Gulfo, who has been an outspoken advocate for cutting regulations and reforming FDA approval policies to speed market access, is rising to a top spot on President Donald Trump's list of potential FDA commissioners, a source in touch with the transition team tells *Inside Health Policy*. Gulfo, in an interview with *IHP*, confirmed he has been in talks with the Trump team, and laid out FDA reform ideas that include letting the agency approve drugs based on a variety of criteria and through a conditional review system -- reforms he said would spur competition and cut drug prices by up to 30 percent without regulatory intervention, thus delivering on Trump's promise of cutting drug prices.

The Trump transition team is also adding former HHS official and former lobbyist Jack Kalavritinos to its team tasked with charting the future of FDA.

Gulfo is currently a senior fellow at the Progressive Policy Institute, executive director and professor of health sciences at the Lewis Center for Healthcare Innovation and Technology at Fairleigh Dickinson University, and CEO of Breakthrough Medical Innovations, a consulting, advertisement and advocacy firm for biopharma and medtech companies.

Gulfo confirmed to *IHP* that he has had conversations with Trump transition officials and their consultants. Gulfo called the opportunity, "very humbling" and "very exciting," but declined to further comment.

A former senior House leadership aid told *IHP* that Trump transition officials and senior congressional staffers have told him that Gulfo is rising to the top of the list for FDA Commissioner picks. "I am hearing Joseph Gulfo is surging. Apparently, the Trump team really appreciates his real world experience in this space -- he's a doctor, business guy, and academic all in one package," the former aid wrote.

Gulfo has also taken to Twitter to express his interest in the FDA commissioner position. "And, I'd be honored to serve @realDonaldTrump and bring real reform to the #FDA," Gulfo tweeted Jan. 19.

Gulfo described himself to *IHP* as an "innovation first guy." He is also a staunch critic of more regulation, calling himself an "originalist when it comes to FDA law."

"[T]he FDA needs to get back to its lawful mission, which is to promote health," Gulfo wrote in a Dec. 2016 blog for *The Hill*, entitled "What President-elect Trump's New FDA Commissioner Needs To Do."

Gulfo told IHP that he takes issue with FDA allegedly moving from promoting health to a focus on protecting health. At a February 2016 Senate Homeland Security hearing on patient access to treatments, Gulfo disputed claims that FDA can truly protect public health.

He told lawmakers that the two missions differ. “[A]s drugs are small molecules designed to have an effect by binding to targets in the body, it is impossible to give assurance that no harm will ever occur. Of course, protecting health is part of promoting health, however, the FDA has elevated 'protecting' health as its main mission. Promoting and protecting health are two different postures -- the latter looks to preserve that which currently exists while the former engenders optimism and belief in the advancement of scientific discoveries as a means of improving the health of Americans. Implicit in promoting health is an understanding that occasionally new products may not be found to be as desirable as we would like them to be, however, the only way to have genuine progress is to accept and deal with 'bleeding edge' issues as we try to bring cutting-edge treatments and diagnostics to patients as soon as possible,” Gulfo stated.

Gulfo declined to highlight any FDA policies that he would immediately put on the chopping block, should he be nominated and confirmed, stating he did not yet have the visibility to make that determination. However, he maintained that if commissioner, he would examine policies and roll back any that decrease efficiency.

Reforming FDA's approval process:

Gulfo is a strong critic of FDA's approval process, and has frequently argued that the agency has gone beyond its statutory mandate by focusing too heavily on pre-approval and post-approval requirements. Instead, Gulfo has advocated for a restatement of safety and effectiveness as the only standards on which FDA may base approval.

“[W]e need to make the FDA return to using safety and effectiveness as the sole basis of approval, as stated in the law. In lieu of safety and effectiveness, the FDA now preferentially mandates long term outcomes, survival, and their evaluation of clinical utility and benefit-risk -- this drives R&D cost, time, and uncertainty,” Gulfo wrote in *The Hill*. Gulfo raised similar concerns in a November 2015 *Wall Street Journal* op-ed, “A Trumpian Cure for the FDA's Chronic Lethargy.”

“The first change involves returning the FDA to its original role under the law. That is to prevent snake oil from getting on the market by ensuring that the only drugs approved for sale have demonstrated biological activity in fighting a disease and can be labeled for safe use. The FDA would no longer require approvals based on long-term health outcomes--a practice that dissuades development and increases the complexity, cost and duration of clinical trials,” Gulfo wrote.

Gulfo does not oppose post-approval studies, but believes they should have no teeth to pull a product from market. “Post-approval studies should be limited to amassing greater safety databases to inform labeling. Studies performed to generate evidence for higher order effectiveness claims shall not result in market withdrawal if higher order effectiveness objectives are not met,” Gulfo stated at the February Senate hearing.

The commissioner candidate believes FDA should be able to approve drugs based on four categories: effect on biomarkers; improvements in clinical signs and symptoms; disease modification and modulation; and long-term outcomes. FDA could approve a product based on any of these categories, so long as it discloses on which category a product's approval was based.

“These categories would form the basis of approval, and the labels would be color-coded so that physicians and patients know precisely the nature of the clinical evidence used to prove that the drugs are effective and what to expect when using them,” Gulfo wrote in the *Wall Street Journal*.

While Gulfo has previously advocated for legislation to create these categories, he maintained Tuesday that FDA could likely do so without legislation under its mandate to promote health.

Establishing conditional approval:

FDA also needs a conditional approval system similar to the European Medicines Agency system, according to Gulfo.

To be approved under the EMA conditional approval system, a product must fulfill four criteria:

1. “The risk-benefit balance of the product is positive.”
2. “It is likely that the applicant will be able to provide comprehensive data.”

3. "Fulfillment of unmet medical need."
4. "The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required."

FDA's Sarepta decision:

Gulfo supported FDA's decision to go against its advisory committee and approve Sarepta Therapeutics'

Duchenne muscular dystrophy drug, arguing that FDA did not lower its approval standard and that the questions asked to the panel skewed the vote.

"So, what is the lesson? One, no, the FDA did not lower its standards in the approval of eteplirsen -- the drug is safe and has biological activity, as well as clinical activity seen in a non-randomized study. Two, the FDA needs to ask its AdComms direct, unambiguous questions that capture their approvability recommendations. Had they done so, there would have been no second-guessing and no Sturm und Drange over their decision to approve eteplirsen," Gulfo wrote.

However, Gulfo argued in a May 2016 *Forbes* column that FDA should have conditionally approved a Duchenne drug earlier. "What is disappointing to DMD patients and their families, and to millions of other Americans, is that the FDA does not have a real conditional approval system. Perhaps, the eteplirsen debate will finally impel the FDA or Congress to establish such a system, akin to the EMA," Gulfo wrote.

Despite an emphasis on getting treatments on the market, Gulfo has distanced himself from controversial commissioner contender Jim O'Neill, who has argued drugs should only be proven safe, not effective. "If you want safe snake oil, Jim O'Neill's your man," Gulfo recently told *MedPage Today*.

Drug Pricing:

Reforming FDA's approval process would reduce development and review times, increase clarity and competition, and create a "steady stream of approvals," ultimately lowering drug prices by up to 30 percent, Gulfo told *IHP*.

Gulfo argued that reforming the FDA approval process would shorten drug development time by two years effectively giving companies two additional years of exclusivity, and this would create "less pressure for very very high pricing." On the issue of competition, Gulfo used a hypothetical example of two drugs in the same class, one of which is approved for disease modification and the other for effect on biomarker. Gulfo argued both should be approved and then payers could decide which to pay more for.

Comparative effectiveness:

Gulfo has spoken out against FDA's use of comparative effectiveness trials.

"Choosing to base FDA decisions on benefits and risks implies that the FDA will take on the decision roles of physicians and patients, attempting to anticipate or predict their future choices. Requiring comparative effectiveness trials is a logical but unfortunate consequence of such an attempt because someone must choose *among* drugs. Requiring comparative effectiveness trials further adds to the cost and time it takes to develop new drugs. If required to better inform medical decision-making, benefits and risks, and comparative effectiveness, can and should be analyzed post-approval, in the medical marketplace. If certain payers demand comparative effectiveness trials, it need not be an FDA function to oversee such trials," Gulfo said at the February 2016 Senate hearing.

"Let markets do more. Don't let it be a matter of regulation," Gulfo told *IHP*.

Drug importation:

Despite calls by Trump to allow for importation of drugs, Gulfo declined to take a stand on the hot-button issue. Gulfo maintained that his two largest concerns are the policy's impact on innovation and the quality of the drugs, and that he would need to look at specific proposals more closely.

Off-label communication:

On off label communication, Gulfo argues for a standard more akin to what he described as the Federal Trade Commission standard, adding a company must be able to prove the claim it is making.

However, he also maintained that medical professionals need information for off-label prescribing, and companies should be able to provide that so long as there are data to back up the company's claims.

"I think off-label promotion is actually a safety issue in reverse," Gulfo told *IHP*.

21st Century Cures:

Gulfo has also spoken out against the 21st Century Cures law, which the most recent FDA Commissioner, Robert Califf, threw his support behind.

The FDA doesn't need the 21st Century Cures Act because "it has already been empowered to the fullest extent possible by the Federal Food, Drug, & Cosmetic Act (FD&C)," Gulfo wrote in an op-ed for *The Daily Caller*.

Cures creates a "completely superfluous" expedited approval pathway for medical devices, according to Gulfo. However, the Advanced Medical Technology Association highlighted that new pathway as the most significant of the provisions in Cures for the device industry.

Gulfo argues that FDA's existing breakthrough designation has "completely corrupted biopharma development efforts preferentially toward narrow niche claims," and that the new device pathway will do the same.

Gulfo also criticized 21st Century Cures for creating more regulation. "The reason that 21st Century Cures was undertaken in the first place is because the FDA has not been performing in a manner consistent with its lawfully mandated parameters with respect to review and approval times. This has occurred despite mounting regulations -- many passed as part of the Prescription User Fee Act and its multiple reauthorizations -- designed to increase the transparency and speed of reviews... All of this has not worked, yet, this is exactly what 21st Century Cures is -- more laws, rules, and guidance documents. And with all of these provisions, some have actually said that the \$550 million is not enough for the FDA to implement 21st Century Cures!" Gulfo wrote.

When asked to comment on the purported benefits of added funding and hiring ability for FDA under Cures, Gulfo argued those wouldn't be necessary if there was less regulation. "[I]f we got back to the original tenants of the law we wouldn't need it, we wouldn't need more budget, we wouldn't need more hiring," Gulfo said.

Gulfo took issue with user fee agreements for similar reasons, however, he maintained he has no problem with user fees, so long as they are clean bills. "I hate that every 5 years we are adding to regulatory law," Gulfo added.

Ending expedited approvals:

At the February 2016 Senate hearing, Gulfo called for an end to FDA's breakthrough, accelerated approval, fast-track, priority review and accelerated approval programs. "[W]ith enforcement of the effectiveness standard...and with the FDA meeting its review time frames, these programs will no longer be needed," Gulfo stated.

Expanding FDA role in compounding oversight:

Despite his disdain for regulation, Gulfo does want greater FDA authority for regulation of compounding. In a column for *Forbes*, Gulfo argues for legislation mandating outsourcing facilities register with FDA and abide by good manufacturing practices.

"Over the past few weeks, the FDA has devoted lots of attention to compounding pharmacies, issuing two new guidance documents pertaining to their fundamental scope, a guidance document regarding insanitary conditions, and revised inspection procedures. Given some recent high profile safety problems, including patient deaths as a result of contaminated sterile compounding products, the FDA has come under great scrutiny. But, it is not the FDA's fault," Gulfo wrote in the August 2016 column.

The Trump transition team is also adding Jack Kalavritinos to its FDA's beachhead team. Kalavritinos' most recent FDA-related job was director of government affairs at Covidien and he previously served as director of HHS' office of intergovernmental affairs. Kalavritinos' *LinkedIn* profile lists him as a team member at "Transition" since December 2016.

A former HHS official turned industry attorney told *IHP* that Kalavritinos will be doing external affairs for the beach head team, but that it is unclear whether he will stay on after an FDA commissioner is tapped.

Beachheads will be integral to determining an agenda for change at FDA and often end up take jobs at the agency, accord to one FDA policy watcher.

"They are the successor to the transition teams -- they will be larger and generally have individuals with legislative or policy experience in the areas covered by the department or agency. The beachhead teams will be getting in-depth briefings and making assessments of how the agency is performing and start to develop an agenda for changes that they think the agency head, once confirmed, should undertake. Many of those in the beachhead will stay on and

serve the new Administration in the agency to which they have been assigned. As the advanced guard, they will be keeping an eye on the acting agency heads, making sure that no decisions are being made that should wait for a new leader to be confirmed," wrote Alliance For a Stronger FDA Deputy Executive Director Steven Grossman. -- *Nicholas Florko (nflorko@iwpnews.com)*

Related News | 21st Century Cures | Medical Devices | Rx Drugs | Trump Transition | 94286

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 9:50 AM
To: DeMarco, Devota R
Subject: RM - The FDA News Summary for Wednesday, October 05, 2016
Attachments: FDA161005.doc; FDA161005.pdf; WSJ FDA Warns on Hepatitis C Drugs.doc

From: Staffa, Edward
Sent: Wednesday, October 05, 2016 7:33 AM
To: Woodcock, Janet; Throckmorton, Douglas C; Temple, Robert; Moscicki, Richard
Cc: Agajelu, Ogochukwu *; Bechtel, Christine; Bennett, Carol; Bernstein, Ilisa; Blount, Aprile; Bolek, Michelle; Buckman, Paul; Buckman-Garner, ShaAvhrée; 'Cain, Brutrinia'; Carpenter, Courtney; CDER Trade Press; Christl, Leah A; Clarke, Mary Beth; Clark-Lynn, Sarah; Corrigan, Dara; Cosgrove, Thomas; Dal Pan, Gerald; Echegoyen, Edwin; Elliott, Deborah; Fischer, Andrea (FDA); Frey, Patrick; Frydl, Andrea; Goldsmith, Jonathan; Guidos, Robert; Huang, Sheilyn; Hunter, Nina L; Ikenberry, Sarah; Iles, Irina *; Jackler, Karen; Jenkins, John K; Jerrick, Morgan; Keller, Melanie; 'Kelly, Christopher'; Kim, Sarah; Kochel, Bridget; Kopcha, Michael; Kornegay, Cynthia J; Kremzner, Mary E; Lee, Tracey (FDA); Lilly, Trudy; Lister, Sherunda; Lowy, Naomi; McCune, Susan; Meyer, Lyndsay; Moeny, David; Mullin, Theresa; OGDREQUEST; O'Grady, Jordana; CDER OSE OCT; Pattee, Suzanne; Peddicord, Sarah; Pinheiro, Simone P; Rausch, Paula (FDA); Rawlings, Kimberly; 'rosa.gonzalez-quevedo@ema.europa.eu'; Rowzee, Anne; Ruiz, Diane; Shaham, Lauren; Sherman, Rachel; Shreeve, Chris; Sims, Anthony E; Sipes, Grail; Sklamberg, Howard; Smith, Harry; Staffa, Edward; Staffa, Judy A; Staton, Anna; Stowe, Ginneh D.; Toigo, Theresa A; Uhl, Kathleen (CDER); Unger, Ellis; Unger, Monica; Wang, Cunlin; Whyte, John; Winthrop, Sally; Yu, Lawrence
Subject: FW: The FDA News Summary for Wednesday, October 05, 2016

Good morning... in the clips today: FDA DSC Announces Boxed Warnings for Hepatitis C Drugs... CNN Profiles Families Affected by DMD in Discussion of the Approval of Eteplirsen... Today's AC Will Discuss Standard Dosage of Naloxone for Overdose... Portman/McCaskill Report: Medicare's Lack Of Federal Controls May Feed Opioid Crisis... Some Advocate for U.S. To Adopt "Drug Checking" Samples of Illegal Drugs... Young Adults In U.S. Were More Likely To Be Addicted To Opioids In 2014 Than 2002, Study Suggests... New Jersey, Maryland Health Officials Warn Providers Against Certain Saline Products Because Of Potential Drug-Resistant Bacteria Outbreak... Report Concludes FDA Guidelines Aimed At Reducing Use Of Antibiotics In Animal Agriculture Are Insufficient.

FDA DSC Announces Boxed Warnings for Hepatitis C Drugs. Following yesterday's (10/4) [DSC](#), the [Wall Street Journal](#) (see attached) reports the FDA "is warning about the risk of reactivation of hepatitis B among patients who have had that disease and who are taking some prominent and expensive newer medicines for hepatitis C," and, "is requiring a so-called black-box warning in the labels for at least nine brand-name direct-acting antiviral drugs, including Sovaldi and Harvoni, Viekira Pak, and Zepatier. [NBC News](#) also reports.

CNN Profiles Families Affected by DMD in Discussion of the Approval of Eteplirsen [CNN](#) profiles the efforts of parents and families who fought for the FDA approval of eteplirsen to treat Duchenne muscular dystrophy (DMD). The article discusses various views on the approval issue.

Today's AC Will Discuss Standard Dosage of Naloxone for Overdose. Referring to [today's AC](#) (10/5) on naloxone, [U.S. News & World Report](#) reports, "A meeting on Wednesday between the FDA and pharmaceutical companies that make the anti-overdose, life-saving medication naloxone could alter the drug's pricing as well as how available it will be to the general public." The article notes there are "only two" naloxone products for overdose on the market: Narcan nasal spray and EVZIO auto-injector --- and

discusses how a central discussion point for this AC will be to help determine standardized dosing for naloxone to treat overdose.

Portman/McCaskill Report: Medicare's Lack Of Federal Controls May Feed Opioid Crisis. The Washington Times reports Sens. Rob Portman (R-OH) and Claire McCaskill (D-MO), who lead the Senate's permanent investigative panel, revealed in a report Monday that "Medicare spending on opioids is skyrocketing, but the agency's investigations into misuse have plummeted in the last couple of years...suggesting that a lack of federal controls could inadvertently be feeding the prescription drug abuse epidemic." Their report "faulted the administration and its contractor for not digging deep enough into prescribing patterns," and cited a physician "who was prescribing an unusual amount of narcotic oxycodone, but was cleared after a cursory search for licensing problems, suspended payments from Medicare or additional complaints about him in their system."

Some Advocate for U.S. To Adopt "Drug Checking" Samples of Illegal Drugs The AP reports "some observers" have suggested that the U.S. should begin testing samples of illegal drugs to identify what substances they contain, a practice known as "drug checking." The article suggests that this practice may have been able to prevent Prince's death from a fentanyl overdose, and explains that some European countries allow drug users to "turn in drug samples for chemical analysis and are alerted if dangerous additives are found," and some are advocating that the US should adopt a similar practice. The article points out that many drug users in the U.S. may take drugs not knowing what they are.

Young Adults In U.S. Were More Likely To Be Addicted To Opioids In 2014 Than 2002, Study Suggests. HealthDay reports the chance that young adults in the US will become addicted to opioids or develop an opioid use disorder increased significantly between 2002 and 2014, according to a recent study published in the journal *Addictive Behaviors*. Researchers from Columbia University also found that the use of heroin among young people "soared" during the same period of time.

New Jersey, Maryland Health Officials Warn Providers Against Certain Saline Products Because Of Potential Drug-Resistant Bacteria Outbreak. The Newark (NJ) Star-Ledger reports New Jersey health officials "are warning nursing homes to stop using pre-filled saline products because of possible contamination with drug-resistant bacteria" after identifying "two possible cases of infection by the *Burkholderiacepacia* bacteria, which has become resistant to many antibiotics." The Baltimore Sun reports that health officials in Maryland "are warning healthcare facilities, providers and others not to use the Nurse Assist brand of pre-filled saline flushes as they investigate a possible link to bloodstream infections, including 11 cases in Maryland." The Texas-based company "told health officials from several states Tuesday that it would issue a voluntary recall on the saline flush because they may be spreading *Burkholderia cepacia* bloodstream infections."

Report Concludes FDA Guidelines Aimed At Reducing Use Of Antibiotics In Animal Agriculture Are Insufficient. STAT discusses a report from Pew Charitable Trusts that concluded new guidelines from the FDA aimed at reducing the use of antibiotics in animal agriculture will be insufficient noting the FDA's new policy contained "loopholes that could allow the food animal industry to keep using the drugs to hit production goals."

From: Bulletin Intelligence [<mailto:FDA@BulletinIntelligence.com>]

Sent: Wednesday, October 05, 2016 6:09 AM

To: FDA@bulletinintelligence.com

Subject: The FDA News Summary for Wednesday, October 05, 2016

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TO: THE COMMISSIONER AND SENIOR OFFICIALS

DATE: WEDNESDAY, OCTOBER 5, 2016 6:00 AM EDT

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FDA IN THE NEWS

CNN Profiles Fight For Approval Of DMD Drug.

CNN (10/4, Kounang, 31.54M) profiles the efforts of Jenn McNary and other families who fought for the FDA approval of eteplirsen to treat Duchenne muscular dystrophy. The article also reviews the controversy within the agency over the drug's approval, quoting several FDA officials and FDA commissioner Dr. Robert Califf, who wrote that "the quality of thinking on both sides reflects the importance of clinical and scientific expertise coupled with due process within the FDA."

MEDICAL PRODUCT SAFETY

Copper Equipment May Reduce Infections In Hospitals, Study Suggests.

The New York Times (10/4, Bakalar, Subscription Publication, 13.42M) reports

copper equipment may reduce infections in hospitals, according to a study published in the American Journal of Infection Control. Researchers installed "copper faucet handles, toilet flush levers, door handles, light switches and other commonly touched equipment" in "nine rooms in a small rural hospital" and found that there was less bacteria in those rooms compared to other rooms with "traditional plastic, porcelain and metal surfaces."

J&J Warns Insulin Pump At Risk For Hacking.

USA Today (10/4, Weise, 6.42M) reports that Johnson & Johnson "issued a warning about a possible cybersecurity issue with its Animas OneTouch Ping Insulin Infusion Pump." Rapid 7, a cybersecurity firm, "discovered that it might be possible to take control of the pump via its an unencrypted radio frequency communication system that allows it to send commands and information via a wireless remote control." J&J said there have been no cases of the device being hacked thus far.

Bloomberg News (10/4, Cortez, 2.49M) reports that J&J "said it has worked to address the issues and laid out steps patients can take to reduce their risk, such as turning off the pump's wireless connection to a blood sugar meter, or setting a limit on the amount of insulin that can be delivered."

Reuters (10/4, Finkle) reports that J&J advised that the probability of such an attack "is extremely low" because "it would require technical expertise, sophisticated equipment and proximity to the pump, as the OneTouch Ping system is not connected to the internet or to any external network."

Additional coverage is provided by the Philadelphia Business Journal (10/4, George, Subscription Publication, 36K), the Washington Times (10/4, Blake, 280K), Fierce Biotech (10/4, Al Idrus, 3K), Mass Device (10/4, Perriello, 1K), mHealth Intelligence (10/4), and BBC News (UK) (10/4, 2.9M).

Some Advocate For US To Adopt "Drug Checking." The AP (10/4, Johnson) reports "some observers" have suggested that the US should begin testing samples of illegal drugs to identify what substances they contain, a practice known as "drug checking." The article explains that some European countries allow drug users to "turn in drug samples for chemical analysis and are alerted if dangerous additives are found," and some are advocating that the US should adopt a similar practice. The article points out that many drug users in the US may take drugs not knowing what they are.

Report Concludes FDA Guidelines Aimed At Reducing Use Of Antibiotics In Animal Agriculture Are Insufficient. The Wall Street Journal (10/4, Bunge, Subscription Publication, 6.37M) highlights a report from Pew Charitable Trusts that concluded new guidelines from the Food and Drug Administration aimed at reducing the use of antibiotics in animal agriculture will be insufficient. The article also mentions different efforts taken by the FDA, the CDC, and other agencies to reduce the unnecessary use of antibiotics.

STAT (10/4, Branswell) reports that the report from Pew Charitable Trusts concluded that the FDA's new policy contained "loopholes that could allow the food animal industry to keep using the drugs to hit production goals."

FDA Meeting Could Determine Standard Dosage Of Naloxone For Public. U.S. News & World Report (10/4, Leonard, 759K) reports that a "meeting on Wednesday between the Food and Drug Administration and pharmaceutical companies that make...naloxone could alter the drug's pricing as well as how available it will be to the general public." The agency "will use Wednesday's meeting to determine whether naloxone devices distributed in

communities should contain a standard dose of the drug." The FDA "declined to comment on the meeting other than to say that making naloxone more accessible is part of ongoing efforts by the administration to respond to the country's opioid epidemic."

FDA Says Hepatitis C Drugs Must Carry Boxed Warnings. The Wall Street Journal (10/4, Burton, Subscription Publication, 6.37M) reports the FDA said it will require boxed warnings on Gilead's Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir), AbbVie's Viekira Pak (ombitasvir/paritaprevir/ritonavir with dasabuvir), and Merck's Zepatier (elbasvir and grazoprevir), all hepatitis C drugs the agency says can possibly reactivate hepatitis B in patients who have already had that form of the disease. The decision on warning labels stems from 24 cases of hepatitis B being reactivated between November 22, 2012 and July 18, 2016. NBC News (10/5, 5.08M) provides additional coverage on its website.

Lack Of Federal Controls May Inadvertently Feed Opioid Crisis, Senators Say. The Washington Times (10/4, Howell, 280K) reports Sens. Rob Portman (R-OH) and Claire McCaskill (D-MO), who lead the Senate's permanent investigative panel, revealed in a report Monday that "Medicare spending on opioids is skyrocketing, but the agency's investigations into misuse have plummeted in the last couple of years...suggesting that a lack of federal controls could inadvertently be feeding the prescription drug abuse epidemic." Their report "faulted the administration and its contractor for not digging deep enough into prescribing patterns," and cited a physician "who was prescribing an unusual amount of narcotic oxycodone, but was cleared after a cursory search for licensing problems, suspended payments from Medicare or additional complaints about him in their system."

Fitness Trackers May Not Improve Health, Study Suggests. The AP (10/4, Cheng) reports that research suggests "wearing a fitness tracker may help you keep tabs on how many steps you take, but the devices themselves – even with the lure of a cash reward – probably won't improve your health." The research was published Lancet Diabetes & Endocrinology. These findings, according to the AP, "seem to reinforce" the findings of another study recently published in the Journal of the American Medical Association, which "found that adding wearable activity tracking devices to a diet and fitness program didn't result in more weight loss." Also covering the story are TIME (10/4, Oaklander, 6.62M) and HealthDay (10/4, Pallarito, 24K).

Debate Over Statins Discussed. In the Washington Post (10/4, 10.14M) "To Your Health" blog, Kerry Lauerman,

the Post's national projects editor, discusses the debate over statins, writing that although "nearly all experts agree that statins are beneficial for people at a substantial risk for heart disease, some medical researchers argue that statins do little or no good – and possible harm – for people at lower risk of heart disease." Lauerman points out that "a 2011 study showed at least 32 million Americans are on a statin, and under 2013 guidelines issued by the American Heart Association and the American College of Cardiology, another 24 million or so Americans should probably be on one...to help prevent heart attacks and heart disease."

Some Men With Prostate Cancer Spending Thousands Of Dollars For New Procedure Whose Long-Term Effects Are Unknown.

Kaiser Health News (10/4, Appleby, 2K) reports that "men hoping to avoid some of the dreaded side effects of prostate cancer treatment are shelling out tens of thousands of dollars for high-intensity focused ultrasound (HIFU), "a new procedure whose long-term effects are unknown, even though insurers, including Medicare, generally won't pay for it." In the US, "advisory committees to the" FDA "twice recommended against applications from manufacturers to market HIFU devices as a treatment for prostate cancer, citing an insufficient amount of long-term evidence." Last year, however, "the FDA approved...SonaCare Medical's device – not for the treatment of prostate cancer per se, but for the ablation of prostate tissue." In its review, the agency said, "While the oncological outcomes from this study are inconclusive, the results provide reasonable assurance of safety and effectiveness of the device in the context of prostate tissue ablation."

Young Adults In US Were More Likely To Be Addicted To Opioids In 2014 Than 2002, Study Suggests.

HealthDay (10/4, Preidt, 24K) reports the chance that young adults in the US will become addicted to opioids or develop an opioid use disorder increased significantly between 2002 and 2014, according to a new study published in the journal *Addictive Behaviors*. Researchers from Columbia University also found that the use of heroin among young people "soared" during the same period of time.

HHS IG Recommends Including Unique Device Identifier On Claims Forms.

Modern Healthcare (10/4, Livingston, Subscription Publication, 235K) reports the HHS Inspector General found that "CMS can't track how much recalled and defective medical devices cost Medicare," because claims forms do not have sufficient medical device information. HHS Inspector General Daniel Levinson

recommends the addition of the "unique device identifier" of any device to "make it easier to count and save costs."

Two Bills Aim For More Regulation Of Cosmetics And Beauty Products.

WebMD (10/4, Edgar, 5.46M) reports the Food and Drug Administration "doesn't have the authority to recall" beauty "products on its own or to test a product for safety until someone complains." Recently, Congressional lawmakers "introduced two bills pushing for more regulation of cosmetics: the Safe Cosmetics Modernization Act, introduced by Rep. Pete Sessions, R-TX, and the bipartisan Personal Care Products Safety Act, co-sponsored by Sens. Dianne Feinstein (D-CA) and Susan Collins (R-ME)." Both measures "would require companies to register with the FDA, submit product ingredient lists, notify the FDA of any reports of serious side effects, and authorize the FDA to prohibit the sale of products that have been found to cause serious health risks." The piece adds, "Ingredients like parabens are endocrine-disrupting and can affect reproduction and organ development, says Heather Patisaul, PhD," who "is a spokeswoman for the 18,000-member Endocrine Society, which supports the Feinstein-Collins bill."

New Jersey, Maryland Health Officials Warn Providers Against Certain Saline Products Because Of Potential Drug-Resistant Bacteria Outbreak.

The Newark (NJ) Star-Ledger (10/4, O'Brien, 438K) reports New Jersey health officials "are warning nursing homes to stop using pre-filled saline products because of possible contamination with drug-resistant bacteria" after identifying "two possible cases of infection by the *Burkholderiacepacia* bacteria, which has become resistant to many antibiotics."

The Baltimore Sun (10/4, McDaniels, 821K) reports that health officials in Maryland "are warning healthcare facilities, providers and others not to use the Nurse Assist brand of pre-filled saline flushes as they investigate a possible link to bloodstream infections, including 11 cases in Maryland." The Texas-based company "told health officials from several states Tuesday that it would issue a voluntary recall on the saline flush because they may be spreading *Burkholderia cepacia* bloodstream infections."

Medicare Spent Billions On Faulty Medical Devices, HHS Audit Reveals.

The Minneapolis Star Tribune (10/4, Carlson, 1.29M) reports an audit published by Daniel Levinson, the inspector general of the Department of Health and Human Services, found that Medicare has spent approximately \$1.5 billion on seven types of defective heart devices that physicians implanted in thousands of beneficiaries. Sens. Chuck Grassley and Elizabeth Warren are endorsing a proposal to require hospitals and physicians

to include a medical device's tracking code on claims forms to prevent future use of defective devices. FDA data show the number of medical device recalls doubled between 2003 and 2012. Analysts said the actual costs of the defective devices to the taxpayer will be higher than the audit suggested, because of "ancillary costs like future adverse health events, the need for continued medical monitoring, and lost wages and productivity."

Former Senator Coburn Calls For FDA Reform.

The Fairfield County (CT) Business Journal (10/4, Forni, 31K) reports that former Sen. Tom Coburn (R-OK), speaking at the Health Tech '16 conference, said, "Every year tens of thousands of people are dying that should not be dying and it's our inability to have a regulatory environment and a leadership system that would solve that problem." Coburn called for faster approval of new drugs and increased funding for the agency, saying, "The limitations of new drugs is one of the things that really hurts us."

FDA Grants Second Breakthrough Therapy Designation To Roche's Alectinib.

Reuters (10/4, Koltowitz) reports that Roche announced that "its lung cancer drug Alecensa (alectinib), developed by its Genentech unit, received a second breakthrough therapy designation (BTD) from the U.S. Food and Drug Administration (FDA) for its anaplastic lymphoma kinase (ALK) inhibitor." The designation "was granted for the treatment of adult patients with advanced ALK-positive non-small cell lung cancer (NSCLC) who have not received prior treatment with an ALK inhibitor."

Fierce Pharma (10/4, Helfand, 3K) reports that the designation "puts the drug on track for a speedy trip down toward approval," and it will also "help Alecensa take on its Pfizer rival, which racked up \$488 million in sales last year with the first-line setting all to itself."

Additional coverage is provided by Healio (10/4, 11K)

FOOD SAFETY

Missouri Company Recalls Eggs Linked To Salmonella Outbreak.

The St. Louis Post-Dispatch (10/4, Bernhard, 723K) reports there is a salmonella outbreak that has infected eight people in three states, which has been linked to eggs from Good Earth Egg Company of Bonne Terre, Missouri. The company has issued a recall and the Centers for Disease Control and Prevention has advised people not to eat the eggs and restaurants not to serve them.

Food Safety News (10/4, Beach, 4K) reports the Food and Drug Administration also issued a notice calling for consumers to not eat the eggs after the CDC issued a report tracing the outbreak to a restaurant in Missouri that served

eggs from the company. The article points out that a salmonella outbreak that sickened 52 people in six states last year was also linked to the company's eggs and that in February, the FDA issued a warning letter based on "a litany of problems documented in December 2015," and that warning letter has still not been resolved.

TOBACCO

Groups Sue FDA To Compel Graphic Warnings On Cigarette Packaging.

The Wall Street Journal (10/4, Mickle, Subscription Publication, 6.37M) reports that several public health groups are suing the Food and Drug Administration to compel the agency to require graphic warning labels be placed on cigarette packaging. Plaintiffs include the American Cancer Society, American Lung Association, Campaign for Tobacco-Free Kids and five other antitobacco groups.

The Boston Globe (10/4, Freyer, 1.14M) reports that the lawsuit claims that the FDA "remains legally obligated to require the warnings," despite a decision by a Federal appellate court that struck down the particular images proposed by the FDA in 2011.

The Hill (10/4, Wheeler, 651K) reports that under the Family Smoking Prevention and Tobacco Control Act, the FDA had "until June 22, 2011 to issue a final rule on graphic warning labels" that "are supposed to cover the top half of the front and back of cigarette packs and 20 percent of cigarette advertising."

The Boston Herald (10/5, Graham, 452K) reports that Michael Felberbaum, an FDA spokesman, said, "The FDA is undertaking research to support a new rule-making consistent with the Family Smoking Prevention and Tobacco Control Act."

Additional coverage is provided by Congressional Quarterly (10/4, Siddons, Subscription Publication, 967) and HealthDay (10/4, Preidt, 24K).

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FDA Warns on Hepatitis C Drugs

The agency is requiring black-box warnings for nine antiviral drugs that can reactivate hepatitis B

By Thomas M. Burton

1 COMMENTS

The Food and Drug Administration is warning about the risk of reactivation of hepatitis B among patients who have had that disease and who are taking some prominent and expensive newer medicines for hepatitis C.

The federal agency said it is requiring a so-called black-box warning in the labels for at least nine brand-name direct-acting antiviral drugs, including Sovaldi and Harvoni from [Gilead Sciences Inc.](#), [GILD-1.01%](#) Viekira Pak from [AbbVie Inc.](#), [ABBV-0.36%](#) and Zepatier from [MerckMRK-0.10%](#) & Co. That is the most serious kind of warning that can be levied by the FDA.

The agency said serious liver problems or death occurred in “a few cases.” These medicines are already threatening the budgets of private and government insurers and of prison systems because of list prices ranging from \$54,000 to \$94,000 a person for a typical 12-week course. Hepatitis C infects millions of Americans and can lead to death after decades in the body.

The newer hepatitis C medicines tend to achieve cure rates of 90% or more, compared with rates of 65% among older medications, which also must be taken for up to a year.

The FDA said it identified 24 cases of hepatitis B reactivation, either reported to it or found in medical literature, from Nov. 22, 2013 through July 18, 2016. Of the cases reported, two patients died and one required a liver transplant. Reactivation of hepatitis B wasn't reported as an adverse event in clinical trials submitted to the FDA for approval of the drugs.

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 5:10 PM
To: DeMarco, Devota R
Subject: RM

From: Goldsmith, Jonathan
Sent: Wednesday, September 28, 2016 1:52 PM
To: Moscicki, Richard
Subject: RE: RPD PRVs

I will recheck

From: Moscicki, Richard
Sent: Wednesday, September 28, 2016 1:24 PM
To: Goldsmith, Jonathan
Subject: Re: RPD PRVs

Ok thanks thought there had been three

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

From: Goldsmith, Jonathan
Sent: Wednesday, September 28, 2016 12:33 PM
To: Moscicki, Richard
Subject: RPD PRVs

Dear Dr. Moscicki:

There have been 7 vouchers including Sarepta's for DMD. The FR notice for Etelpirsen Voucher is in clearance and will publish in less than 30 days.

Two RPD PRVs have been redeemed:

PCSK9 Inhibitor (Praluent) Sanofi

Insulin Glarine and Lixisenatide (T2DM) Sanofi

Jonathan

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 9:54 AM
To: DeMarco, Devota R
Subject: RM : WSJ eteplirsen story

From: Throckmorton, Douglas C
Sent: Monday, September 19, 2016 8:37 PM
To: Scott, Meghan; Guidos, Robert; Moscicki, Richard
Cc: Adams, Michelle; Safford, Melissa
Subject: RE: WSJ eteplirsen story

No worries. I'm adding Rich Moscicki for awareness. D

Douglas C. Throckmorton MD
Deputy Director for Regulatory Programs
CDER, FDA
301-796-5400

From: Scott, Meghan
Sent: Monday, September 19, 2016 8:27 PM
To: Throckmorton, Douglas C; Guidos, Robert
Cc: Adams, Michelle; Safford, Melissa
Subject: Re: WSJ eteplirsen story

Sorry, Doug. Here it is!

FDA Approves Sarepta's Muscular Dystrophy Drug

Approval comes after panel failed to back drug; Sarepta shares hit multiyear highs

At the FDA panel hearing, many parents gave often-emotional testimony about how—despite the scientific data—they were convinced that their children had benefited from the drug.

By

Thomas M. Burton

The U.S. Food and Drug Administration on Monday gave accelerated approval to the first drug for the crippling disease Duchenne muscular dystrophy, from Sarepta Therapeutics Inc., **SRPT 93.20 %** after sharp disagreements within the agency.

The circumstances of the approval at the agency were highly unusual, and included sharp internal protests that were ultimately resolved by FDA Commissioner Dr. Robert M. Califf.

An advisory committee to the FDA in April voted 7-3, with 3 abstentions, that the data for the drug weren't enough for agency approval. Specifically, they focused on the fact that the company's hope for approval largely was based on a single study of 12 patients.

On Monday, Sarepta shares surged 88% to \$52.93 after hitting an earlier high of \$56.18, its highest point since March 2002. The stock in April fell as low as \$8 after the FDA panel failed to back the drug, but the price had been rising in recent weeks amid optimism for FDA approval. The gains Monday valued the company at \$2.5 billion.

Duchenne is progressive, severely crippling illness that afflicts male children. It is estimated that it affects about 1 in 3,500 boys world-wide. It destroys muscles and frequently kills patients by the time they are in their 30s. At the FDA panel hearing, many parents gave often-emotional testimony about how—despite the scientific data—they were convinced that their own children had benefited from taking the drug. By late May, Sarepta had announced that the FDA wouldn't make a decision by the deadline and that it would work with the agency in its examination of the data. Before that panel meeting, FDA staffers had indicated they were “prepared to be flexible with respect to a devastating illness with no treatment options.”

An incident at the advisory committee meeting presaged what became an unusually contentious process within the FDA. At the meeting, Dr. Janet Woodcock, director of the FDA's center for drugs, signaled a complex decision lay ahead and said the agency had “flexibility and that's where we should take the views of the community into account.” Several doctors who had heard the evidence expressed skepticism then and since that the FDA decision should be anything other than a strict consideration of the very limited evidence.

The agency's staffers who had studied that evidence concluded that the small study's design “did not provide interpretable evidence of benefit.”

Ultimately, Dr. Woodcock, a controversial figure within the FDA whom some prominent critics say tends to lean in industry's direction, decided to approve the drug. Dr. Ellis Unger, a senior physician in the drug division, objected to her decision and filed a protest that reached Dr. Califf, the commissioner.

Dr. Califf, in a decision dated Friday, wrote that he had reviewed the evidence and that his “decision following this review is to defer to Dr. Woodcock's judgment and authority” to make the decision to approve the drug. The FDA's acting chief scientist and chair of an FDA committee that resolves internal disputes, concluded the opposite: Dr. Luciana Borio said, according to a memo from Dr. Califf, that she “does not believe the available data and information support accelerated approval of” the drug, which is called eteplirsen.

The approval also comes a week after the FDA confirmed that Dr. Ronald Farkas, who led the FDA review team that evaluated Sarepta's data, had left the agency.

The FDA said it wouldn't make any of its staff available for interviews. The decision prompted different reactions from the medical community.

Michael A Carome, director of the Public Citizen Health Research Group, said, “The decision by Dr. Woodcock to approve eteplirsen, against the strong objections of FDA experts who reviewed the drug and the advice of its advisory committee, represents a disturbing disregard for the agency's legal standards for approving new drugs. In particular,

such action eviscerates the FDA's longstanding requirement that there be substantial evidence of effectiveness for new drugs—even drugs for serious rare diseases—before they are marketed.”

Steven M. Derks, president of the Muscular Dystrophy Association, said, “This is the outcome MDA dreamed of 25 years ago when it was the first to invest in the breakthrough research that led to development of eteplirsen.”

Write to Thomas M. Burton at tom.burton@wsj.com

From: Throckmorton, Douglas C
Sent: Monday, September 19, 2016 8:21 PM
To: Scott, Meghan; Guidos, Robert
Cc: Adams, Michelle; Safford, Melissa
Subject: RE: WSJ eteplirsen story

Can't read most of it; hopefully the whole thing will be in the clips tomorrow. D

Douglas C. Throckmorton MD
Deputy Director for Regulatory Programs
CDER, FDA
301-796-5400

From: Scott, Meghan
Sent: Monday, September 19, 2016 2:16 PM
To: Throckmorton, Douglas C; Guidos, Robert
Cc: Adams, Michelle; Safford, Melissa
Subject: WSJ eteplirsen story

Tom Burton posted about an hour ago, does discuss appeals process: <http://www.wsj.com/articles/sarepta-wins-fda-approval-for-duchenne-drug-1474297124>

Meghan H. Scott
Senior Advisor for Oversight
U.S. FDA
Desk: 301.796.4675
Mobile: 202.731.2922

Philips, Howard

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: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 4:05 PM
To: DeMarco, Devota R
Subject: RM

From: Moscicki, Richard
Sent: Friday, September 16, 2016 2:55 PM
To: Woodcock, Janet (Janet.Woodcock@fda.hhs.gov)
Subject: IHC baseline differences

I spoke with Ash again and we confirmed that images were prepared differently for analysis between the images used for week 48 and those for week 180, starting of course with new stains prepared concurrently with the staining for the new wk 180 biopsies but also several other steps that would expectedly have conservatively reduced the number of positive staining cells both in baseline and wk 180 samples. Again, no surprise in the different baseline numbers. Also confirmed that bioquant for wk 180 was done correctly in assessing randomly selected images from baseline and similarly from wk 180 for the relevant subject and the entire field was used but focused on the fiber images. This would be the correct way to do this and it was also positive achieving a fluorescent intensity value of about half of Beckers patients in the same analysis. Rich.

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 4:04 PM
To: DeMarco, Devota R
Subject: RM

From: Moscicki, Richard
Sent: Thursday, September 15, 2016 4:14 PM
To: Woodcock, Janet (Janet.Woodcock@fda.hhs.gov)
Subject: New memo

Hi Janet, I looked at the email from Ellis, I don't quite get it as that information was available. It seems strange that he is only now recognizing this. I reviewed the same information and so did Ash when we all discussed the information and I believe that you too were aware of it. We understand that the methods for analyzing the immunohistochemistry and the rules for positive and negative fibers were different in the different analyses that he is referring to in the IHC and that explained the difference in how baselines were counted. The important thing is that irrespective of the method and the consequent baseline there was a substantial increase in positive fibers in subsequent biopsies. The finding was also consistent with the method employed later to analyze immunofluorescent intensity. The data does not negate the Western blots which you used primarily to make your decision. Your use of the literature told you that even small amounts of dystrophin might make a difference, I don't think you were trying to say that the numbers were directly comparable from study to study. I can go back to the data and make sure the specific numbers he is talking about are how I am remembering it. Rich.

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 9:57 AM
To: DeMarco, Devota R
Subject: RM -FW: memo

From: Woodcock, Janet
Sent: Thursday, September 15, 2016 7:08 PM
To: Moscicki, Richard
Subject: RE: memo

Tx much. Jw

From: Moscicki, Richard <Richard.Moscicki@fda.hhs.gov>
Date: September 15, 2016 at 5:31:33 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: RE: memo

So I checked and indeed you mentioned the discrepancy in your memorandum so you were very aware and understood the reason for it. The Bioquant assay report for the 180 day samples is where I thought the target (entire field vs just positive fibers) had changed but could not verify that in the report when I looked it up. Nevertheless it also showed a positive change.

From: Woodcock, Janet
Sent: Thursday, September 15, 2016 7:20 AM
To: Moscicki, Richard
Subject: Fwd: memo

Can you figure out what Ellis is talking about here? Re the IHC data! His memo is in DARRTS. Feel free to talk to Ash. I think I had already figured this out myself. Jw

From: Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Date: September 14, 2016 at 6:51:46 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>, Borio, Luciana <Luciana.Borio@fda.hhs.gov>
Subject: RE: memo

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

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 4:03 PM
To: DeMarco, Devota R
Subject: RM
Attachments: Sareptafinal.docx

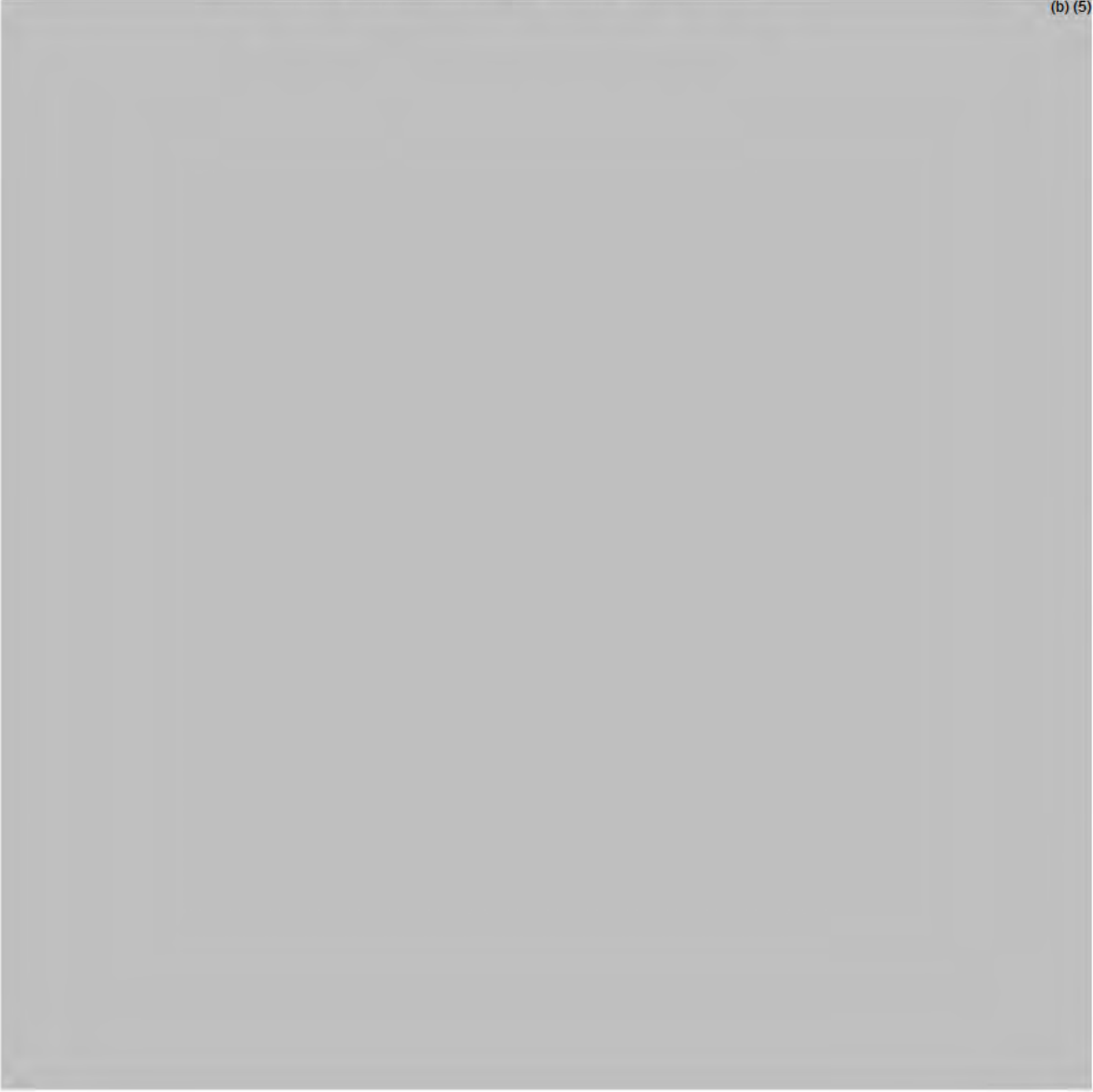
-----Original Message-----

From: Moscicki, Richard
Sent: Thursday, July 21, 2016 2:49 PM
To: Woodcock, Janet (Janet.Woodcock@fda.hhs.gov)
Subject: Sareptafinal.docx

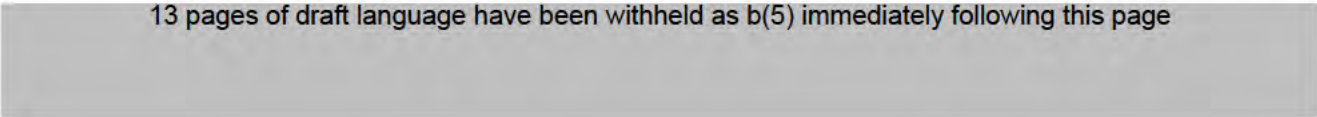
As I said this morning, I think this is very good but I thought I would also pass along some minor thoughts. Rich.

CENTER DIRECTOR DECISIONAL MEMO

(b) (5)



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



Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 9:58 AM
To: DeMarco, Devota R
Subject: RM; Thanks for reading the draft
Attachments: Sareptafinal.docx

From: Woodcock, Janet
Sent: Wednesday, July 20, 2016 12:56 PM
To: Moscicki, Richard; Throckmorton, Douglas C; Buckman-Garner, ShaAvhrée
Subject: Thanks for reading the draft

Here is the final version of my memo on eteplirsen. Rich and Doug, I had to considerably beef it up because of the appeal. jw

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

SUMMARY

This memorandum explains the CDER's final decision on the above application. I have read the reviews and recommendations by Drs. Unger (Office level), Bastings (Division level), Farkas (Cross-Discipline Team Lead), Breder and Rao (Clinical Reviewers), Ling (Statistical Reviewer), and Bhattaram, Wu, and Rogers (Clinical Pharmacology Reviewers). In addition to the review memoranda, I have also reviewed the Advisory Committee briefing materials, pertinent portions of the sponsor's submission, and multiple scientific statements submitted by the public, including a letter from a large number of DMD experts.

The review team has done an exemplary job in performing a detailed evaluation of the data submitted with the application. Nevertheless, I disagree with certain of their findings and come to a different conclusion, as discussed below.

I find that the data contained in NDA 206488 meet the standard for accelerated approval under 21 CFR 314.510 based on the surrogate endpoint of increased dystrophin protein production, a surrogate endpoint that I conclude is reasonably likely to predict clinical benefit.

DISCUSSION

Extensive analyses have been performed by the team on the clinical results of the long-term experience of 12 patients administered the drug, and I will not recapitulate these.

Approval under 314.510 is based, among other things, on adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Below, I discuss how both of parts of this standard are met.

A. Are the Data on Dystrophin Protein Production From One or More Adequate and Well-Controlled Studies?

The characteristics of adequate and well-controlled studies are laid out in 21 CFR 314.126. Three lines of evidence are pertinent to the conclusion that eteplirsen results in increased dystrophin production.

- Production of an appropriate mRNA transcript
- Quantitative assessment of dystrophin content in muscle biopsies by Western blot
- Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry (IHC) techniques

The sponsor provided data demonstrating an increase in mRNA expression following treatment with eteplirsen. The drug's proposed mechanism of action is to bridge a section of the pre-RNA to result in a shorter mRNA with an open reading frame, e.g., "exon skipping." In this case, the production of an appropriate mRNA transcript has been documented by PCR and Sanger sequencing. Although this establishes proof of mechanism, it does not mean that there is increased protein production.

In the following, I discuss the assessments related to dystrophin protein production (2. and 3.) in some detail. 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. With FDA's assistance, the sponsor improved the design and conduct of the assays and performed repeat biopsies on 11 of 12 patients at week 180. The control samples for these week 180 biopsies were stored baseline tissue (in 3 of 11 subjects) and baseline biopsies from subjects with exon 51 amenable mutations enrolled in another trial by the sponsor. FDA reviewers had the following concerns about these controls, leading them to conclude that the studies were not adequate and well controlled.

1. Most of the baseline biopsies were not from the same subjects as the week 180 biopsies (as the original tissue had been used up for the previous assays). Given this, the control subjects could differ in unknown ways from the test subjects.
2. The biopsies taken at week 180 were from different muscles in the upper extremity than the baseline biopsies, including subjects with baseline tissue as well as for control samples. It is hypothesized that there may be differences in dystrophin protein content among various muscles in DMD patients.
3. The existing baseline biopsies for the three subjects with 180 week data had been stored frozen for several years and may have changed (apparent decrease in dystrophin protein content) over time.

In my judgment, these issues increase the uncertainty around the results, but do not necessarily render them an inadequate basis on which to draw a conclusion. The non-treated control subjects were very similar in age and dystrophin mutation site to the treated subjects (sponsor Appendix 10, AC briefing package). The single deltoid muscle biopsy in the untreated control group (subject 7, sponsor Appendix 14, AC briefing package) had replicate dystrophin levels of 0.3% and below the limit of quantification, averaging out at below 0.3%, and not different than biceps biopsy results in other patients, suggesting

that variations in upper extremity biopsy site (concern b above) did not result in large differences in the findings. There was little difference in the dystrophin protein content found in the stored baseline samples and the frozen samples, as discussed below.

The data submitted with the original application, supporting the finding that eteplirsen increases the production of dystrophin protein, come from the quantitative assessment of (internally truncated) dystrophin in muscle tissue by Western blot using the controls described above. Much of the controversy around this method relates to the fact that the apparently achieved dystrophin levels are very much lower than originally hoped (and previously claimed by the sponsor and investigators).

In the 180 week assessment, the three subjects with baseline biopsies available had baseline dystrophin levels (reported as % of normal) below the level of quantification of the assay used (0.25%). These results were similar in magnitude to the baselines of the six additional control biopsies drawn from subjects in another study (highest level 0.37%). At week 180, two treated subjects had (an average of replicate) dystrophin levels above 2%, two had over 1%, and two additional had about 1%. Of these individuals, two subjects having both baseline and week 180 samples had clearly increased levels at week 180 compared to baseline. (The third subject with a baseline sample did not consent to a week 180 biopsy). Unsurprisingly, some subjects had week 180 dystrophin levels similar to the overall baseline control levels. Not all individuals are expected to respond to a drug intervention. 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. The following data are relevant to this issue.

Because the original data on the presence of dystrophin by Western blot suffered some difficulties in interpretation because of lack of availability of baseline samples from most patients, the sponsor of this application submitted, subsequent to the Advisory Committee meeting on this drug, additional Western blot data from 12 patients with baseline and 48 week eteplirsen exposure, using baseline and post-treatment muscle biopsies from the same patients and muscle groups. This experiment clearly shows, using adequate controls, that the drug increases dystrophin protein production in some of the patients. The mean baseline dystrophin values in this study were very similar to the mean baseline values in the 180 week study. The achieved levels of dystrophin in these patients are lower than those seen in the Western blots from the week 180 patients. Only 2 of 12 patients achieved a level over 1% of normal control. It is not known if this result is due to a shorter duration of drug exposure or to other factors. Putting together the 180 week data and the additional 48 week data, I conclude that there is substantial evidence from Western blot experiments of increased dystrophin protein production, albeit at a low level.

A finding of increased dystrophin was also seen in several IHC assays performed by the sponsor. Both assays were originally performed with baseline and several pre-180 week assays by the sponsor as a part of the clinical trial. The validity of the results of these assays were questioned by FDA because of methodological problems in their conduct, as documented in the primary clinical review and in the inspection report. Therefore, I will not further consider the results of these original assays. As discussed for the Western blot above, the sponsor responded by performing an additional 180 week biopsy and repeating the assays. Baseline tissue was available, as for Western blot, from recut samples

in only three cases. In one of these, the subject did not consent to a biopsy at 180 weeks. To supplement the three baseline samples the sponsor included six other untreated patients from a different trial, as discussed above for the Western blot. In both assays, greater staining or intensity was observed after drug exposure at week 180 compared to controls. The results are described in more detail below.

A Percent Dystrophin Positive Fibers analysis was a semi-automated evaluation performed at 180 weeks and compared to the controls used for the 180 week study as discussed above. The percentage of positive fibers was assessed using a blinded read by Nationwide Children's Hospital and by three independent pathologists through Flagship Biosciences. The technique used to assess percent positive fibers was modified from the original assay in the following ways:

1. A computer algorithm (MuscleMap from Flagship) that performs non-linear mapping of all fibers was used for consistent and automated analysis of low intensity values, in contrast to a manual and non-standardized fiber counting technique in the prior assay.
2. The images were inverted and amplified to score the total fibers (the denominator for the percent positive fiber scoring).
3. An isotype matched secondary antibody staining step was incorporated to confirm lack of non-specific staining and reduce background noise. The background signal was subtracted from test sample values in calculation of percent intensity.
4. 8% of the images for re-analysis were blinded, renamed, randomized, and rotated 180 degrees.
5. A rejection factor for the inter-rater analysis score of <4 was established.
6. The images were acquired in a more systematic and random fashion to minimize bias, with predefined rules for random sampling of fields and avoiding artifacts.

These changes were likely to result in a more conservative reading of Percent Dystrophin Positive Fibers, and indeed the results, including the new untreated baseline controls, were read at 1.1% positive fibers (in contrast to a higher result in the prior baseline using the original technique). The 180 week cohort had a score, using this technique, of 17.4% positive fibers, showing a statistically significant difference. Now, these results are subject to the same caveats as discussed for the Western blot (1-3 above), in that there were only two baseline to 180 week pairs, that the baseline samples had been frozen for years, and that the external controls might differ in some way. So, these results cannot stand alone.

Other reviewers have pointed out that the (much higher) baseline values for Percent Positive Fibers from the original experiment are not very different from the 180 week values in this new experiment. However, I would point out that experimental conditions changed quite a bit, and very low values for all the external controls, statistically comparable to the frozen baseline results, were obtained in this recent experiment, suggesting that it returned a more conservative result. I do not believe that comparison of the original baseline data, obtained under one set of experimental conditions, can be compared to the later 180 week results, done under different, more optimized conditions and yielding very different results for new (external control) baseline samples.

The sponsor also performed a Mean Relative Fluorescence Intensity assay for dystrophin. This assay is commonly performed by laboratories evaluating DMD patients and is intended to be a semi-quantitative evaluation of dystrophin content. Using the six external baseline samples and the three stored study patient baseline samples, the mean intensity approximately doubled from baseline to 180 weeks. The technique for this assay did not change significantly from the technique used in the assay done as part of

the original protocol, and the baseline means for the patient samples were roughly comparable to the baseline means obtained in the new experiment.

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). The accompanying microscopy images also demonstrate correct localization of the molecule within the muscle fibers, a very important factor in any translation to clinical benefit.

In summary, I conclude that there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells.

B. Is the Effect on the Surrogate Endpoint “Reasonably Likely to Predict Clinical Benefit”?

In this case, the standard for clinical benefit does not require “cure” or “conversion to Becker MD (BMD) phenotype.” Clinical benefit encompasses improvements (including slowing of disease progression) in how an individual feels or functions, or an improvement in survival. There is no question that, for DMD patients and their families, small improvements in function or delays in loss of function are meaningful benefits. Therefore, the question is:

What amount of increase in dystrophin production is reasonably likely to predict clinical benefit (even small benefits)?

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. The following summarizes the existing scientific literature on this topic and the challenges in interpreting it.

1. The clinical classification of disease severity (i.e., phenotype) in the literature appears broad, variable, and somewhat subjective.

Experts usually classify patients clinically as DMD (severely affected at a young age); intermediate MD (also called DMD/BMD); or BMD, which can range from severe BMD to asymptomatic individuals with biochemical abnormalities, usually increased creatine phosphokinase (CPK). There is clearly a wide spectrum of disease wherein the ends of the spectrum are easily distinguishable, but the zone of real interest for this discussion, between DMD and intermediate presentations, is not rigorously categorized. In part, this is because “intermediate muscular dystrophy” (IMD) is less common, due to the consequences of having either in-frame mutations with a truncated protein expressed (leading to BMD) or out-of-frame mutations with little-to-zero protein expressed (leading to DMD), as discussed below.

2. Much of the prior data reporting the relationship of dystrophin protein levels to phenotype have been from IHC studies using a variety of techniques and antibodies.

Anthony, et al., (*Neurology*, 83, 2014) in a collaborative cross-laboratory study, investigated the variability of techniques used to quantify dystrophin in individuals with muscular dystrophy. Blinded tissue sections from three DMD and three BMD muscle biopsies were tested in five

different laboratories accustomed to performing dystrophin quantification. Estimates of dystrophin expression using a somewhat standardized IHC technique were about 20%, 11% and 10% of normal for the three DMD samples, on average among the laboratories. Corresponding estimates of dystrophin content by Western blot, using an actin antibody to normalize for loading, but not a serially diluted standard control, resulted in dystrophin estimates of about 11%, 0, and 0.4% respectively, with fairly high CV's. Therefore, in this small sample, repeated across five experienced laboratories, IHC estimates were about 10 percentage points higher than Western blot estimates.

Significantly higher estimates by IHC by fluorescence intensity (overall about 23% of normal) than by Western blot were also seen in the evaluation of week 180 muscle biopsies in the Sarepta trial. Because much of the historical data on protein content vs phenotype has been reported using IHC analysis, extrapolating these findings to the current trial data is challenging. Additionally, Anthony et al., found that the inter-laboratory variability was greatest for the low levels of dystrophin found in the DMD patients. Western blot data in the literature quantifying dystrophin and relating it to phenotype is often from experiments that were not designed to distinguish among dystrophin levels below 10% of normal. These may have been reported out as "less than 10%." From this sponsor's well-controlled studies, the analytically accurate dystrophin baseline for many DMD patients might be in the range of 0.02-0.35 % normal, hence previous estimates of 5-10% might be an over-estimation using non-standardized and semi-quantitative methods.

3. Both IHC analyses and WB results are influenced by the anti-dystrophin antibodies used, as well as other experimental conditions

Significantly, if the epitope recognized by the antibody is modified by the deletion, the dystrophin isoform may not be recognized and a result read out as zero. For this reason, recent studies use multiple antibodies against known regions. Additionally, muscle biopsies in patients with BMD and DMD may be quite variable in degree of fibrosis and fatty replacement; this may decrease the reproducibility and representativeness of muscle biopsy estimates of dystrophin content by Western blot. Additionally, imaging methods, choices for normalization, biopsy handling, background standing, and a multitude of other experimental conditions can influence results.

4. The phenotype is significantly influenced by *dystrophin isoform quality* as well as *dystrophin quantity*.

Dystrophin is a very large protein with multiple functional domains. Generally, DMD results from an out-of-frame mutation (often a deletion) that leads to an unstable or unreadable mRNA transcript. Thus, DMD patients usually have zero or very low levels of dystrophin, but the DMD phenotype can also result from in-frame mutations that result in a unstable transcript or dysfunctional dystrophin isoform. BMD usually results from an in-frame mutation (often an exon deletion) that affects the functional quality of the protein and also the quantity produced. It remains unclear what role protein function plays vs quantity in leading to the wide range of variability in BMD phenotypes. There are a vast number of mutations that can lead to each of these phenotypes (Tuffery-Giraud, et al., *Hum Mutat*, 30, 2009), all of which can have different effects on protein function as well as protein production. This micro-heterogeneity is common in genetic diseases and is highly germane to

evaluation of interventions targeting the gene, gene expression, or protein function. There are also non-dystrophin-related factors that can modulate phenotype.

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.

I note that in the decades since 1988, much technical progress has been made in standardizing Western blot techniques, and the results from early studies may not be fully comparable to those from recent experiments.

- a. The seminal 1988 paper on this subject (Hoffman et al., *NEJM*, 318(21)) found that the majority of patients with DMD had undetectable levels of dystrophin using their Western blot technique and that 35 of 38 had levels below 3% in their assay. They also reported that one of seven “intermediate” patients had dystrophin levels below 3% of normal, as did one of the 18 patients with a BMD phenotype.
- b. Beggs et al., (*Am J Hum Genet*, 49, 1991) published one of the early studies on the correlation between the level of dystrophin on Western blot and clinical features of BMD. Western blot was performed using a polyclonal serum and had about a 20% variability between blots according to the authors. In this study a number of patients with BMD or intermediate phenotype (DMD/BMD) were found to have dystrophin contents that overlapped with those of the DMD patients. Of four patients included with DMD phenotype, two had less than 5% dystrophin, and two had 10%, by their assay. Of patients with BMD/DMD phenotypes, eight were found to have 10% of normal dystrophin, two had 15%, one had 50%, and one had 100%. Three BMD patients with dystrophin levels of 10% were found; two of these had relatively mild disease.
- c. Nicholson et al., (*J Med Genet*, 30, 1993) studied patients across a wide range of DMD and BMD phenotypes. They used loss of ambulation as a criterion to establish five functional groups, grouped from one (most severe, LOA before age 9) to five (LOA past age 40) (pre-steroid era). *They found a linear relationship overall between dystrophin levels (Western blot with Dy4/6D3 antibody, using myosin for a loading control) and their five categories, with more dystrophin protein translating to better function. They found no significant difference between any two adjacent groups however, which they interpreted as showing considerable overlap, as reflected in their patient level data (Appendix 1), which showed a number of less severe patients (e.g., Group 2 or 3) registering no or very low dystrophin abundance on their Western blot assay.* Of note, they reported a higher average level of dystrophin protein in severe DMD patients than other investigators, partly resulting from 5 of their 21 severe patients reported to have dystrophin protein levels above 20.
- d. Neri et al., (*Neuromuscular Disorder* 17, 2007) reported on families with X-linked Dilated Cardiomyopathy. In these families, mutations give rise to absent dystrophin in heart muscle, but only reduced levels of nearly normal dystrophin in muscle tissue. One patient in their series had a normal neurological exam at age 23, an elevated CPK, and 29% of normal dystrophin protein in skeletal muscle by Western blot. This example can contribute to understanding the role of abundance of dystrophin protein vs compromised function.

- e. Anthony et al., (*JAMA Neurology*, 71, 2014) evaluated the correlation between phenotype and mRNA and protein expression in patients with both in-frame and out-of-frame mutations amenable to exon 44 or 45 skipping. Studying a group of patients with closely related deletions could diminish variability due to differences in function of the truncated protein. Five samples from patients with clinical “mild” BMD and in-frame mutations underwent Western blot analysis using the Dys-2 antibody. Their mean protein expression was 17% (normalized to actin) with a standard deviation of 7.5%. Two of the “mild” patients had dystrophin levels in this assay of around 10%. Based on comparisons of IHC experiments with various antibodies, the authors found “*no clear correlation between the level of dystrophin transcript or protein expression with clinical severity*” in 13 patients with in-frame mutations leading to BMD. The finding of Neri et al., above, along with this report, reinforce the concept that protein function (i.e., quality) is an important determinant of clinical severity and undermine the concept that 10% dystrophin protein content is a threshold, since these patients had “mild” BMD.
- f. Van den Bergen et al., (*J Neurol Neurosurg Psychiatry*, 85, 2014) compared dystrophin levels by Western blot with clinical severity in 27 patients with a clinical diagnosis of BMD. Dystrophin expression ranged from 4-71% and 3-78%, depending on the antibody used. *The authors found no linear relationship between dystrophin expression by Western blot using newly acquired muscle biopsies and clinical severity, muscle strength, or fatty infiltration on MRI.* Although this was the case for the majority of the patients, who had dystrophin levels above 20% of normal, four patients had levels at or below 10%. These patients generally had a more severe phenotype: one patient with a dystrophin level of 10% was wheelchair dependent at 45 years; one patient with a level of 7% developed trouble with stair walking at age 21; one patient with a level of 4% had a DMD phenotype with wheelchair dependency at age 10, one patient with a level of 3% had wheelchair dependency at age 25.
- g. Anthony et al., (*Brain*, 134, 2011) studied 17 BMD patients with exon 51 or 53 skipping-amenable mutations by IHC methods. These patients primarily had very mild or asymptomatic disease; the one patient classified as severe was ambulatory at age 25 but unable to run. *There was a statistically significant difference in dystrophin expression by IHC when patients classified as mild disease were compared to asymptomatic patients.*
- h. Bello et al., (*Neurology* 87, 2016) published a detailed study of loss of ambulation in DMD patients with particular exon deletions, using the CINRG-DNHS, a prospective natural history study. 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. 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.

- i. Cirak et al., (*Lancet*, 378, 2011) published a study (AVI-4658) using intravenously administered eteplirsen that showed a detectable increase in dystrophin protein levels using both Western blot and immunofluorescence in 3/19 patients. The authors reported that the functional properties of restored dystrophin were confirmed by assessing increased levels and co-localization of neuronal nitric oxide synthase (nNOS) and sarcoglycan with dystrophin. Such a protein assembly is suggested to be indicative of functional restoration of the dystrophin-associated glycoprotein complex in muscle fibers (Molza et al., *JBC*, 290, 2015; Wells KE et al., *Neuromuscul Disord*, 2003). Cirak et al., reported that the restoration was more so in patients with exon 49-50 deletions than in those with 45-50 deletions, which is consistent with a previous observation that nNOS binding domain is located in dystrophin exons 42-45 (Lai Y et al., *J Clin Invest*, 2009). These studies suggest that important functional domains are included in the dystrophin protein induced by eteplirsen.

To summarize what is known about the association between dystrophin levels and phenotype, dystrophin content above about 10% on Western blot is usually associated with a BMD phenotype, except in patients with higher levels of dystrophin (including above 50%) who potentially have functionally deficient protein leading to a DMD phenotype. Within the BMD phenotype, a proportional inverse relationship between disease severity and protein expression has not generally been demonstrated (i.e., between 10-100%), although there may be a broad association, as seen in the Anthony study (*Brain*, 134, 2011). This may be due to the fact that protein quality, rather than quantity, plays a key role in determining phenotype in BMD. Patients with DMD are usually found to have no detectable, or very low levels of, dystrophin. Dystrophin content in the 3-10% range has been associated with DMD, DMD/BMD, and BMD phenotypes. 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. Generally, the divide between DMD and BMD, in terms of protein, is the result of the consequences of an OOF or an in-frame mutation, respectively. I believe that the conventional threshold, at or below 10% protein, was derived from the IHC data that seem to estimate low-level protein content about 10% percentage points higher on IHC than on Western blot, so that the majority of DMD patients would read out at 10% of normal dystrophin on IHC. I believe that evidence from Western blot and other experiments discussed above show 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.

These findings are germane to the determination of “reasonably likely to predict clinical benefit.” 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.

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 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 non-randomized 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.

Several facts militate against this conclusion. First, one of the exon 52 deletion trial subjects (subject 6) had a fairly low score on the 6MWT at entry and a very low score on the NSAA, compared to other subject around his age. He also was the only subject in the trial noted to be unable to rise without external support at baseline. Additionally, the Italian external cohort had exon 52 deletion representation.

Questions have been raised about the correlation of dystrophin levels from Western blot with clinical outcomes. The 6 Minute Walk Test does not show a strong correlation. I evaluated the NSAA in children who could still walk (because the NSAA primarily scores activities related to walking) and who also had a dystrophin result at 180 weeks (Table 1). I did this because the NSAA includes multiple measures and therefore might have some noise averaged out. I looked at the absolute decline in NSAA in patients since study initiation, and did not correct for the initial time some patients spent on placebo. I only evaluated patients who were ambulatory. There was a positive (inverse) correlation between dystrophin by Western blot and rate of decline in NSAA score, . (Figure 1) This adds additional support to the idea that dystrophin production is “reasonably likely to predict clinical benefit.” In totality, I find that the comparative disease course data provide additional support for the use of the surrogate endpoint of an increase in dystrophin expression as “reasonably likely to predict clinical benefit.”

Therefore, 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.

CONFIRMATORY TRIALS

The sponsor is currently conducting a nonrandomized, concurrently controlled trial in patients with mutations amenable to exon 51 skipping compared to untreated DMD patients with other exon deletions. Because of the relatively low level of protein induced, additional doses should be aggressively pursued and, if successful, a dose-comparison trial could be confirmatory. The sponsor has also planned to initiate a randomized trial with a related compound in other exons. The clinical results from these trials can inform the predictive value of the surrogate endpoint.

EXPLORATION OF ADDITIONAL DOSES, REGIMENS, AND DRUG-MUTATION INTERACTION

The dystrophin levels achieved in this development program are well below those initially hoped for. I agree with Dr. Farkas and other reviewers that the sponsor should aggressively explore higher doses or more frequent administration of eteplirsen. It appears that this is possible given the toxicology data and the clinical safety profile observed to date.

Because patients in the Sarepta 180 week cohort had a range of deletions in the dystrophin gene, variability in the pharmacodynamic response among deletions is of great interest. The two patients with over 2% dystrophin in the 180 week Western blot both had exon 52 deletions. These patients also fared fairly well, clinically. This raises the question of whether patients with this exon deletion naturally produce more dystrophin. One of these subjects had a baseline sample available. It was found to be below the limit of quantitation. There was an exon 52 subject included in the added baseline controls. This subject's assay had replicate results of 0.3% and below the limit of quantification, respectively, as discussed above. This suggests that baseline dystrophin levels are not higher in exon 52 deletion subjects and that there may be a drug-deletion interaction, wherein subjects with this deletion may have a more robust pharmacodynamic response to the drug. There were a number of apparent non-responders to the drug. It will be important to find out if this is mutation specific. It is likely that more detailed knowledge about each patient's specific mutation will have to be generated to study this in detail.

COMMENTS ON THE DEVELOPMENT PROGRAM AND REVIEW

The development program for eteplirsen was seriously deficient in a number of respects that may have led to delay in broad access and certainly led to difficulties in regulatory review. In my assessment, the most egregious flaw was the lack of robust and high-quality assays early in the development program. Inaccurate conclusions from the assays used led to a flawed development program. Additionally, the entire drug development field must recognize that there is no such thing as an "exploratory study" for a serious, life-threatening illness without therapeutic options. Randomization should be performed very early in the development program, and open-label studies should be avoided. When possible, seamless adaptive dose-finding and early efficacy studies should be carried out with the goal of most efficiently generating the data needed to demonstrate safety and effectiveness.

The flaws in the eteplirsen development program led to severe challenges in regulatory review. 21 CFR 312.80, concerning drugs intended to treat life-threatening or severely-debilitating illness, states that FDA has determined "that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness...Physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses than they would accept from products that treat less serious illnesses." I note that the acceptable risks include greater uncertainty about the effects of the drug. The Peripheral and Central Nervous System Drugs Advisory Committee met on this application on April 25, 2016. There was a split vote (7 against, 6 for) on the question of accelerated approval for this drug, reflecting the greater than usual uncertainty about the application. This vote was taken before the additional data on protein expression were submitted.

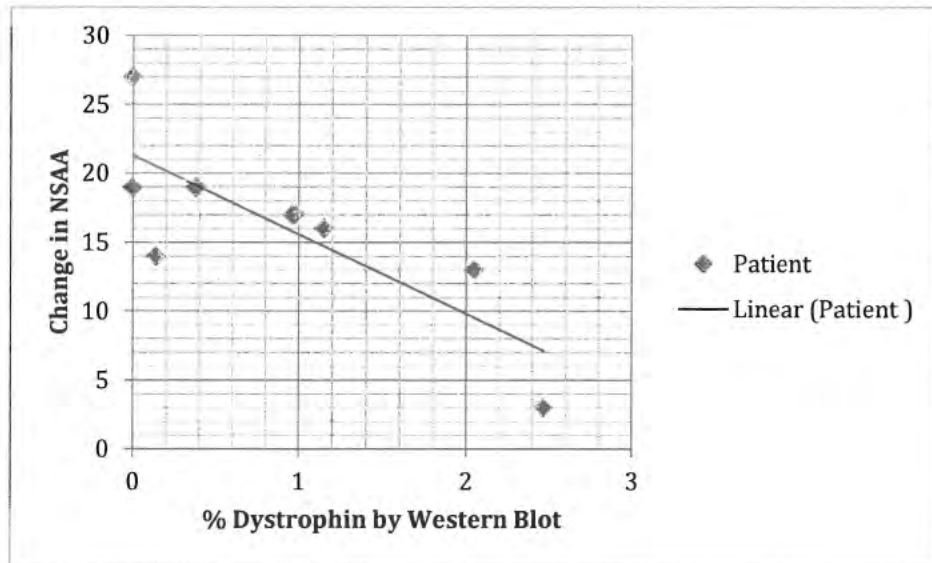
Table 1 Patient Data on Change from Baseline in 6MWT and NSAA

180 Weeks
Change from
Baseline

Subject	Baseline WB	180 Week WB	Fiber Intensity	PDPF	Δ 6MW	Δ NSAA
002	N/A	0.14	MD	4.54	-67	-14
003	N/A	0	7	1.42	-174	-27
004	N/A	0.96	28	29	-168	-17
005	0	N/A	N/A	N/A	-231	-19
006	N/A	2.47	29	21	-23	-3
007	N/A	0	12	7	-197	-19
008	N/A	0.98	26	12	-291	-17
009	N/A	0.52	23	22	0	0
010	N/A	1.62	21	24	0	0
012	N/A	0.38	26	33	-114	-19
013	0	1.15	32	19	-170	-16
015	0	2.05	30	18	-1	-13

Data from Sarepta
Therapeutics, Inc. PCNSD
Advisory Committee Briefing
Document, Appendix 5, p.
149 (6MW and NSAA)
Appendix 11, p. 155, (Percent
Positive Dystrophin Fibers
(PPDF), Appendix 12 p. 156
(fiber intensity) 14, p. 159.
(Western blot),

Figure 1. Decline in NSAA by % Dystrophin on Western blot



Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 10:00 AM
To: DeMarco, Devota R
Subject: RM Duchennes and eteplirsen

From: Woodcock, Janet
Sent: Thursday, July 07, 2016 1:11 PM
To: Moscicki, Richard
Subject: RE: Duchennes and eteplirsen

Tx jw

From: Moscicki, Richard
Sent: Wednesday, June 29, 2016 3:04 PM
To: Woodcock, Janet
Subject: Duchennes and eteplirsen

Janet, in thinking about possible postmarketing studies I think it important to do a dosing study but with an untreated prospective matched control group as well. The current dose should be studied against a higher dose, preferably (if affordable), a dose half a log higher ie 3x. I realize that could be too expensive for the company given the cost of goods that they have mentioned several times, but then at least 2x. The duration should be two years with an interim analysis at one year. The contemporary untreated control could be recruited outside the US but should be prospectively matched for the major factors, age and ambulatory status. Having said that, I do believe that it would also be important to analyze the current dystrophin data based on the deletions each patient has, as it appears that some patients do not seem to make identifiable dystrophin but others do. If in fact deletional factors can be identified then that might need to be a major consideration in attempting matching. Dose groups should be randomized. Sample size for cohorts will need to be determined by stats. This may be an important place to consider Bayesian approaches for comparisons of treated to untreated. I would also consider supplementing the contemporary controls with currently acquired retrospective data available if that could increase the power of the comparison. Endpoints should perhaps be analyzed on a responder basis with each patient having an identified predetermined endpoint for response. This should be structured as to maintenance of status vs decline rather than improvement. Rich.

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 1:28 PM
To: DeMarco, Devota R
Subject: RM FW: Sarepta inspection interim update

From: Woodcock, Janet
Sent: Sunday, June 26, 2016 5:58 PM
To: Rao, Ashutosh; Moscicki, Richard
Subject: Re: Sarepta inspection interim update

Thanks very much for doing this. Look forward to the complete analysis. Looks as if the drug is resulting in some patients in small increases in dystrophin. Jw.

From: Rao, Ashutosh <Ashutosh.Rao@fda.hhs.gov>
Date: June 26, 2016 at 1:30:10 PM EDT
To: Moscicki, Richard <Richard.Moscicki@fda.hhs.gov>, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: Sarepta inspection interim update

Dear Janet and Rich,

We completed the Sarepta inspection on Friday and I am in the process of writing up my portion of the inspection report. In brief, we found the site to have followed their SOP during the analyses of 13 matched pairs of patient samples. I did not observe any inappropriate manipulation of the assay procedure or data analyses, neither did the OSIS and ORA investigators with me. I observed the technicians on-site to be diligent and competent. At no point did any of us have reason to believe that the blinding was compromised. The reasonably quantitated % dystrophin levels from some of the blinded samples showed levels up to 1.57%

Below is a brief summary of the observed raw data, it may take about a month for the three of us to write up a single formal inspection report with exhibits. The table below is a % dystrophin data summary provide by Sarepta of all of the 13 pair of samples analyzed. Each sample was run twice hence there are 26 rows. The columns labeled "% dystrophin (Lane 7)" and "% dystrophin (Lane 8)" reflect the blinded pairs of baseline/ week 48 treated samples run side-by-side with the serially diluted healthy and negative control (DMD) sample on each gel. There were some gels with lower quality data due to higher background noise than I would have liked to see but I believe this imprecision reflects a limitation of the method itself and need for better methods but not an intended or inappropriate manipulation by the technicians. The data with a higher background data are still useful for review from my perspective because the dystrophin bands themselves are discernable. In the table below, some of the samples did not pass their acceptance criteria for the R-square of the standard curve because of the higher noise but I asked them to include all data so the Agency can review everything.

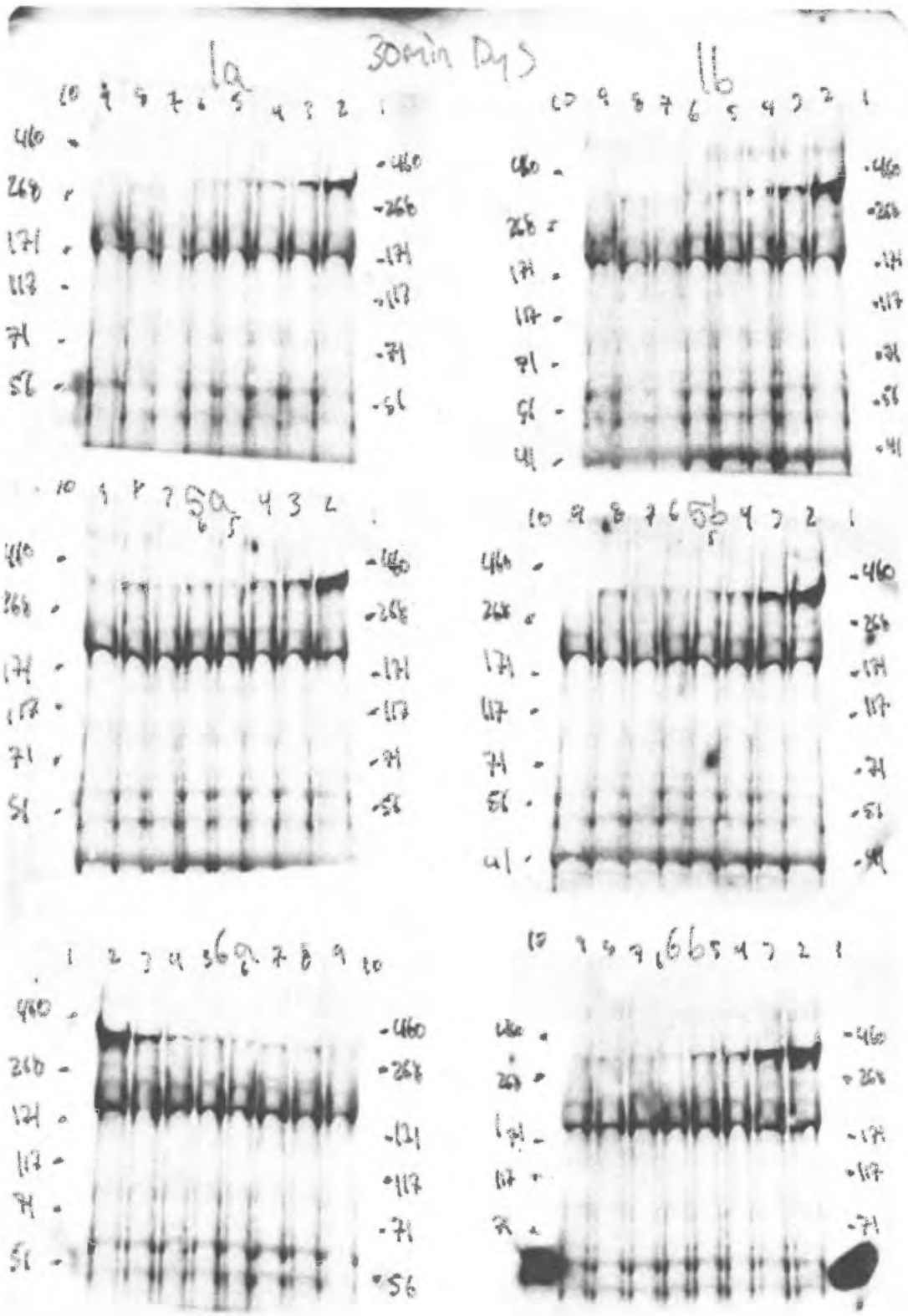
SR-CP-16-003: DYS1 - 20 minute exposure

Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)
1	1a	0.14	0.27	0.99	Pass	14425 (8609)
2	1b	0.07	0.21	0.96	Pass	39798 (13235)
3	2a	0.36	0.35	0.99	Pass	26926 (14147)
4	2b	0.10	0.12	0.90	Pass	47296 (73341)
5	3a	0.13	0.50	0.93	Pass	22937 (31305)
6	3b	0.09	0.22	1.00	Pass	64945 (29088)
7	4a	0.04	0.08	0.95	Pass	44795 (16235)
8	4b	0.04	0.18	0.89	Fail	60820 (25524)
9	5a	0.10	1.08	0.80	Fail	86479 (40898)
10	5b	0.07	0.74	1.00	Pass	88695 (18462)
11	6a	0.20	0.37	0.97	Pass	34429 (30177)
12	6b	0.15	0.18	0.94	Pass	23477 (32971)

SR-CP-16-003: DYS1 - 18 minute exposure

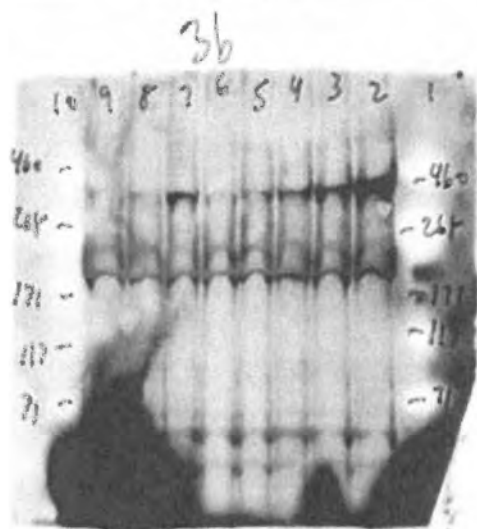
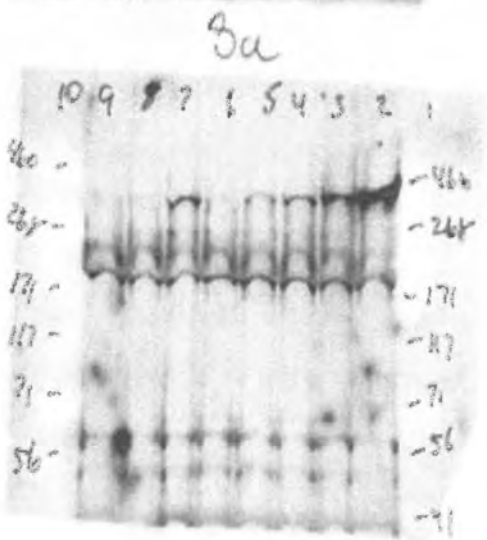
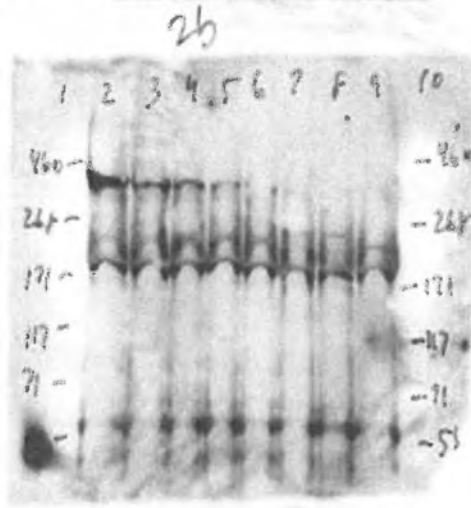
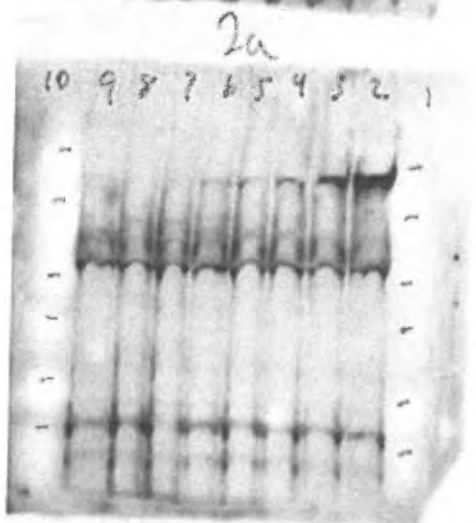
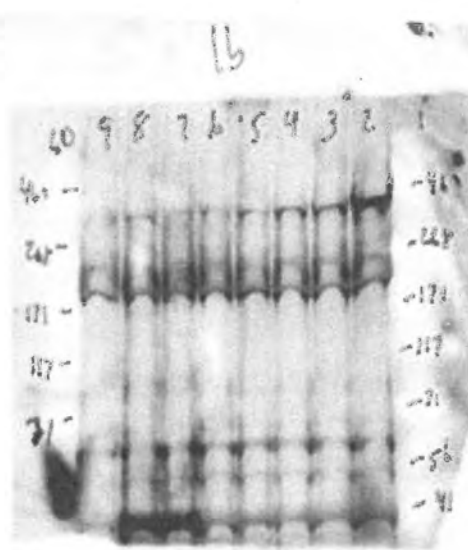
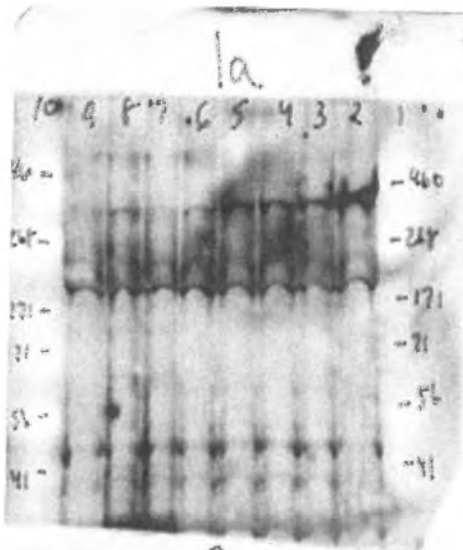
Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)
13	1a	0.00	0.00	0.38	Fail	67389 (47602)
14	1b	0.17	0.42	0.97	Pass	64418 (58077)
15	2a	0.08	0.03	0.95	Pass	87476 (58586)
16	2b	0.14	0.05	0.83	Fail	21686 (20515)
17	3a	1.17	0.14	0.88	Pass	22073 (35280)
18	3b	1.57	0.24	0.98	Pass	49106 (27627)
19	4a	0.11	0.12	0.93	Pass	40030 (8873)
20	4b	0.05	0.11	0.98	Pass	35834 (39241)
21	5a	0.31	0.01	0.93	Pass	110706 (46980)
22	5b	0.63	0.05	0.93	Pass	93278 (52055)
23	6a	0.09	0.02	0.91	Pass	77556 (51852)
24	6b	0.02	0.00	0.78	Fail	108111 (64389)
25	8a	0.34	0.34	0.94	Pass	38943 (83782)
26	8b	0.18	0.21	0.97	Pass	20460 (19812)

Two example of raw data images are pasted below. The dystrophin bands are discernable in each gel at around 427 kDa. The hand-written Lane 7 and 8 represent the matched patient samples.



SB-CR-16-003 21 Jun 2016
 Fred Schell 10619 pages 1-26
 Cas Donoghue 00618 pages 1-24

Lane Key: 00619-PS 25
 00618 PS 21
 PS 21 Jun 2016
 CD 21 Jun 2016



SR-CR-16-003
23 Jun 2016
P 23 Jun 2016

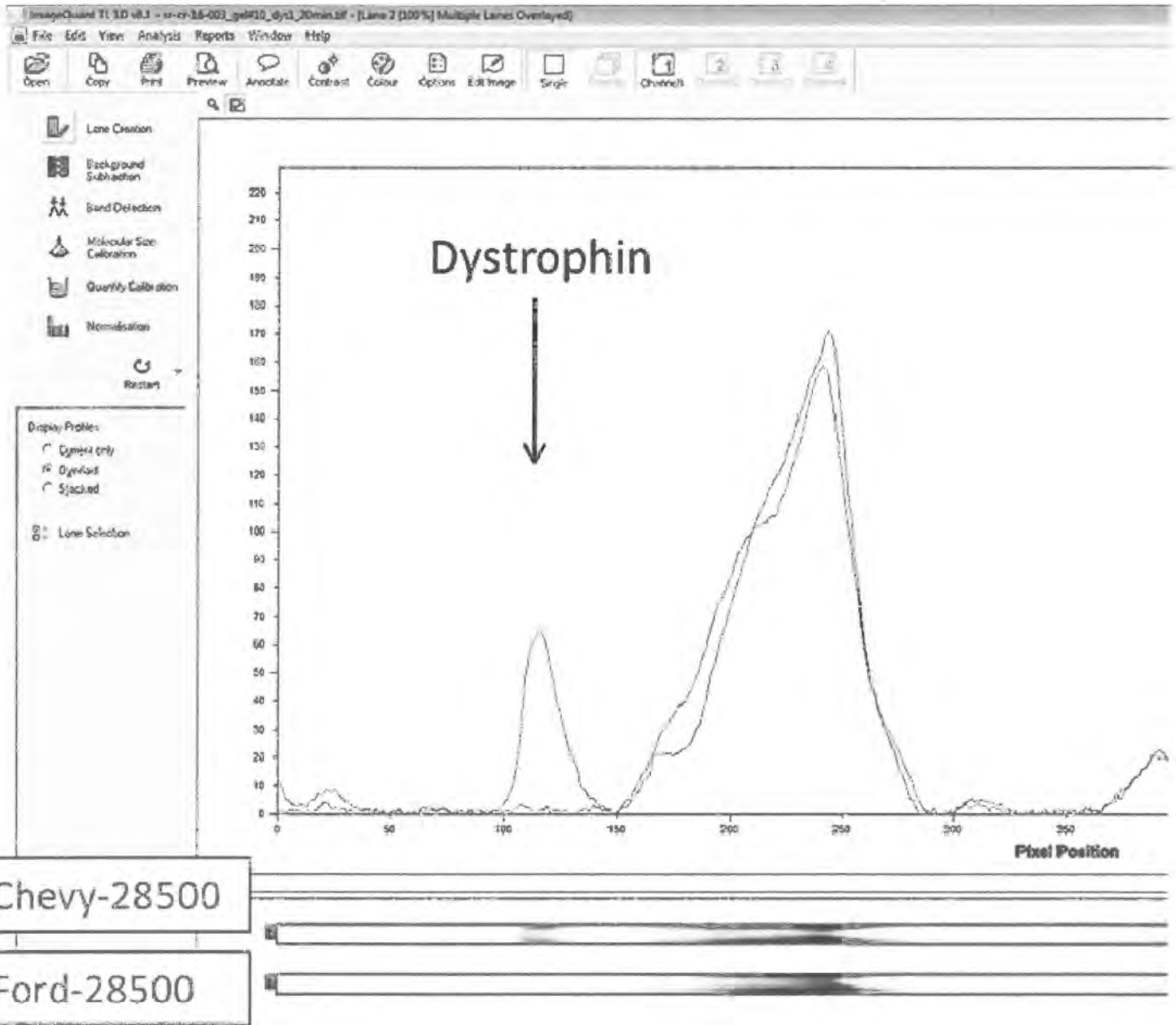
Fred Schreck
Caj Anthony
CO 23 Jun 16

00618 P5 45
00619 P5 1-46

Lane Key:
00618 P5 39
00619 P5 42
P 23 Jun 2016

Some of the quantitative differences were small but apparent by looking at the raw data and densitometry quantitation so I asked them to include a chromatographic trace of the quantitation of each lane of all of the gels with the Lane 7 and Lane 8 traces overlaid to visually explain the quantitative differences seen from the Gel images and Tables. One example where the difference between lanes 7 and 8 is obvious is pasted below. The arrow reflects the location of the 427 kDa dystrophin band.

Image Filename: SR-CR-16-003_Gel#10_DYS1_20min.tif



6/26/2016

SR-CR-16-003

Sarepta may choose to re-run some of the QC-failed gels with high background to get cleaner results because their SOP allows for it but the relative trend between the two samples on each gel is unlikely to change and verifiable with all the raw data we

brought back with us. I am attaching a PPT with a more comprehensive summary of the data for each of the 13 patient samples for reference. Please let me know if there are any questions.

Thank you.

Best,

Ash

Summary of the observed dystrophin analyses of
13 matched samples from study 4658-301 at
Sarepta's Corvallis, OR, laboratory site

June 20-24, 2015

Ashutosh Rao, Ph.D. (OBP)

Young Moon Choi, Ph.D. (OSIS)

Mark Babbit (ORA)

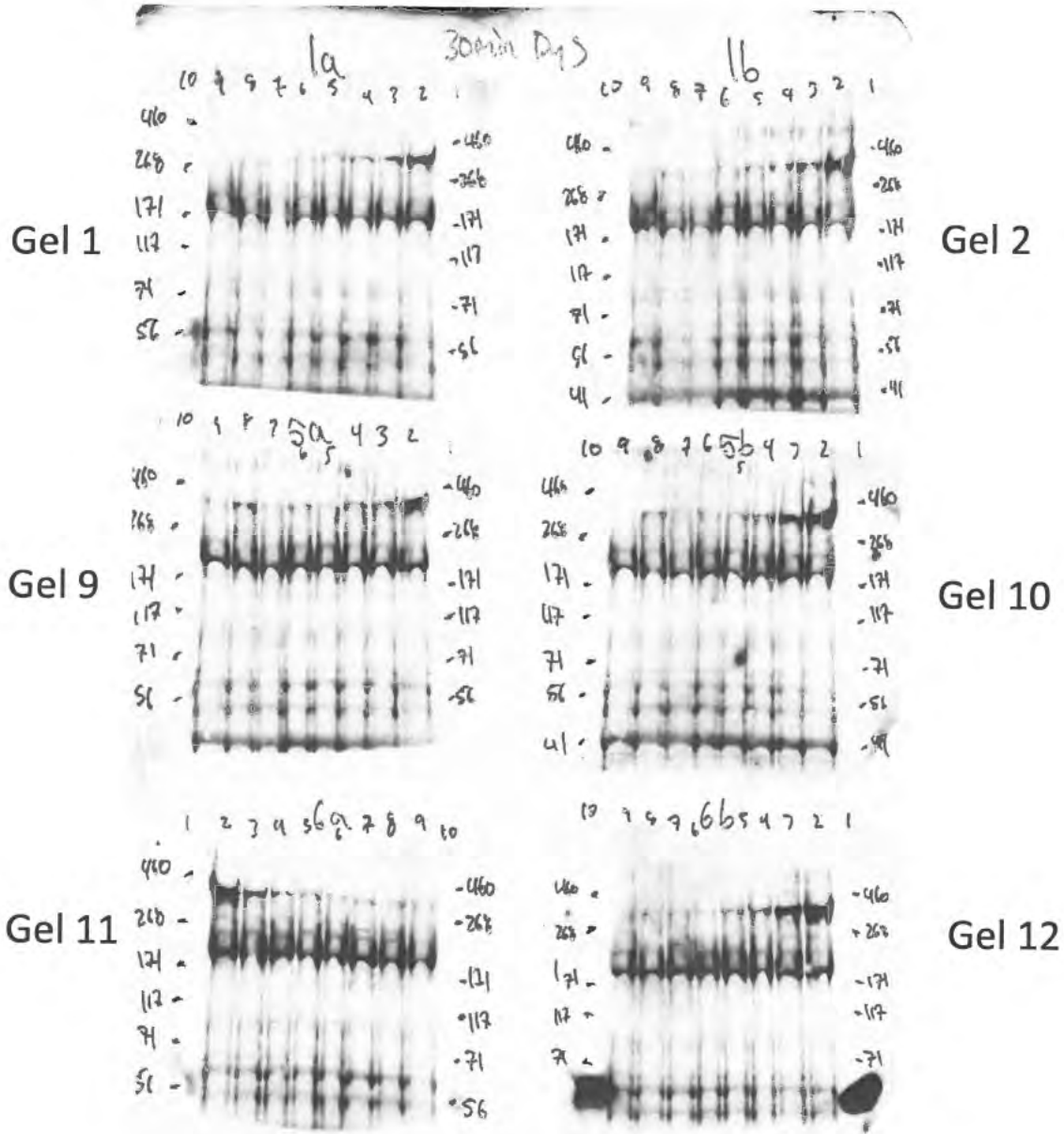
Summary Tables showing the % dystrophin from the matched pairs of samples from 13 patients. Numbers under Lane 7 and Lane 8 refer to the blinded pair of baseline/week 48 bicep samples.

SR-CR-16-003: DYS1 - 20 minute exposure							
Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)	Neg CT <0.25%
1	1a	0.14	0.27	0.99	Pass	14425 (8649)	Pass
2	1b	0.07	0.21	0.96	Pass	39798 (15235)	Pass
3	2a	0.36	0.35	0.99	Pass	26926 (14147)	Pass
4	2b	0.10	0.12	0.90	Pass	47296 (73361)	Fail
5	3a	0.13	0.50	0.98	Pass	22397 (31305)	Fail
6	3b	0.09	0.22	1.00	Pass	64945 (29089)	Pass
7	4a	0.04	0.08	0.95	Pass	44795 (16235)	Pass
8	4b	0.04	0.13	0.89	Fail	60880 (35534)	Pass
9	5a	0.10	1.08	0.80	Fail	86479 (40898)	Pass
10	5b	0.07	0.74	1.00	Pass	33696 (13462)	Pass
11	6a	0.30	0.37	0.97	Pass	31429 (30177)	Pass
12	6b	0.15	0.18	0.94	Pass	23477 (32971)	Fail

SR-CR-16-003: DYS1 - 15 minute exposure							
Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)	Neg CT <0.25%
13	1a	0.00	0.00	0.38	Fail	67389 (47602)	Pass
14	1b	0.17	0.42	0.97	Pass	64418 (58077)	Pass
15	2a	0.08	0.08	0.95	Pass	37476 (58536)	Fail
16	2b	0.14	0.05	0.83	Fail	21696 (20615)	Pass
17	3a	1.17	0.14	0.98	Pass	22073 (35280)	Fail
18	3b	1.57	0.24	0.98	Pass	49106 (37627)	Pass
19	4a	0.11	0.12	0.93	Pass	40030 (8873)	Pass
20	4b	0.05	0.11	0.98	Pass	35884 (39241)	Fail
21	5a	0.31	0.01	0.98	Pass	110706 (48990)	Pass
22	5b	0.63	0.08	0.93	Pass	93278 (52055)	Pass
23	6a	0.09	0.02	0.91	Pass	77556 (51352)	Pass
24	6b	0.02	0.00	0.78	Fail	108111 (64389)	Pass
25	8a	0.34	0.34	0.96	Pass	38943 (83782)	Fail
26	8b	0.18	0.21	0.97	Pass	20460 (19812)	Pass

- The Gel images on the next slide are from the first 3 of the 6 matched pairs of patient samples that were run on June 21st 2016.
- Each sample was run twice. The gels next to each other are the duplicate runs.
- Each gel has a serial dilution of healthy control and DMD negative control

30 min Dys1

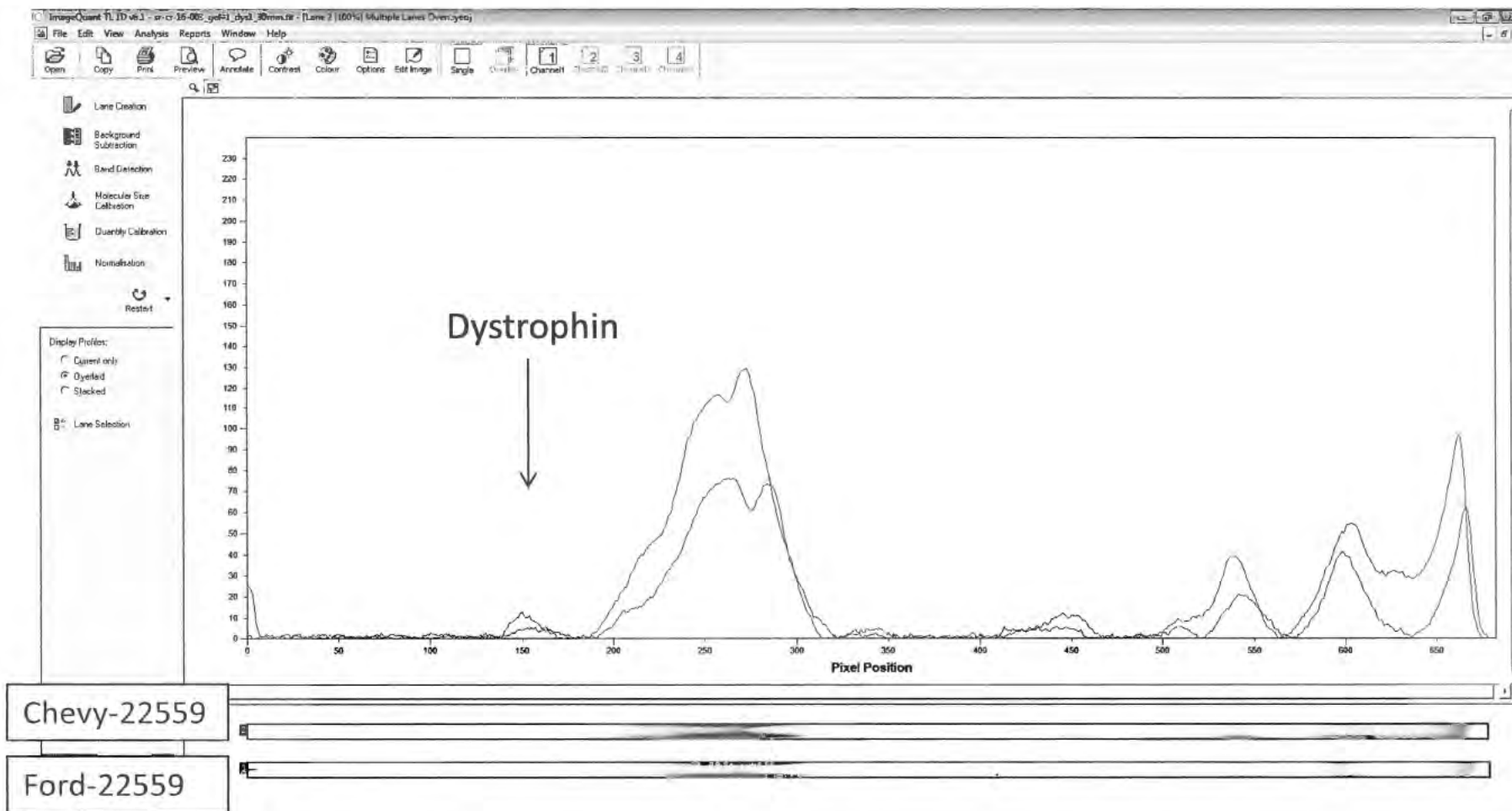


SE-02-16-003 21 Jun 2016
Fred Schrell 00619 pages 1-26
Cas Donoghue 00618 pages 1-26

Lane Key: 00619-p325
00618-p321
p3 21 Jun 2016
CD 21 Jun 2016

- The graphs on the next 6 slides show the chromatographic traces of the quantitation of bands from Lane 7 and Lane 8 overlaid with each other. The peak corresponding to the ~427 kDa dystrophin band is marked with an arrow by the applicant.
- These graphs were made from the gels on the preceding slide.

Image Filename: SR-CR-16-003_Gel#1_DYS1_30min.tif

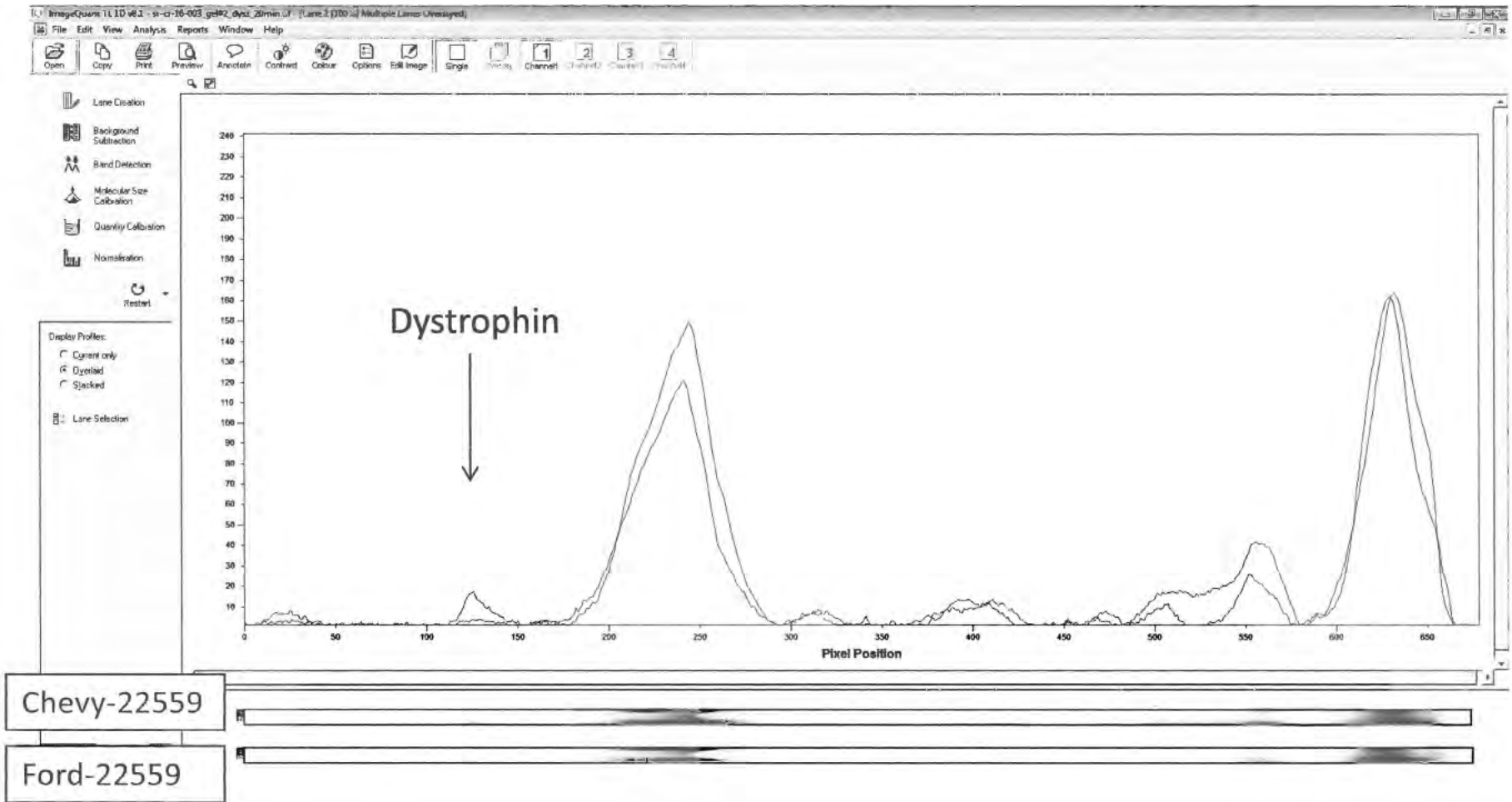


8/3/2017

SR-CR-16-003

6

Image Filename: SR-CR-16-003_Gel#2_DYS1_20min.tif

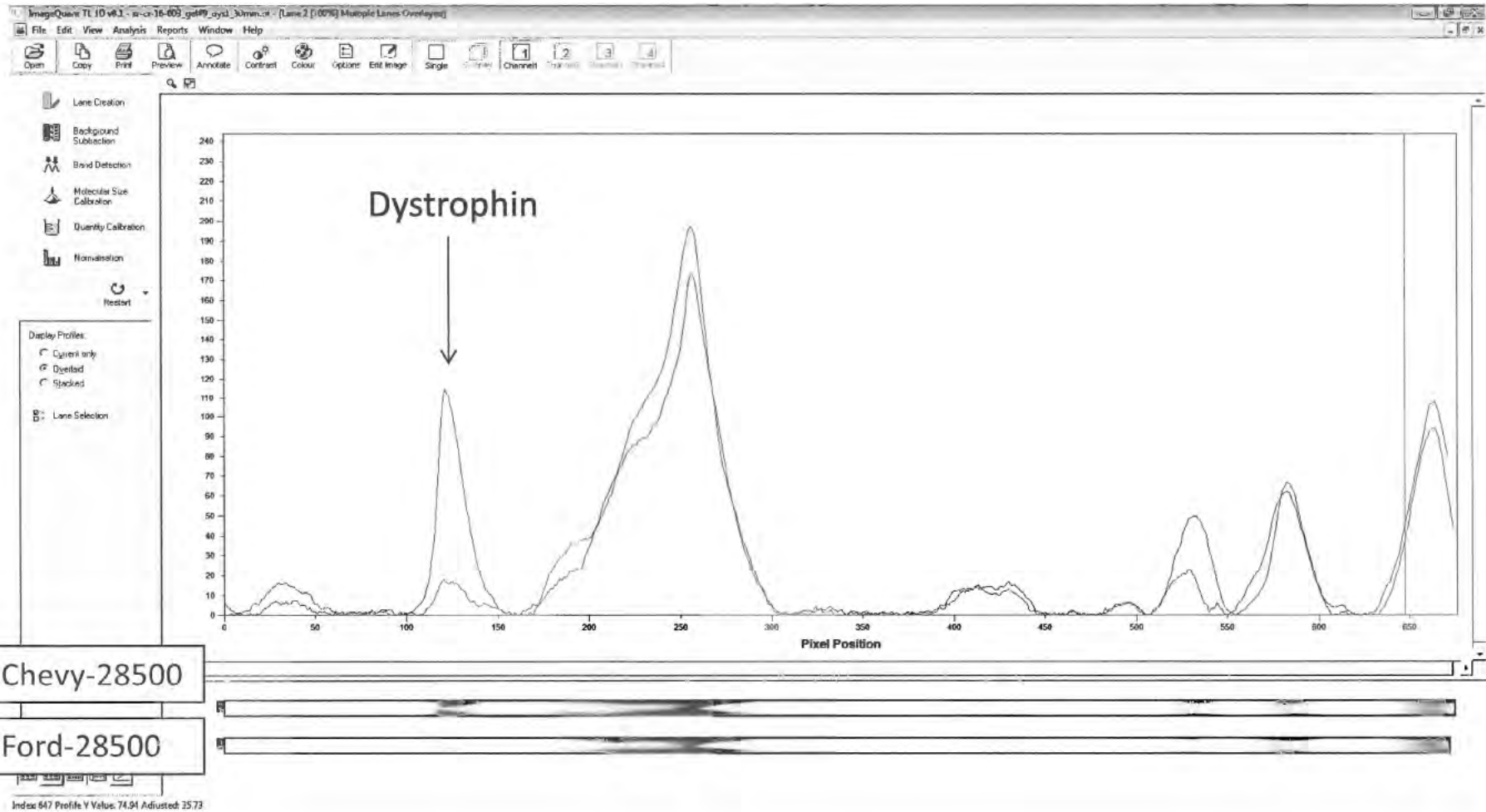


8/3/2017

SR-CR-16-003

7

Image Filename: SR-CR-16-003_Gel#9_DYS1_30min.tif



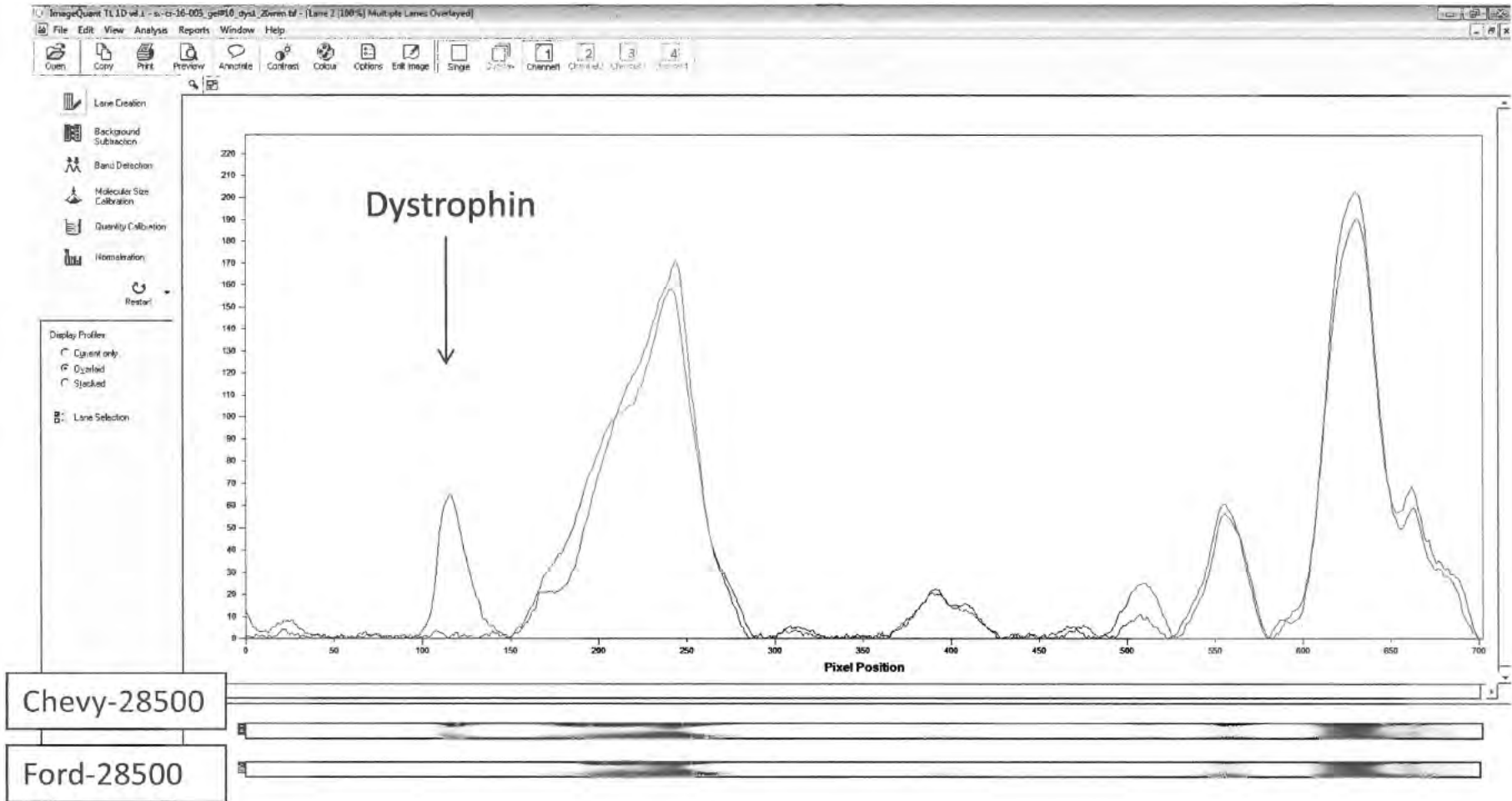
8/3/2017

SR-CR-16-003

8

FDACDER0005386

Image Filename: SR-CR-16-003_Gel#10_DYS1_20min.tif



8/3/2017

SP-CR-16-003

9

Image Filename: SR-CR-16-003_Gel#2_DYS1_20min.tif

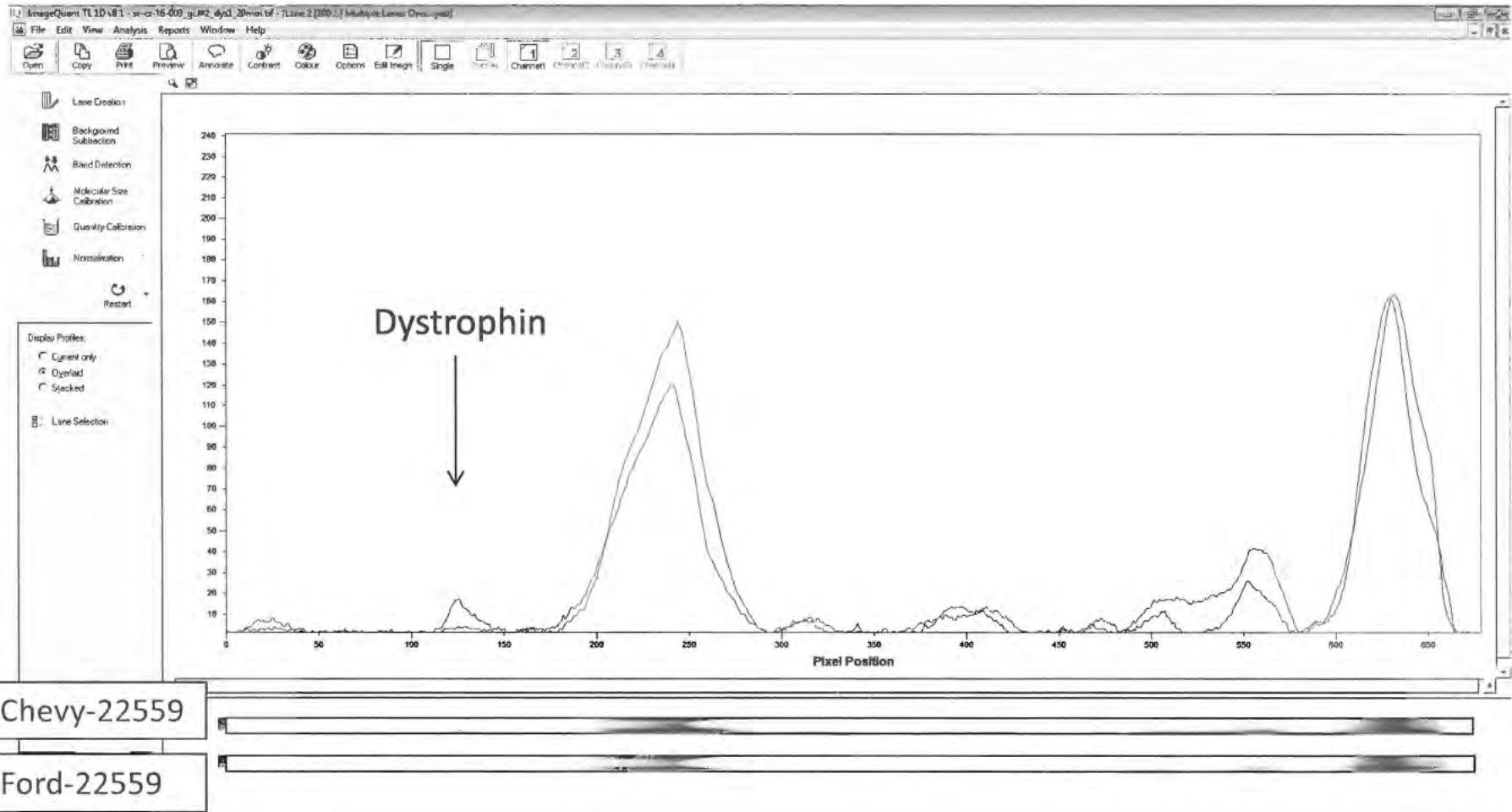
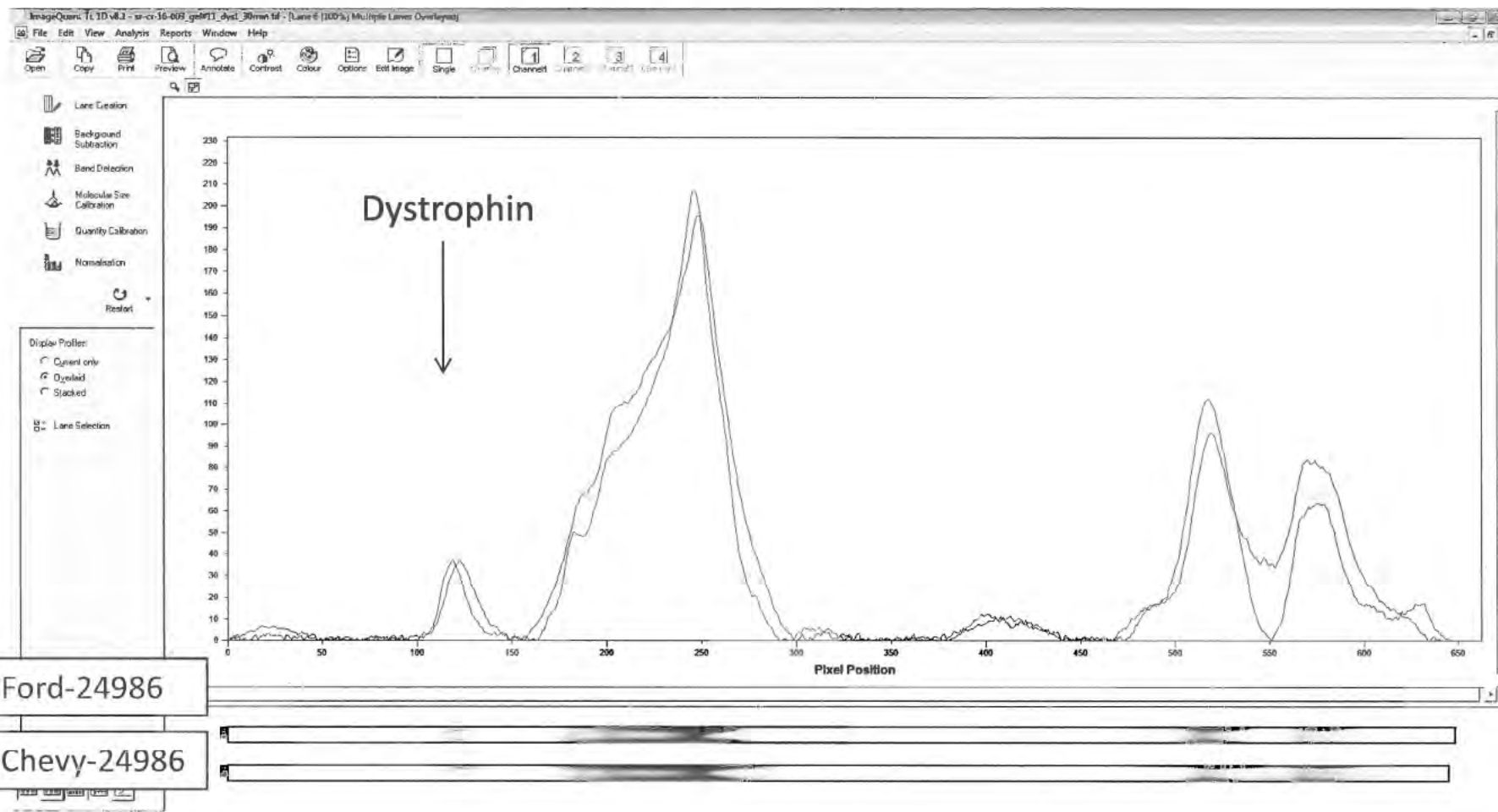


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8/3/2017

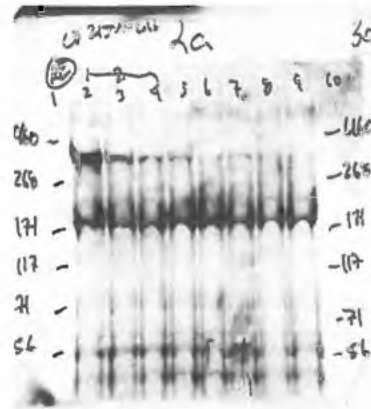
SR-CR-16-003

11

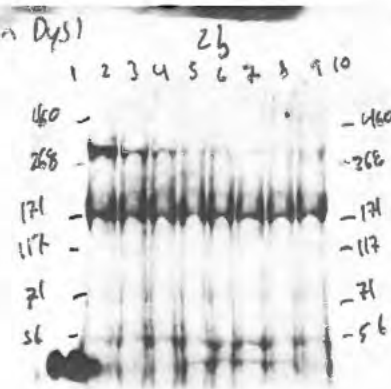
- The Gel images on the next slide are from the next 3 of the 6 matched pairs of patient samples that were run on June 21st 2016.
- Each sample was run twice. The gels next to each other are the duplicate runs.
- Each gel has a serial dilution of healthy control and DMD negative control

30 min Dys1

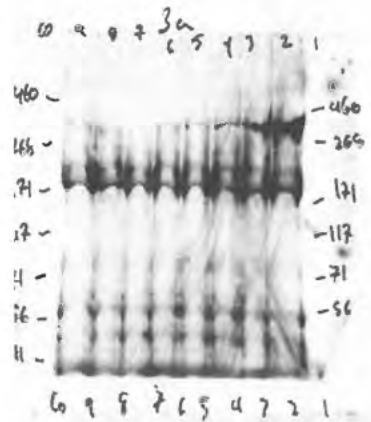
Gel 3



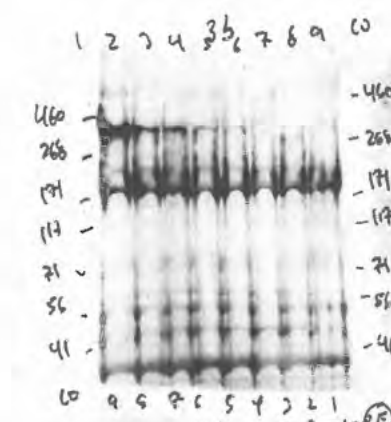
Gel 4



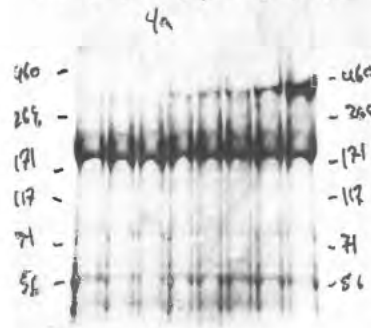
Gel 5



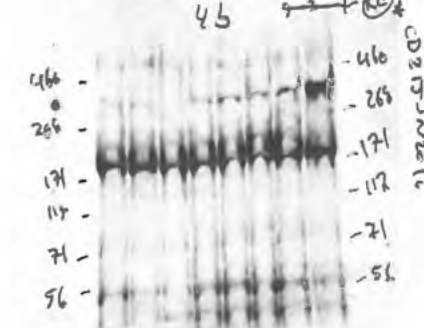
Gel 6



Gel 7



Gel 8



SP-CR-16-003
Fred Schnell
C&S Donoghue
21 JUN 2016

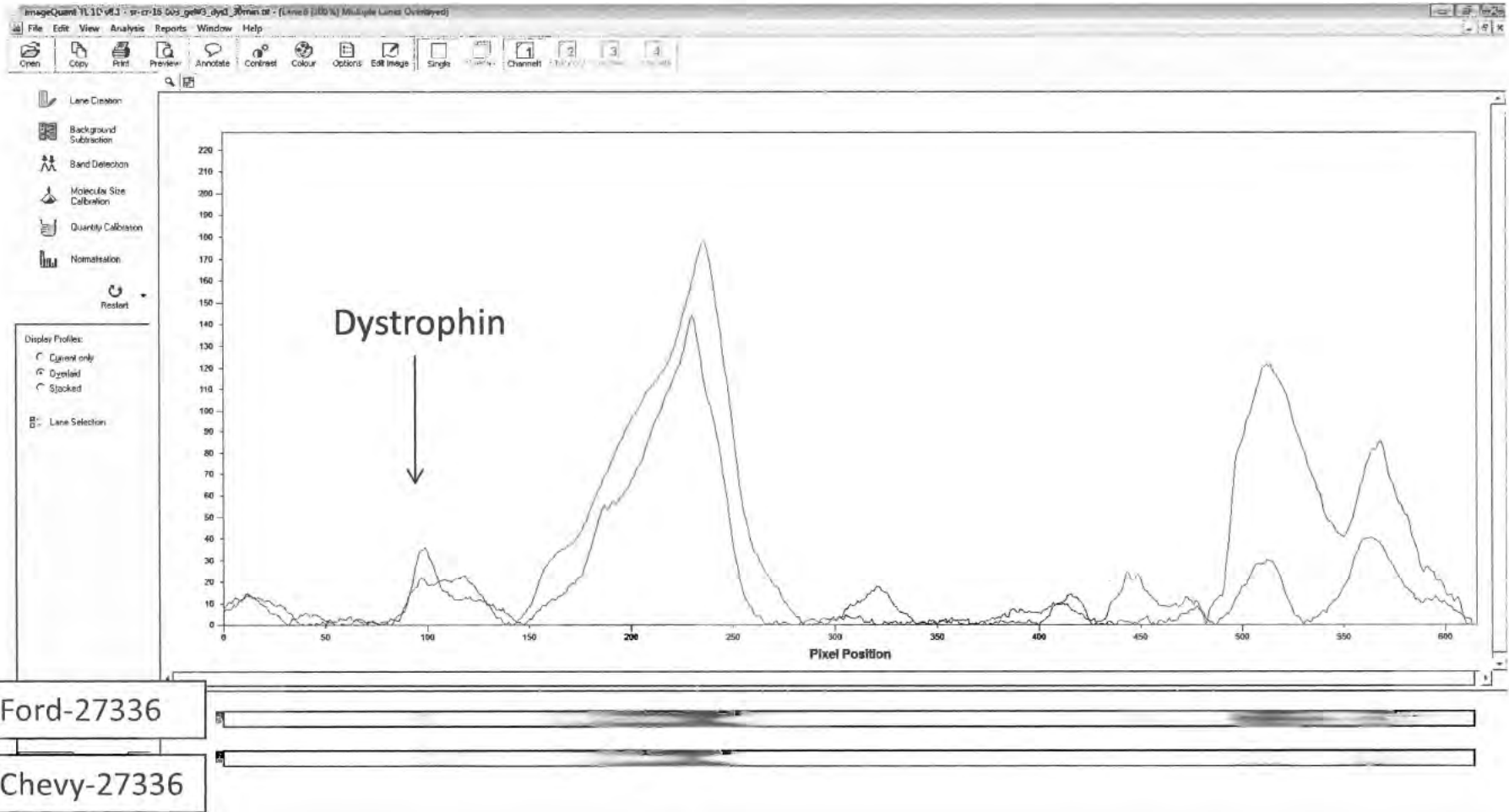
00619 pg 21
00618 pg 29

Locking:
00619 pg 25
00618 pg 21

CD 4150216
FS 2150208

- The graphs on the next 6 slides show the chromatographic traces of the quantitation of bands from Lane 7 and Lane 8 overlaid with each other. The peak corresponding to the ~427 kDa dystrophin band is marked with an arrow by the applicant.
- These graphs were made from the gels on the preceding slide.

Image Filename: SR-CR-16-003_Gel#3_DYS1_30min.tif

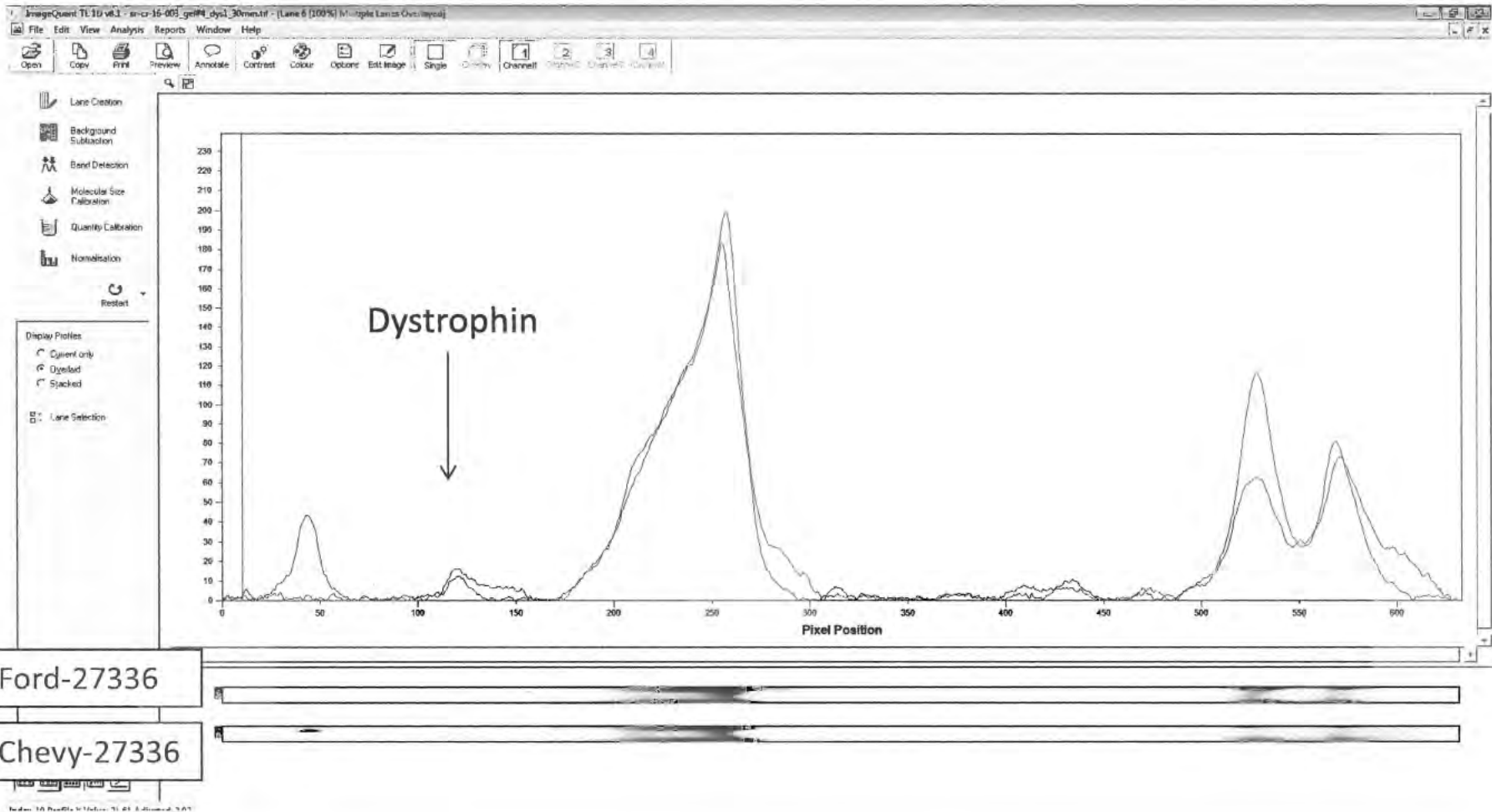


8/3/2017

SR-CR-16-003

15

Image Filename: SR-CR-16-003_Gel#4_DYS1_30min.tif



8/3/2017

SR-CR-16-003

16

Image Filename: SR-CR-16-003_Gel#5_DYS1_30min.tif

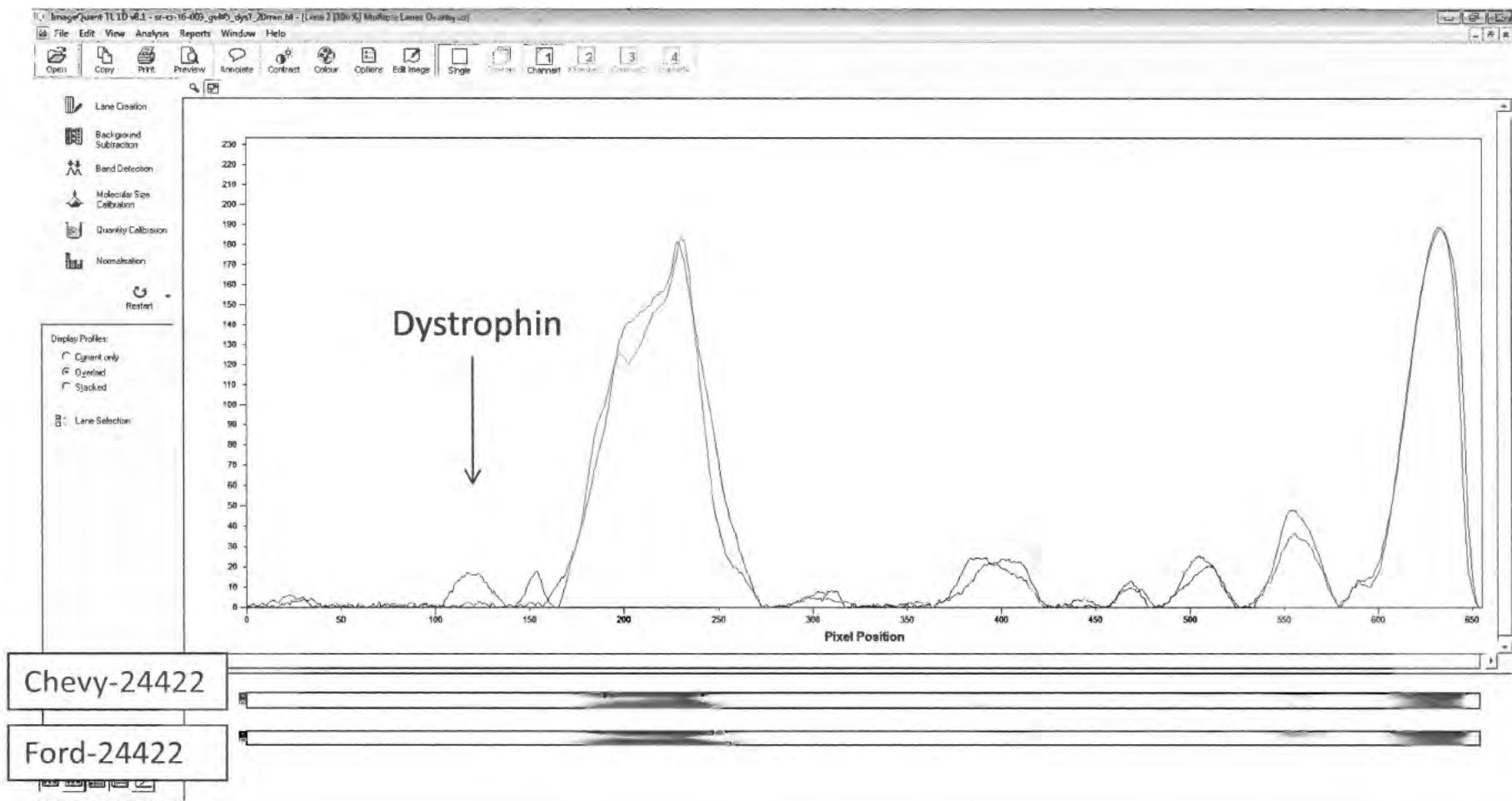
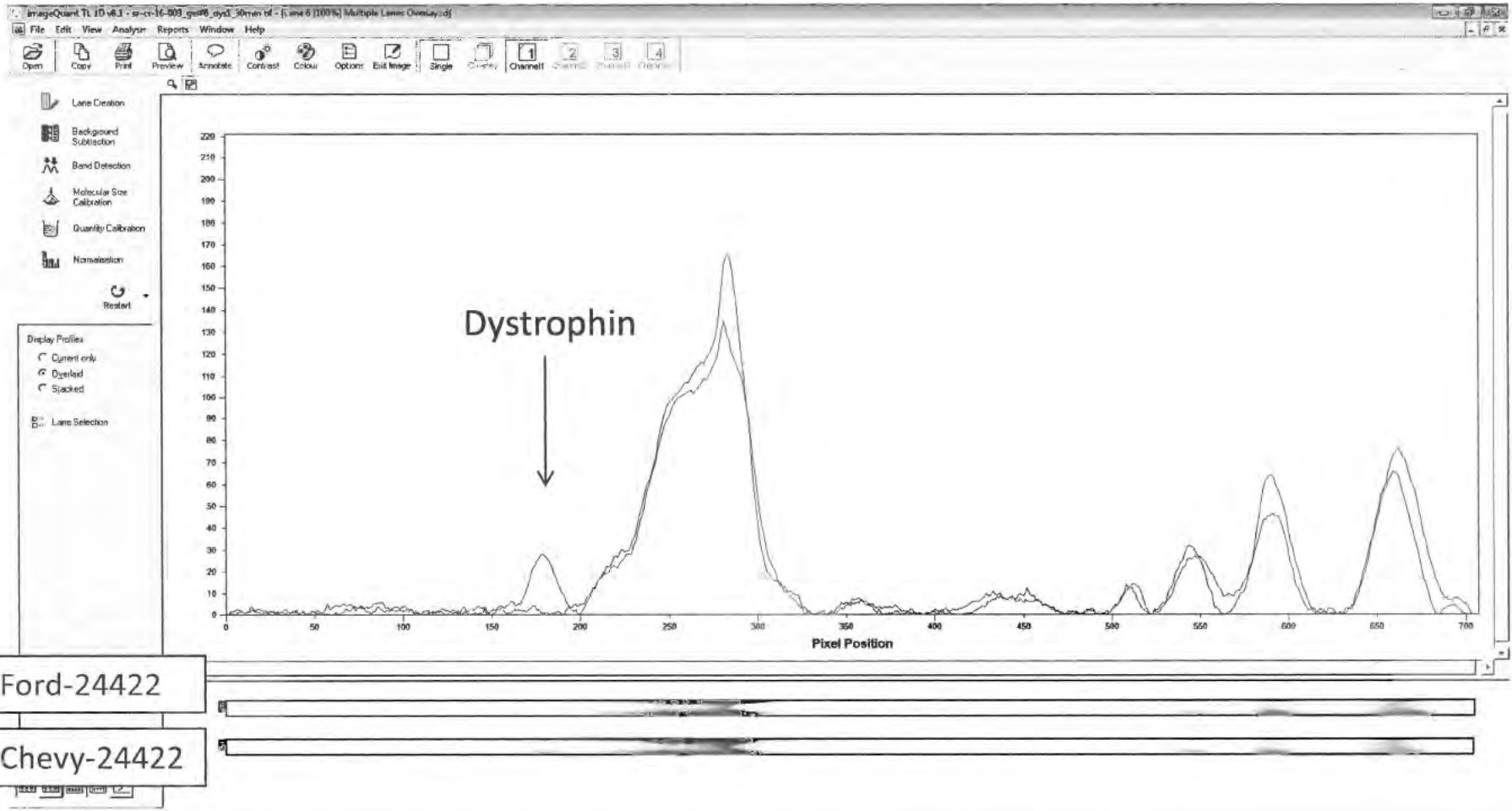


Image Filename: SR-CR-16-003_Gel#6_DYS1_30min.tif

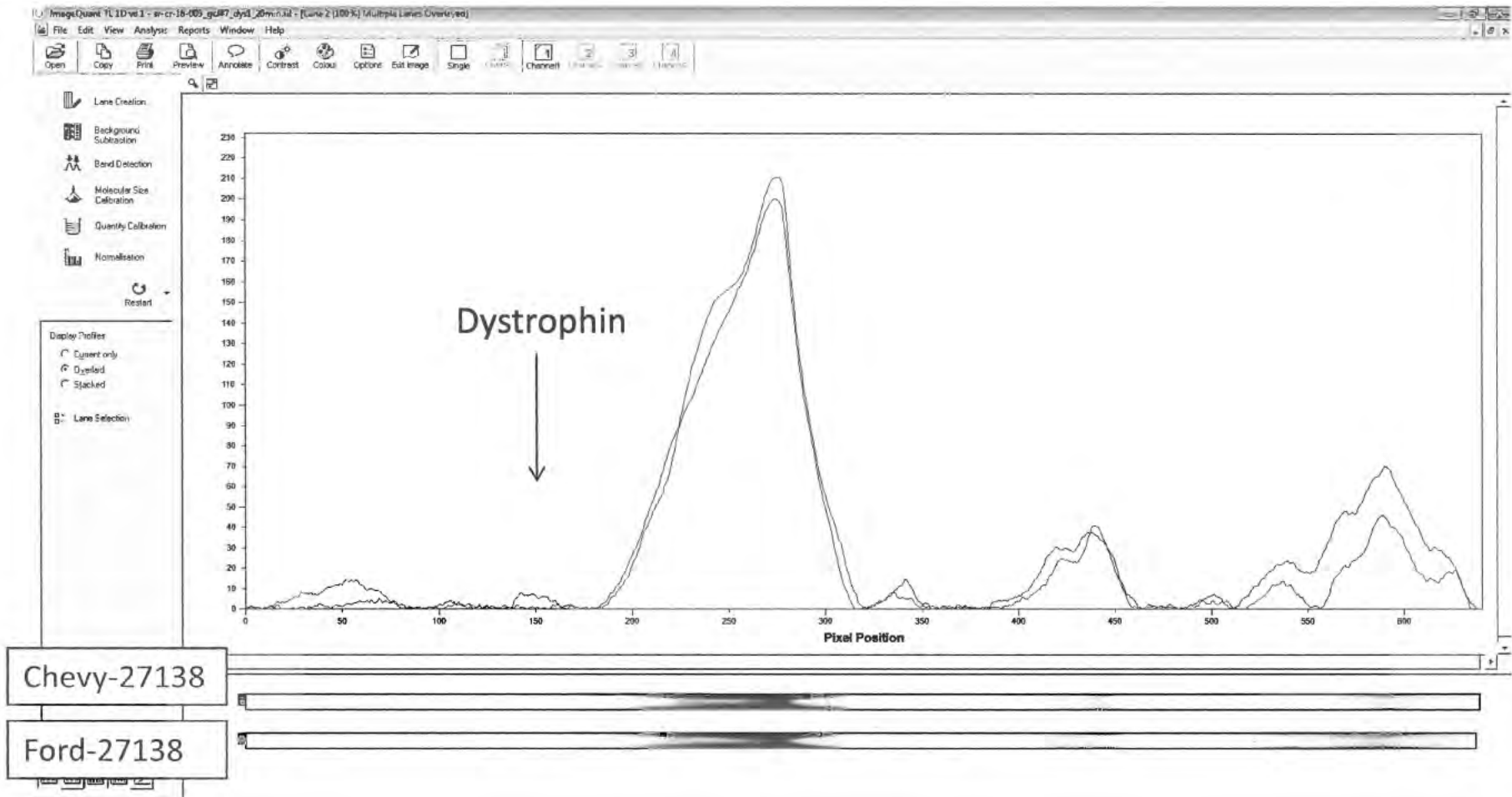


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SR-CR-16-003

18

Image Filename: SR-CR-16-003_Gel#7_DYS1_20min.tif

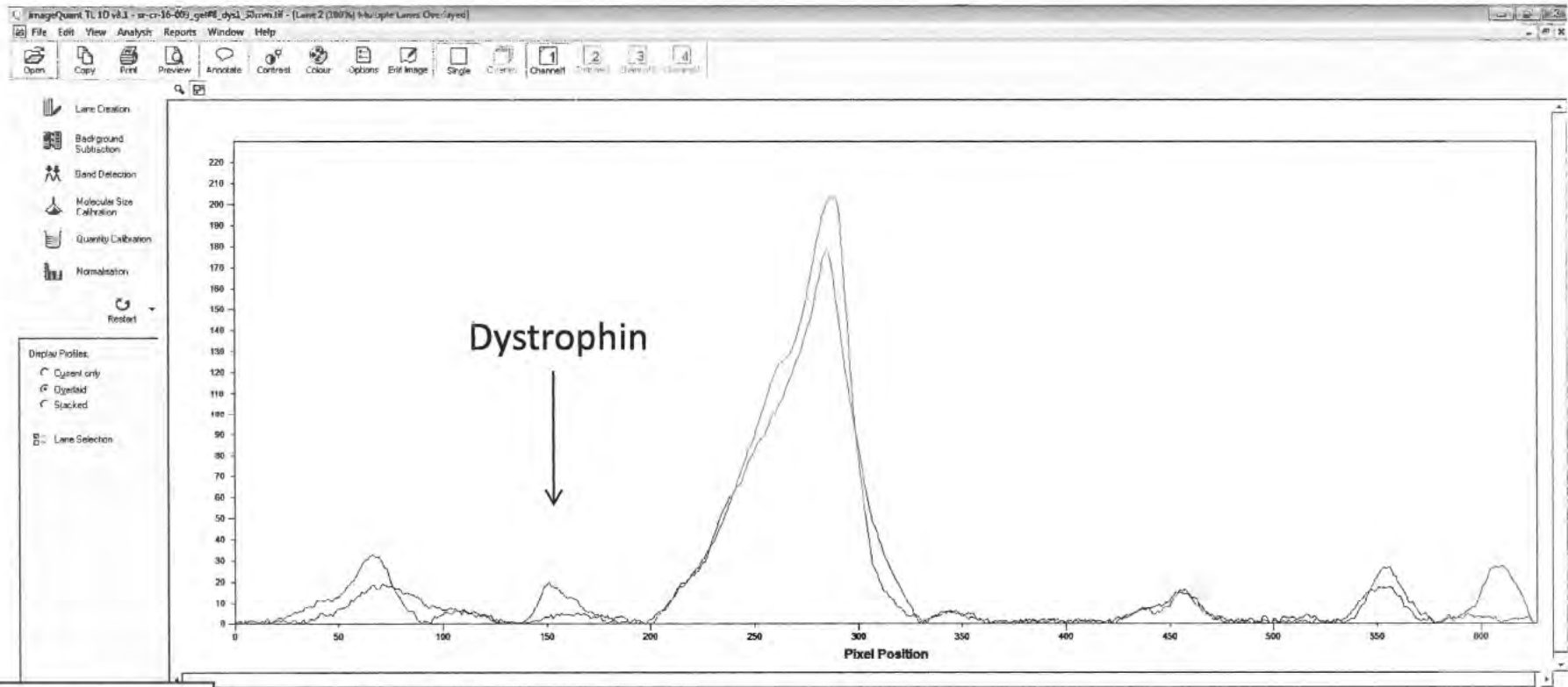


8/3/2017

SR-CR-16-003

19

Image Filename: SR-CR-16-003_Gel#8_DYS1_30min.tif



Chevy-27138

Ford-27138



8/3/2017

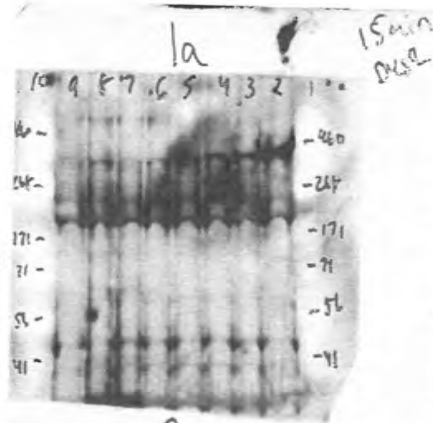
SR-CR-16-003

20

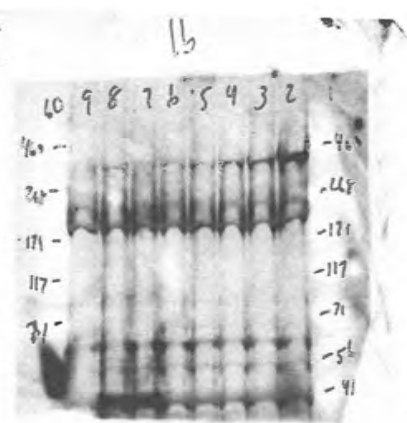
- The Gel images on the next slide are from the first 3 of the 7 matched pairs of patient samples that were run on June 23rd 2016.
- Each sample was run twice. The gels next to each other are the duplicate runs.
- Each gel has a serial dilution of healthy control and DMD negative control

15 min Dys1

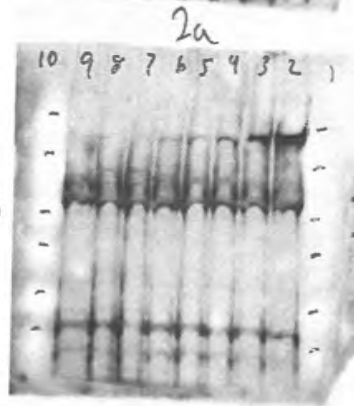
Gel 13



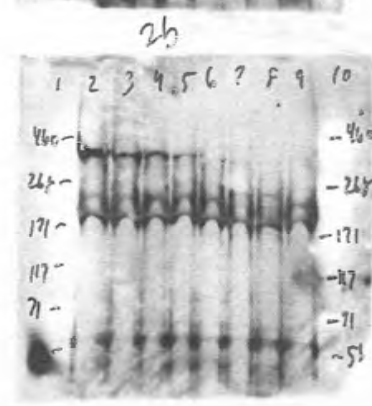
Gel 14



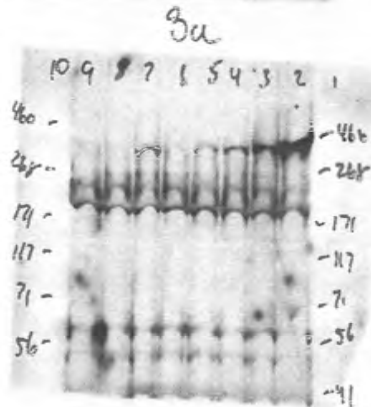
Gel 15



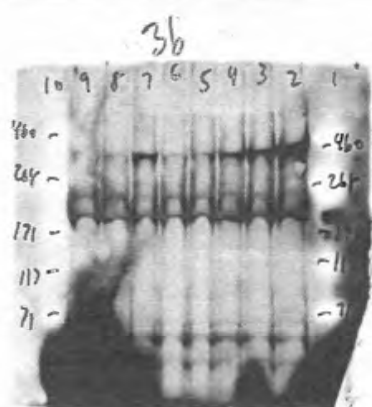
Gel 16



Gel 17



Gel 18



SR-CR-16-003
23 Jun 2016
PS 23 Jun 2016

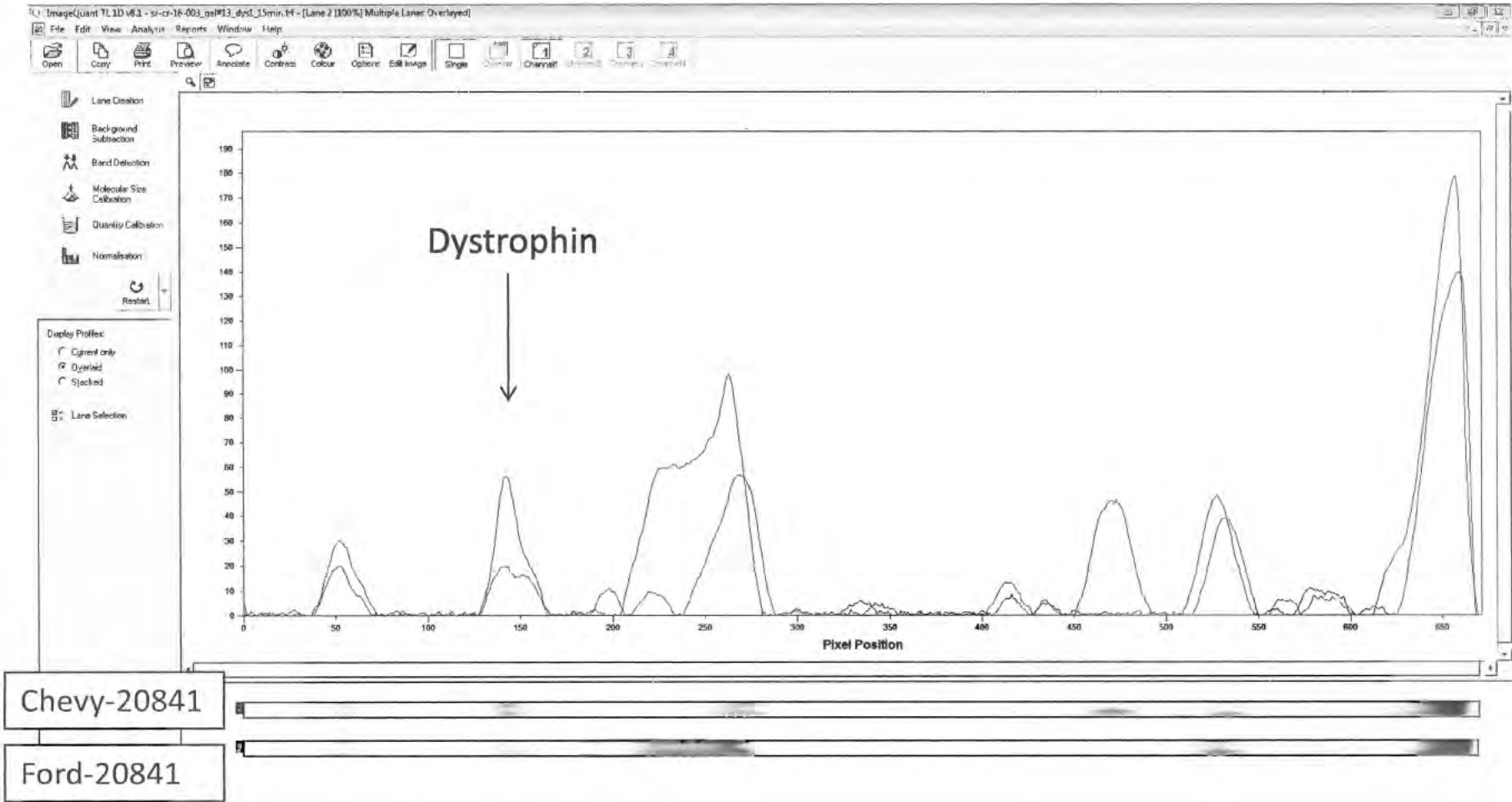
Fred Schmidt
Caj Ameghine
CO 23 Jun 2016

00618 P5 45
00619 P5 1-46

Lane Key:
00618 P5 39
00619 P5 42
00619 P5 2016

- The graphs on the next 6 slides show the chromatographic traces of the quantitation of bands from Lane 7 and Lane 8 overlaid with each other. The peak corresponding to the ~427 kDa dystrophin band is marked with an arrow by the applicant.
- These graphs were made from the gels on the preceding slide.

Image Filename: SR-CR-16-003_Gel#13_DYS1_15min.tif



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SR-CR 16-003

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Image Filename: SR-CR-16-003_Gel#14_DYS1_15min.tif

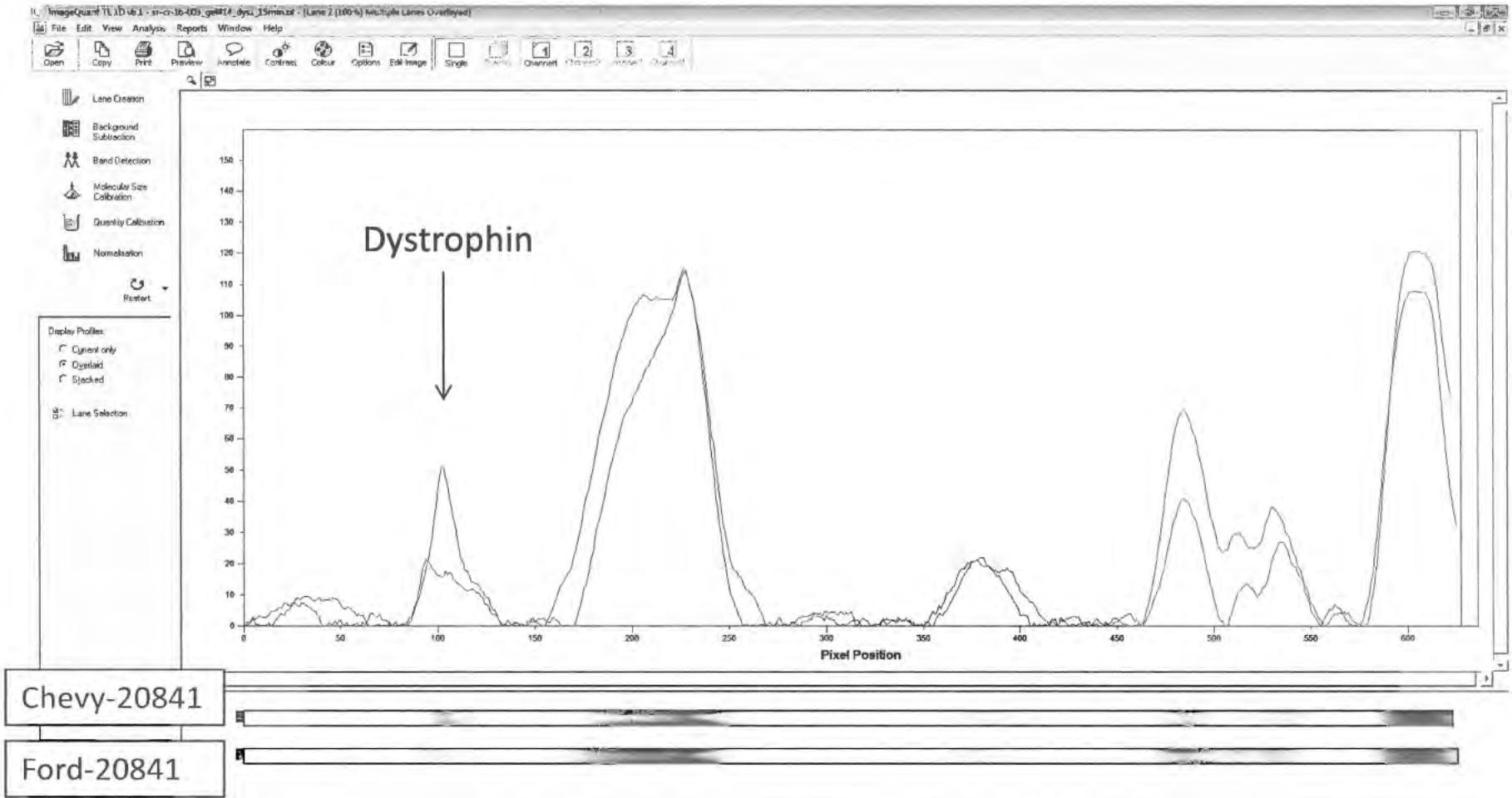


Image Filename: SR-CR-16-003_Gel#15_DYS1_15min.tif

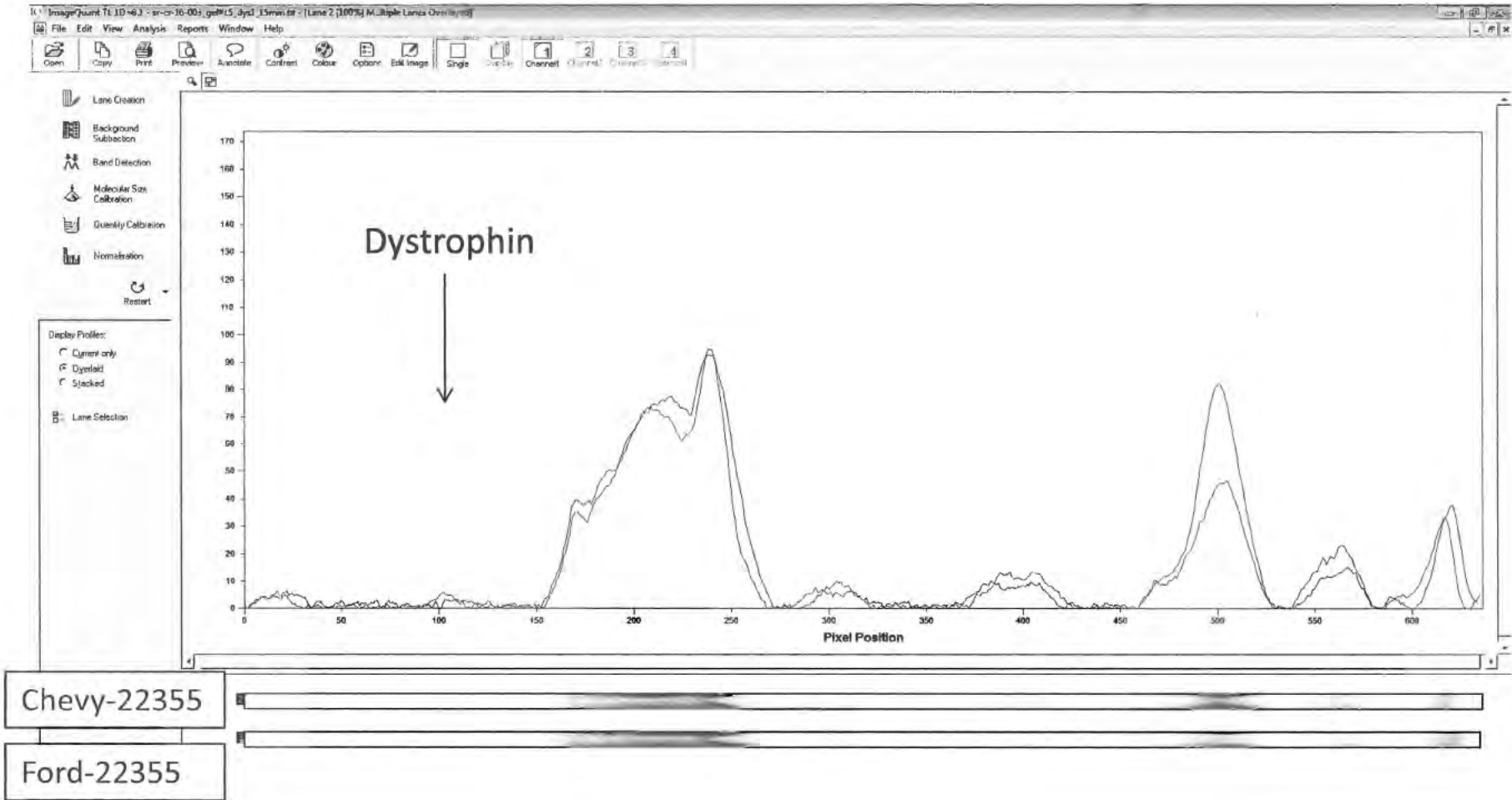
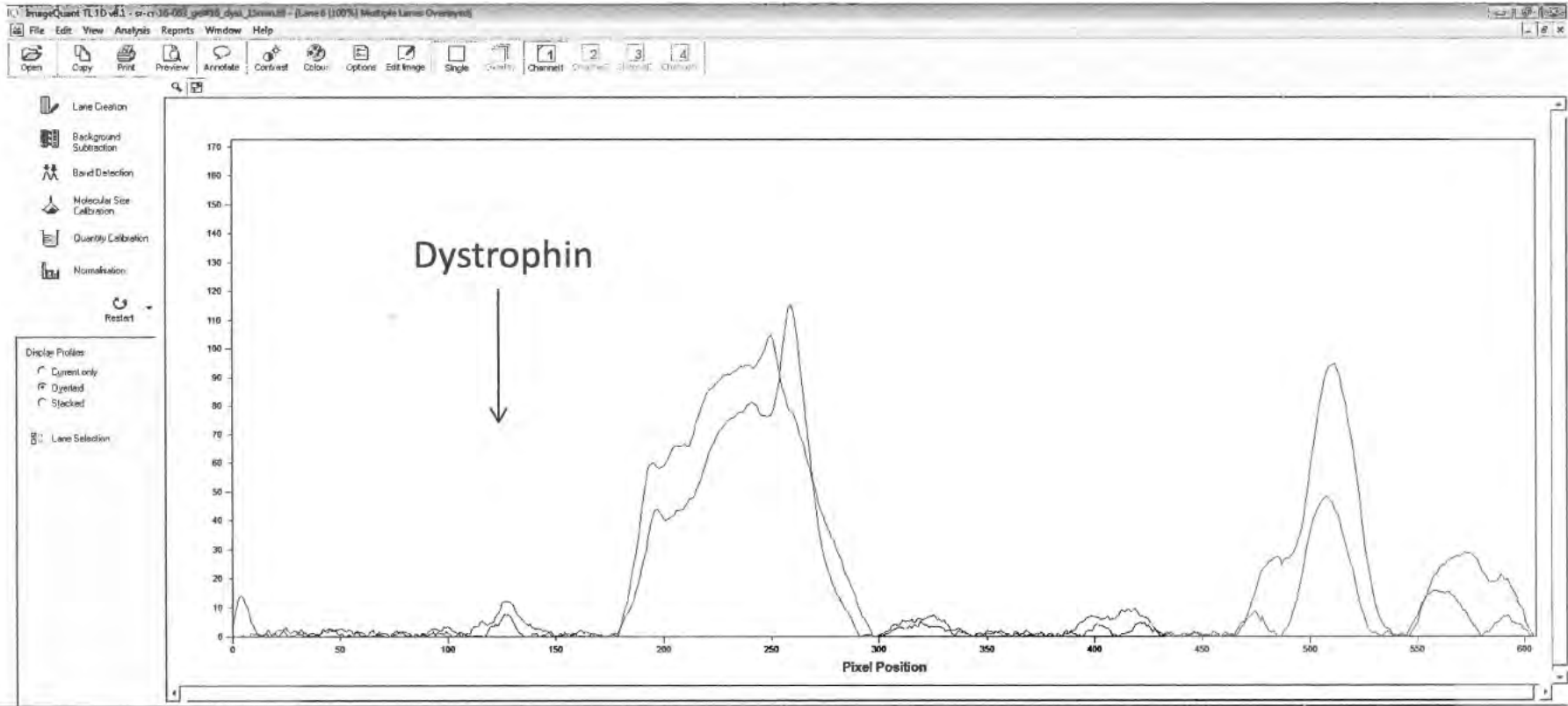


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Ford-22355

Chevy-22355

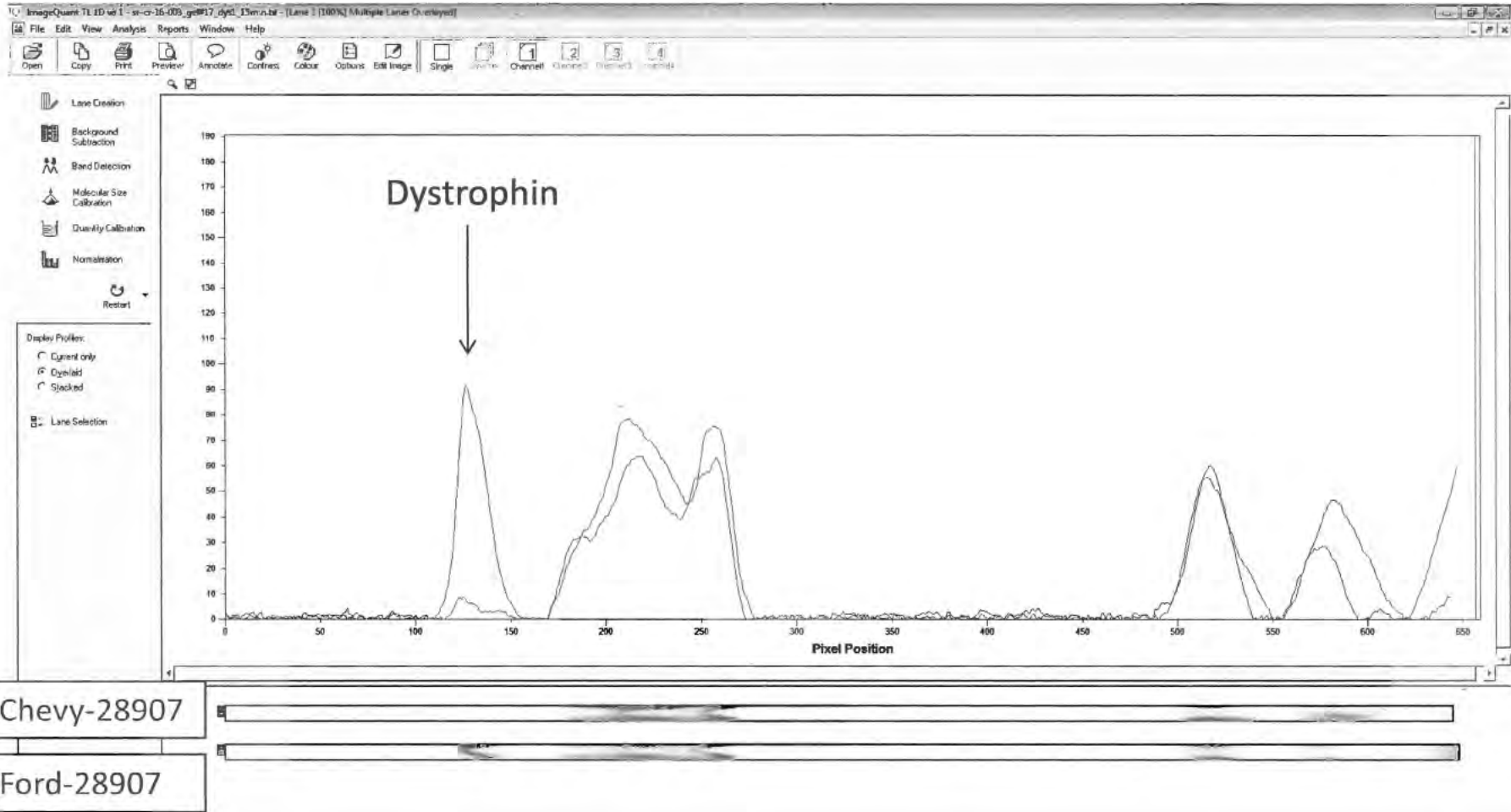


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SR-CR-16-003

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Image Filename: SR-CR-16-003_Gel#17_DYS1_15min.tif



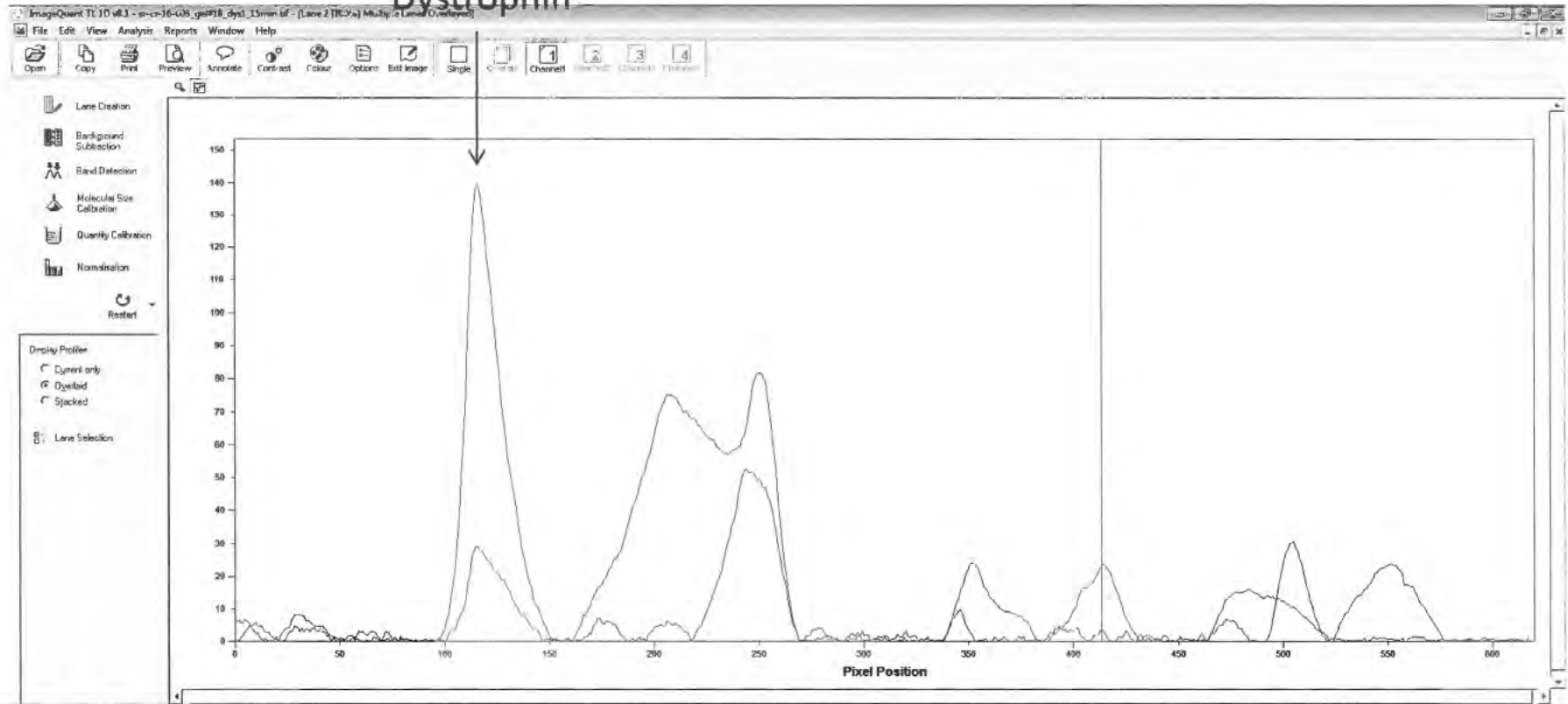
8/3/2017

SR-CR-16-003

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Image Filename: SR-CR-16-003_Gel#18_DYS1_15min.tif

Dystrophin



Chevy-28907

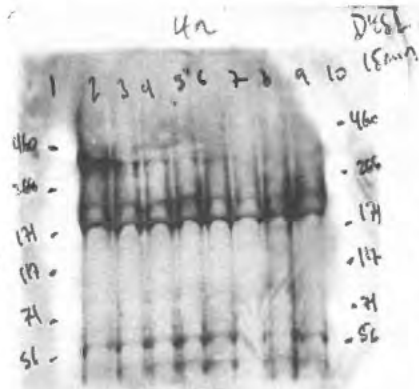
Ford-28907

Index_414 Profile Y Value: 201.24 Adjusted: 23.97

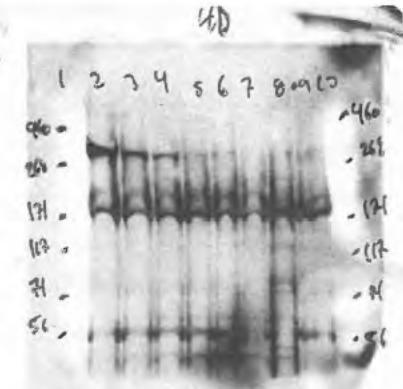
- The Gel images on the next slide are from the next 3 of the 7 matched pairs of patient samples that were run on June 23rd 2016.
- Each sample was run twice. The gels next to each other are the duplicate runs.
- Each gel has a serial dilution of healthy control and DMD negative control

15 min Dys1

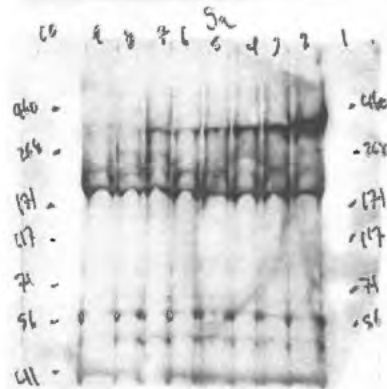
Gel 19



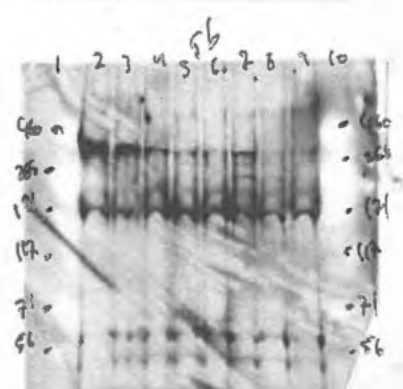
Gel 20



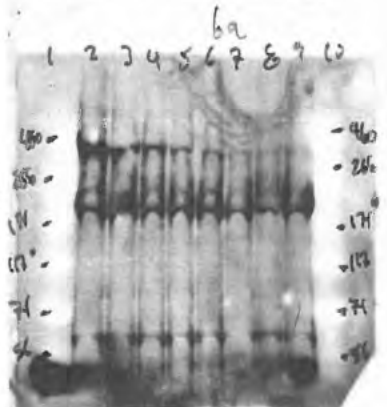
Gel 21



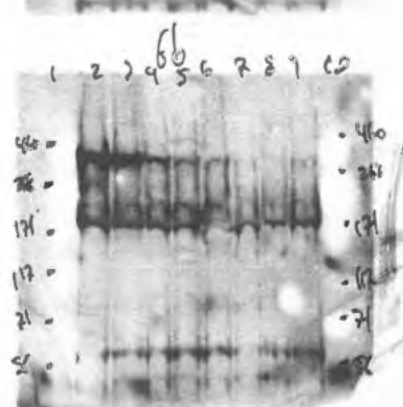
Gel 22



Gel 23



Gel 24



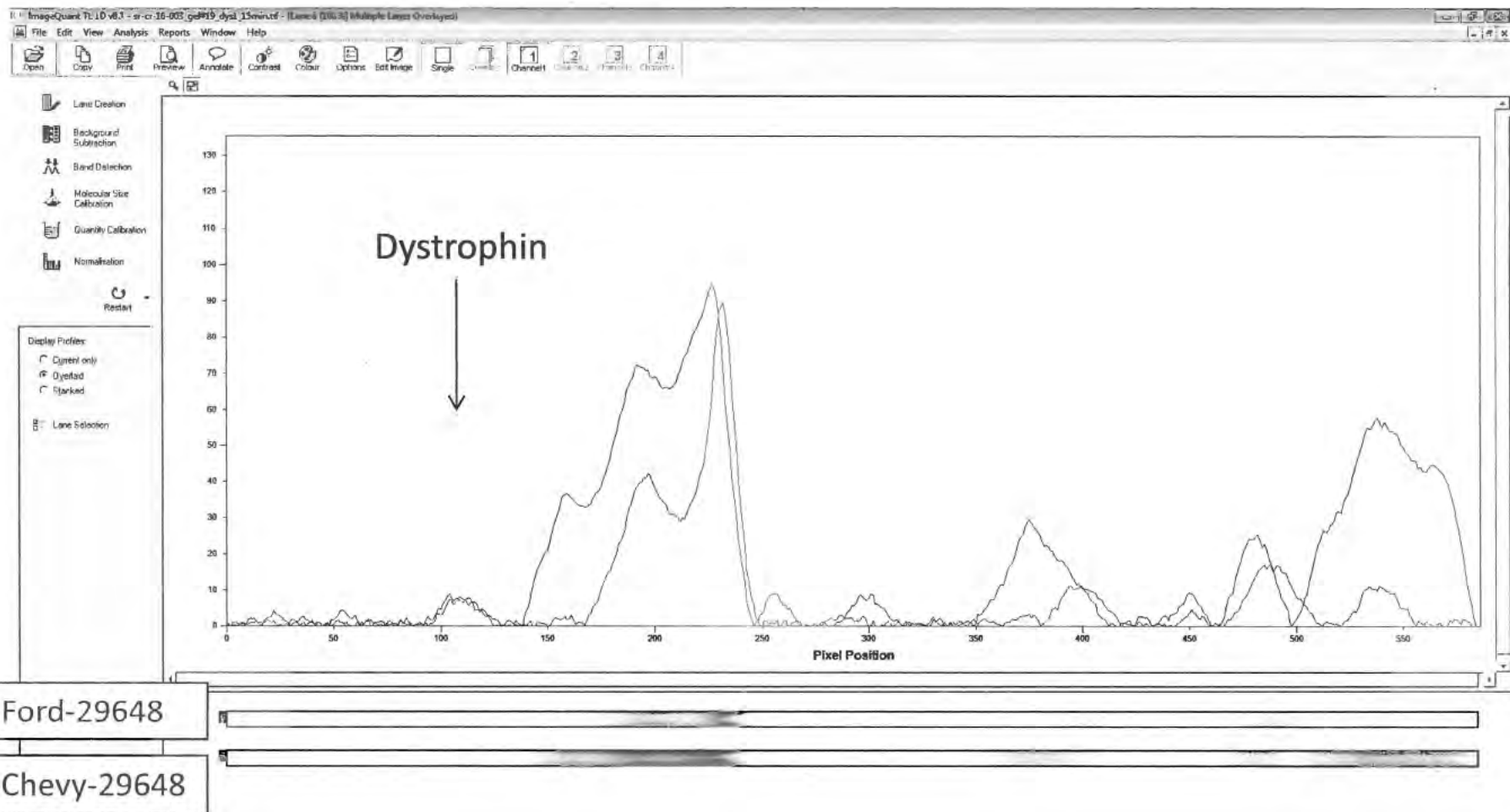
SP-CR-16-003 00618 pg 1-45
23 JUN 2011 00619 pg 1-46
Fred Schnell
Caus Docteur
CD 23 JUN 2011 F.S. 2016

Cont. key:
00618 pg 39
00619 pg 42

26

- The graphs on the next 6 slides show the chromatographic traces of the quantitation of bands from Lane 7 and Lane 8 overlaid with each other. The peak corresponding to the ~427 kDa dystrophin band is marked with an arrow by the applicant.
- These graphs were made from the gels on the preceding slide.

Image Filename: SR-CR-16-003_Gel#19_DYS1_15min.tif



8/3/2017

SR-CR-16-003

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Image Filename: SR-CR-16-003_Gel#20_DYS1_15min.tif

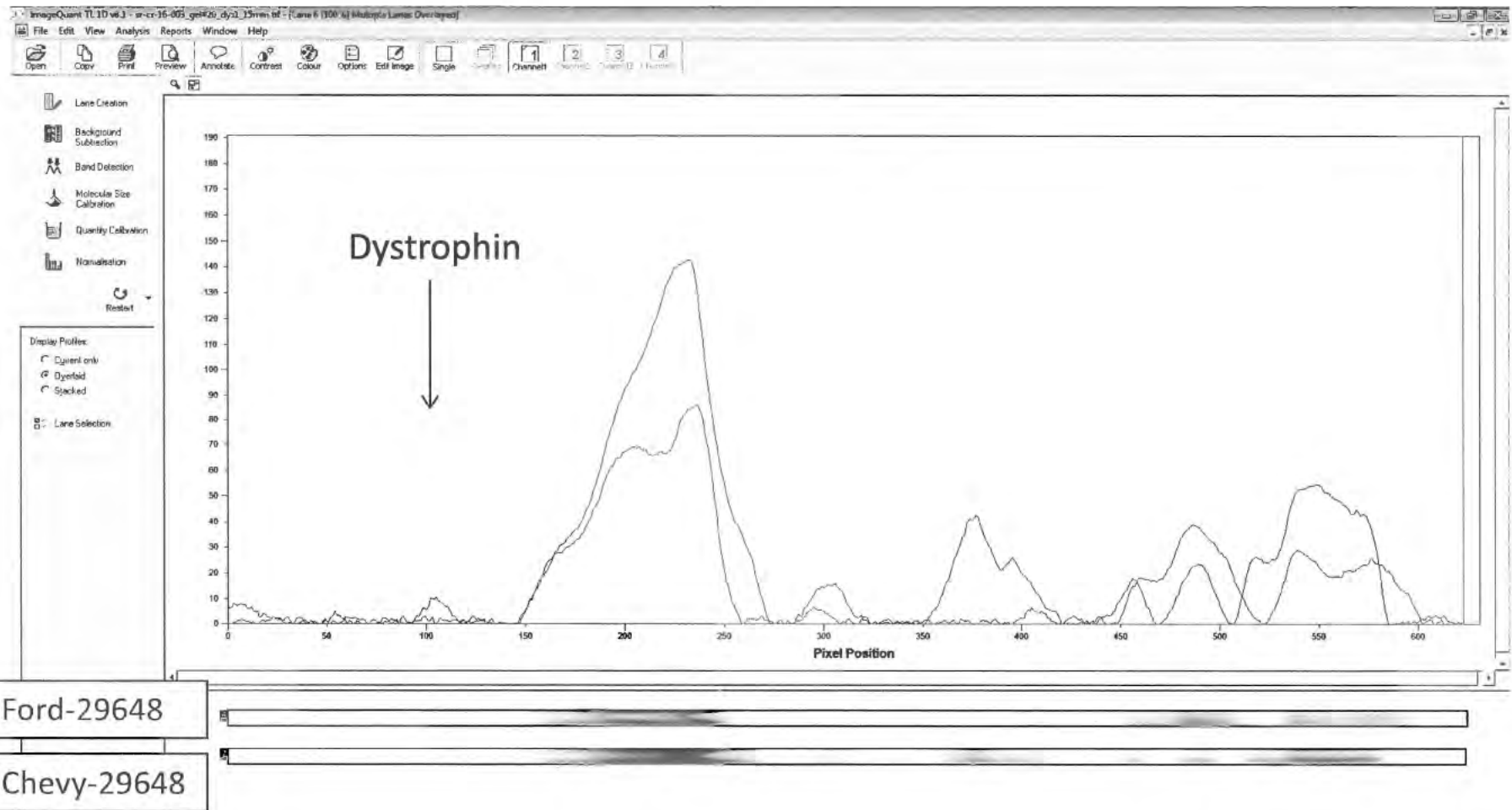
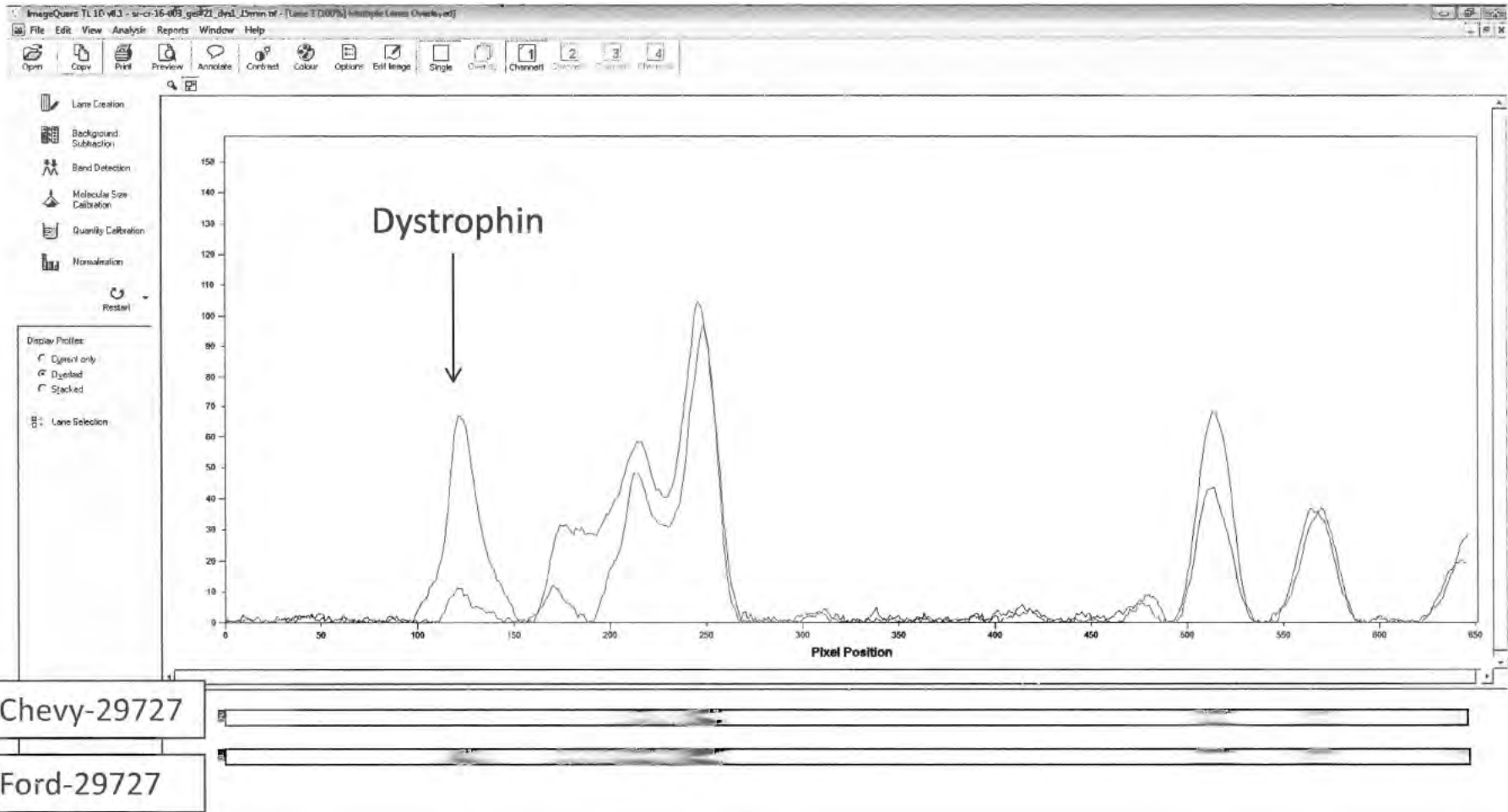


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SR-CR-16-003

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Image Filename: SR-CR-16-003_Gel#22_DYS1_15min.tif

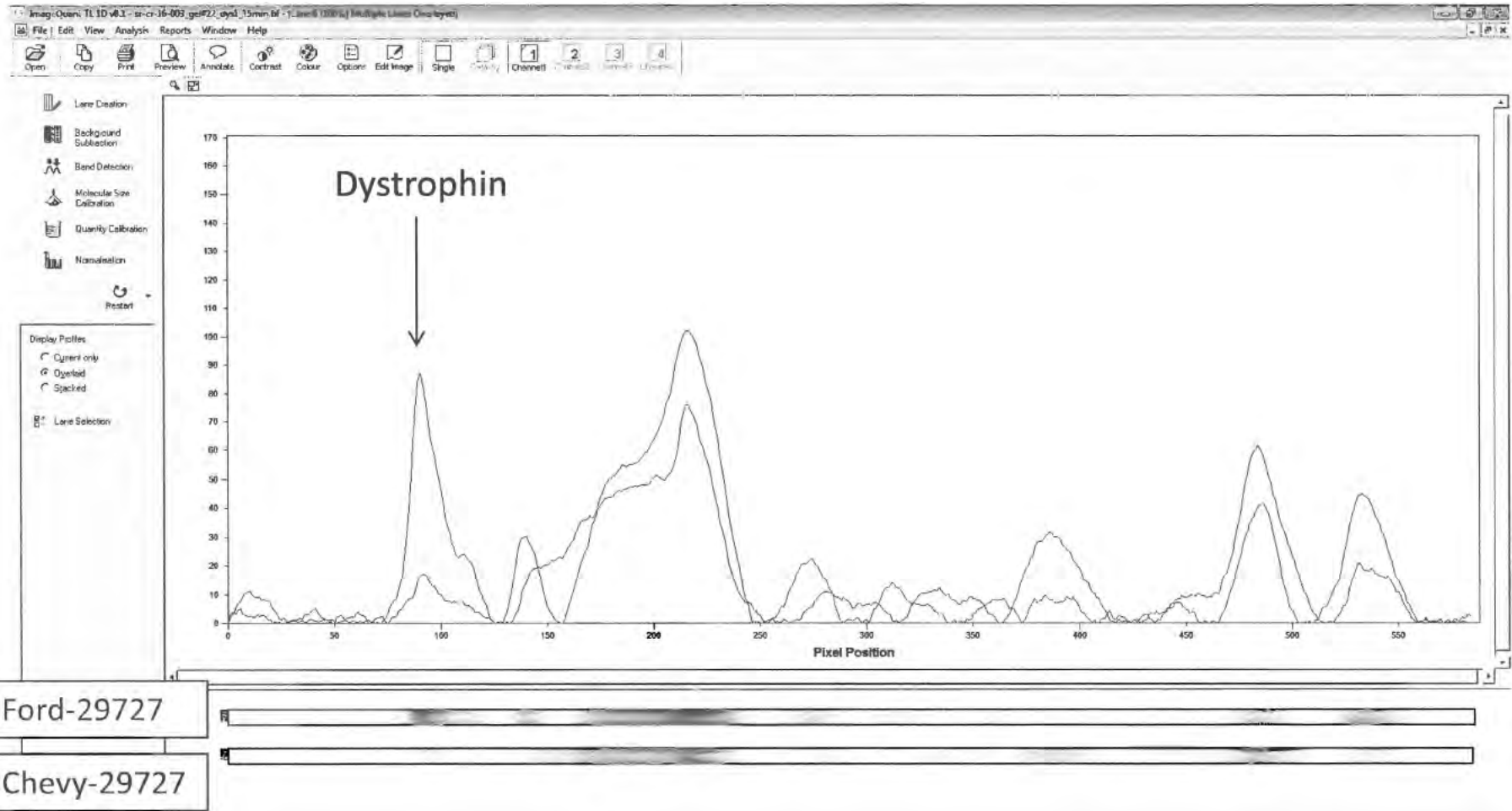


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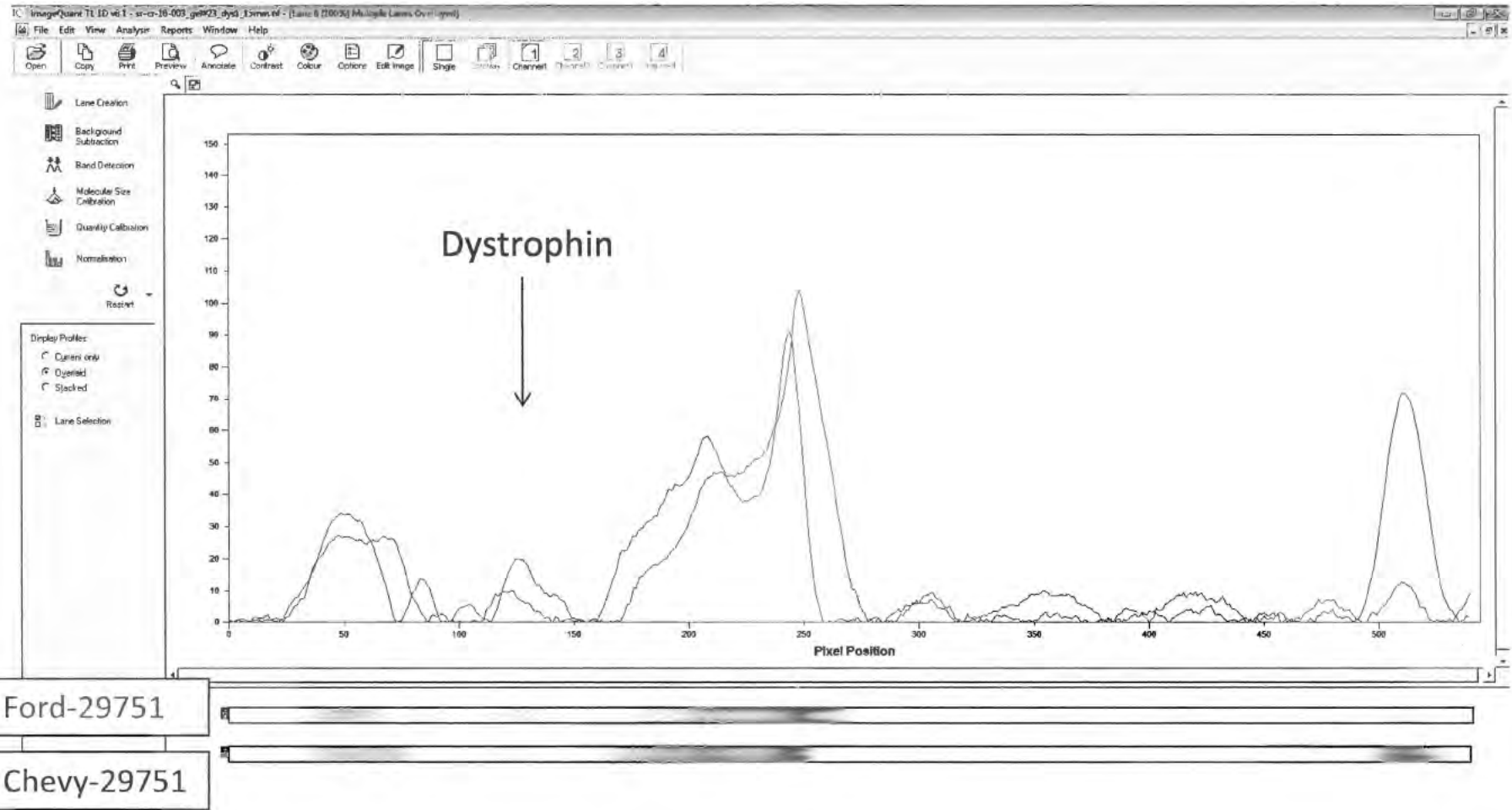
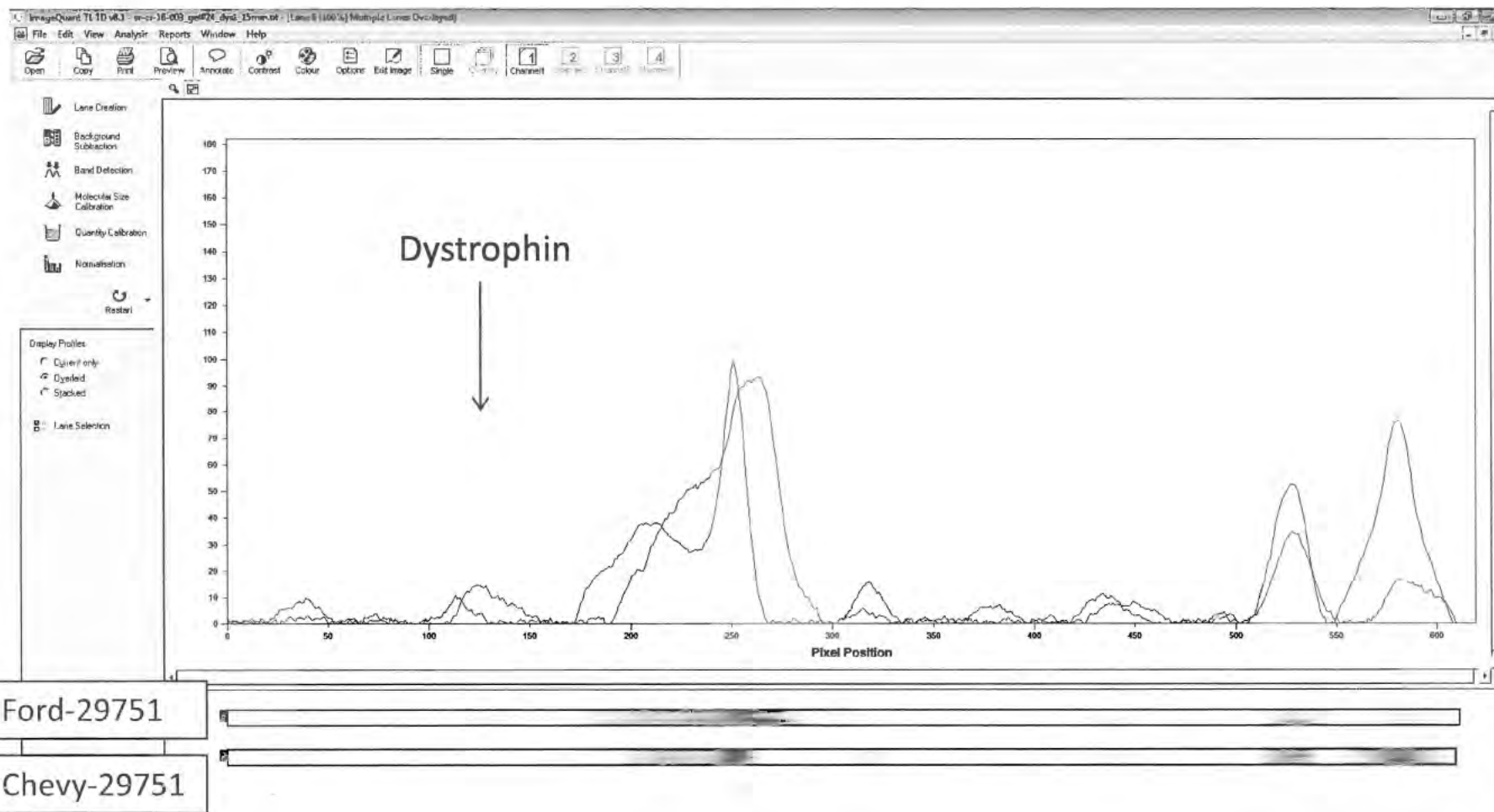


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8/3/2017

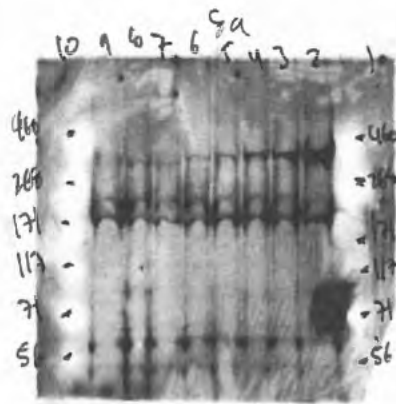
SR-CR-16-003

38

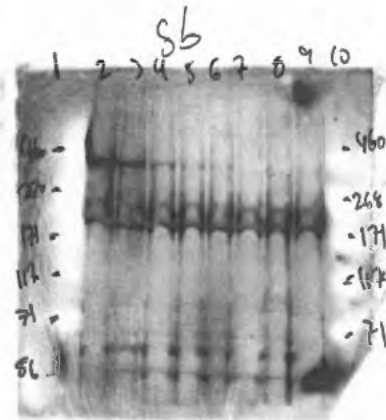
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- Each sample was run twice. The gels next to each other are the duplicate runs.
- Each gel has a serial dilution of healthy control and DMD negative control

15 min Dys1

Gel 25



Gel 26



SR-CR-16-003

23 Jun 2016

Fred Schnell

Cas Donoghue

CD 23 Jun 2016

PS 23 Jun 2016

00618 pg 1-45

00619 pg 1-46

Lane Key:

00618 pg 39

00619 pg 42

- The graphs on the next 1 slide show the chromatographic traces of the quantitation of bands from Lane 7 and Lane 8 overlaid with each other. The peak corresponding to the ~427 kDa dystrophin band is marked with an arrow by the applicant.
- These graphs were made from the gels on the preceding slide.

Image Filename: SR-CR-16-003_Gel#25_DYS1_15min.tif

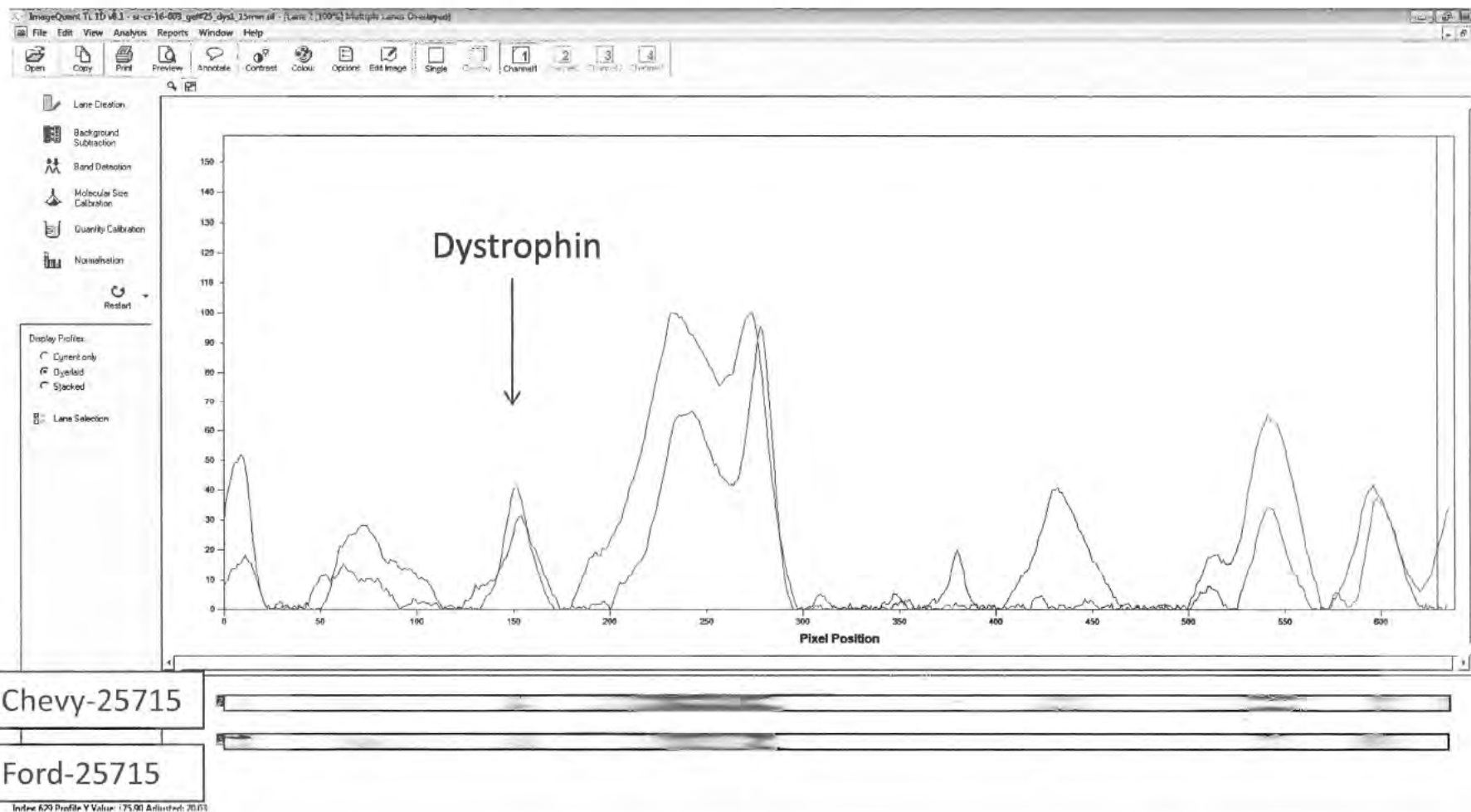
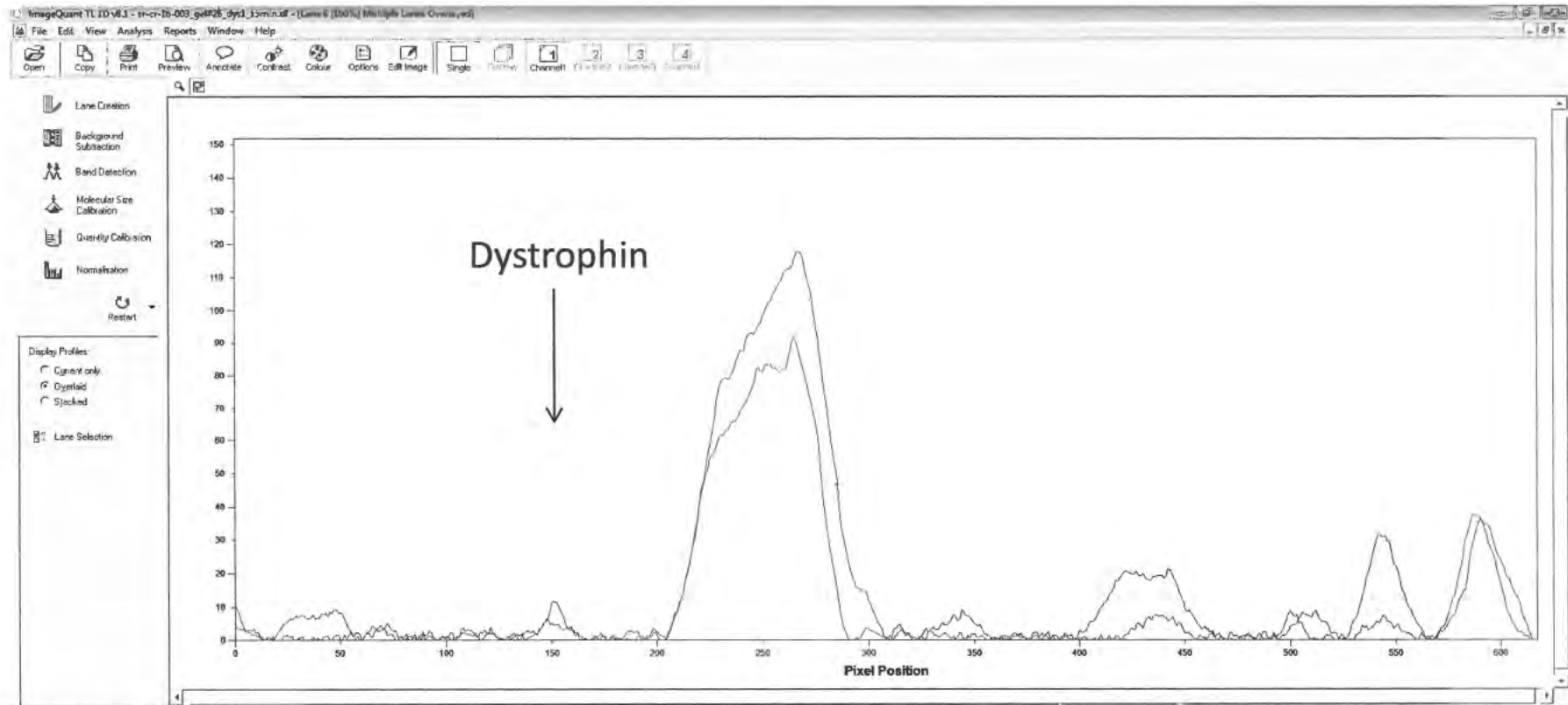


Image Filename: SR-CR-16-003_Gel#26_DYS1_15min.tif



Ford-25715

Chevy-25715

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 5:16 PM
To: DeMarco, Devota R
Subject: RM

From: Rao, Ashutosh
Sent: Thursday, June 16, 2016 4:13 PM
To: Woodcock, Janet; Moscicki, Richard
Cc: Rosenberg, Amy; Kozlowski, Steven
Subject: Feedback before Sarepta inspection?

Dear Janet and Rich,

I wanted to check in and see if you had any additional comments or suggestions for when I am on site and reviewing Sarepta's western blot analyses next week. You may have gotten progress updates from the clinical division already. After negotiating the protocols with the clinical division, both the Iowa and Oregon site inspections were coordinated with Sarepta. OSIS is currently wrapping up the Iowa inspection and I am scheduled to visit the Oregon site in collaboration with OSIS and ORA next week starting Sunday.

As previously discussed, my task during the visit would be to (1) observe the western blotting procedure for the clinical samples from their ongoing study, (2) verify compliance with the negotiated SOP, (3) confirm the documentation to support blinding/unblinding steps with OSIS's help and (4) observe them enter raw data into a format that could be verified when submitted as a formal submission to the Agency (e.g. screen shots and worksheet copies). Please let me know if you have other thoughts or suggestions.

Thanks

Regards,
Ash

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 5:03 PM
To: DeMarco, Devota R
Subject: RM

From: Woodcock, Janet
Sent: Friday, June 03, 2016 1:36 PM
To: Rao, Ashutosh
Cc: Moscicki, Richard
Subject: RE: URGENT: Follow Up From Telecon This Morning

Great, very thorough, thanks. jw

From: Rao, Ashutosh
Sent: Friday, June 03, 2016 1:35 PM
To: Woodcock, Janet
Cc: Moscicki, Richard
Subject: RE: URGENT: Follow Up From Telecon This Morning

Dear Janet,

Thanks for your email. Some follow-up thoughts -

1. We should check with the clinical division to make sure they agree with the protocol and suggested deviations. For instance, they say that they will need to unblind the samples and adapt their previous protocol for this testing. The changes in protocol should not undermine the other endpoints in the clinical study for its primary/secondary endpoints, otherwise we may be risking the whole study and its value.
2. If the clinical division is in agreement with the modified approach and risk, I believe it would be best to onsite for a targeted visit between June 20-24 because, according to the flow chart they provided, this is when they will be running the western blots and starting to prepare data tables. I don't think we need to be there for the receipt of consumables, equipment, and other logistical steps but we could have an ORA person there if desired. My task during the visit would be to (1) observe the western blotting procedure for the clinical samples from their ongoing study, (2) confirm compliance with their pre-established SOP, (3) confirm the documentation to support blinding/unblinding steps (I will need help from OSIS for this), and (4) observe them enter raw data into a format that could be verified when submitted as a formal submission to the Agency.
3. For the inspection, we should have an OSIS (formerly OSI) person go with me because the visit should be appropriately documented and reported. One OSIS inspector could go to the Iowa site and one would go with me. Sean Kassim is the OD for OSIS.
4. If this gets a final 'go ahead', I will need help from your office or OSI with expedited travel arrangements and would prefer that this visit is not advertised outside FDA to avoid any unwanted attention during or after the visit. Once completed, the visit and inspection report will become part of the official record.

I have discussed this with Steve and Amy and they are okay with this strategy.

Best,
Ash

From: Woodcock, Janet
Sent: Friday, June 03, 2016 8:46 AM
To: Rao, Ashutosh
Subject: Fwd: URGENT: Follow Up From Telecon This Morning
Importance: High

FYI. I will ask them to send the protocol jw.

From: Shamim Ruff <SRuff@Sarepta.com>
Date: June 2, 2016 at 6:17:35 PM EDT
To: Moscicki, Richard <Richard.Moscicki@fda.hhs.gov>, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Cc: Ed Kaye <EKaye@Sarepta.com>
Subject: URGENT: Follow Up From Telecon This Morning
Importance: High

Dear Dr. Woodcock and Dr Moscicki

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

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

Deliverables:

- Success is defined as demonstration of an increase in dystrophin using Western Blot assay.

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

Regards,

Shamim

From: Shamim Ruff <SRuff@Sarepta.com>

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

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

Cc: Ed Kaye <EKaye@Sarepta.com>

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

Dear Dr Woodcock and Dr Moscicki

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

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

Regards,
Shamim

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

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

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Wednesday, June 01, 2016 10:54 AM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>

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

Dear Shamim:

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

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

Please confirm receipt of email.

Regards,
Fannie

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

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Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 3:56 PM
To: DeMarco, Devota R
Subject: RM - Ed Kaye
Attachments: PROMOVI Dystrophin Assay June 2016 SR.pptx

Importance: High

From: Moscicki, Richard
Sent: Friday, June 03, 2016 10:32 AM
To: Woodcock, Janet (Janet.Woodcock@fda.hhs.gov)
Subject: FW: URGENT: Follow Up From Telecon This Morning
Importance: High

I assume you saw this, Ed Kaye called me as well to propose this idea. How did the review division respond? I wonder if Ash can do this? How can I help, shall I speak with Ash? Rich.

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

Dear Dr. Woodcock and Dr Moscicki

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

1. **We must start the process by June 6, 2016.** There is no room for flexibility with this date due to our dire financial constraints as a result of the ongoing delays.
2. **Dr. Rao will be an observer/advisor throughout the whole process** (3-4 weeks during June in Iowa and Oregon) since he is the only FDA representative with the requisite knowledge, expertise and familiarity with the eteplirsen dystrophin analyses/protocol.
3. Dystrophin assays will be conducted using an adapted, pre-defined protocol based on the Week 180 methodology, e.g. no blinding.
4. A different "normal" control to Week 180 will be used due to lack of availability of previous/Week 180 normal control tissue.

5. Non-GLP facility - the assays will be performed at the Sarepta Corvallis site in Oregon by trained Sarepta personnel. As discussed, our Corvallis site is in the process of being closed down so will not be in an ideal state although the lab is still functional.

Deliverables:

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

Regards,

Shamim

From: Shamim Ruff <SRuff@Sarepta.com>

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

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

Cc: Ed Kaye <EKaye@Sarepta.com>

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

Dear Dr Woodcock and Dr Moscicki

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

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

Regards,

Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality

p 617-274-4009 c (b) (6)
e sruff@sarepta.com

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

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

Dear Shamim:

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

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

Please confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

considering the above scenario, please notify us immediately by contacting the sender either electronically, oral address, direct phone, and delete and destroy all copies of this message.

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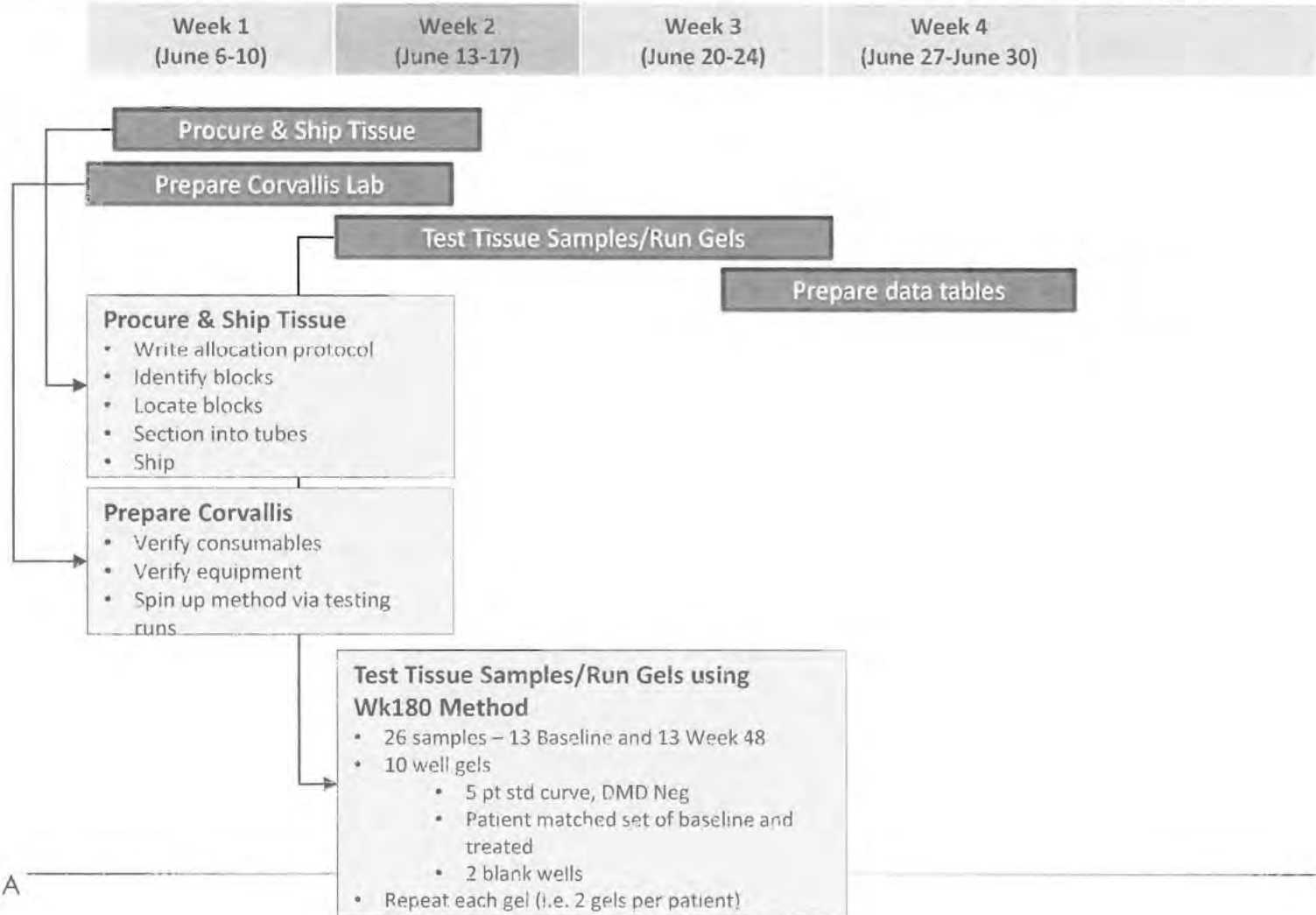
SAREPTA
THERAPEUTICS

PROMOVI DYSTROPHIN ASSAY
TIMELINE

02June2016

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WORKFLOW AND TIMELINE OVERVIEW



ASSUMPTIONS

- **We must start the process by June 6, 2016.** There is no room for flexibility with this date.
- **Dr. Rao will be an observer/advisor throughout the whole process** (3-4 weeks during June in Iowa and Oregon) since he is the only FDA representative with the requisite knowledge, expertise and familiarity with the eteplirsen dystrophin analyses/protocol.
- Dystrophin assays will be conducted using an adapted, pre-defined protocol based on the Week 180 methodology, e.g. no blinding.
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DELIVERABLES FOR ACCELERATED APPROVAL

- Success is defined as demonstration of an increase in dystrophin, using Western Blot assay.
- FDA will confirm – by June 3, in writing, that Accelerated Approval will be granted by the end of June when an increase in dystrophin is demonstrated.
- Labeling discussions and post-marketing commitments to be conducted concurrently and completed by the end of June or sooner.

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 10:01 AM
To: DeMarco, Devota R
Subject: RM - Today's CD Briefing on Eteplirsen
Attachments: Sarepta dct.docx

-----Original Message-----

From: Eby, Michelle
Sent: Tuesday, May 31, 2016 12:52 PM
To: Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Choy, Fannie (Yuet); Dunn, Billy; Breder, Christopher D; Rao, Ashutosh; Ware, Jacqueline H; Bhattaram, Atul; Kozauer, Nicholas; Hung, Hsien Ming J; Ling, Xiang; Jin, Kun; Nevius, S Edward; Rosenberg, Amy
Cc: Rawlings, Kimberly; Bolek, Michelle; Shreeve, Chris; Diggs, Felicia; LaVange, Lisa
Subject: Today's CD Briefing on Eteplirsen

Dear All,

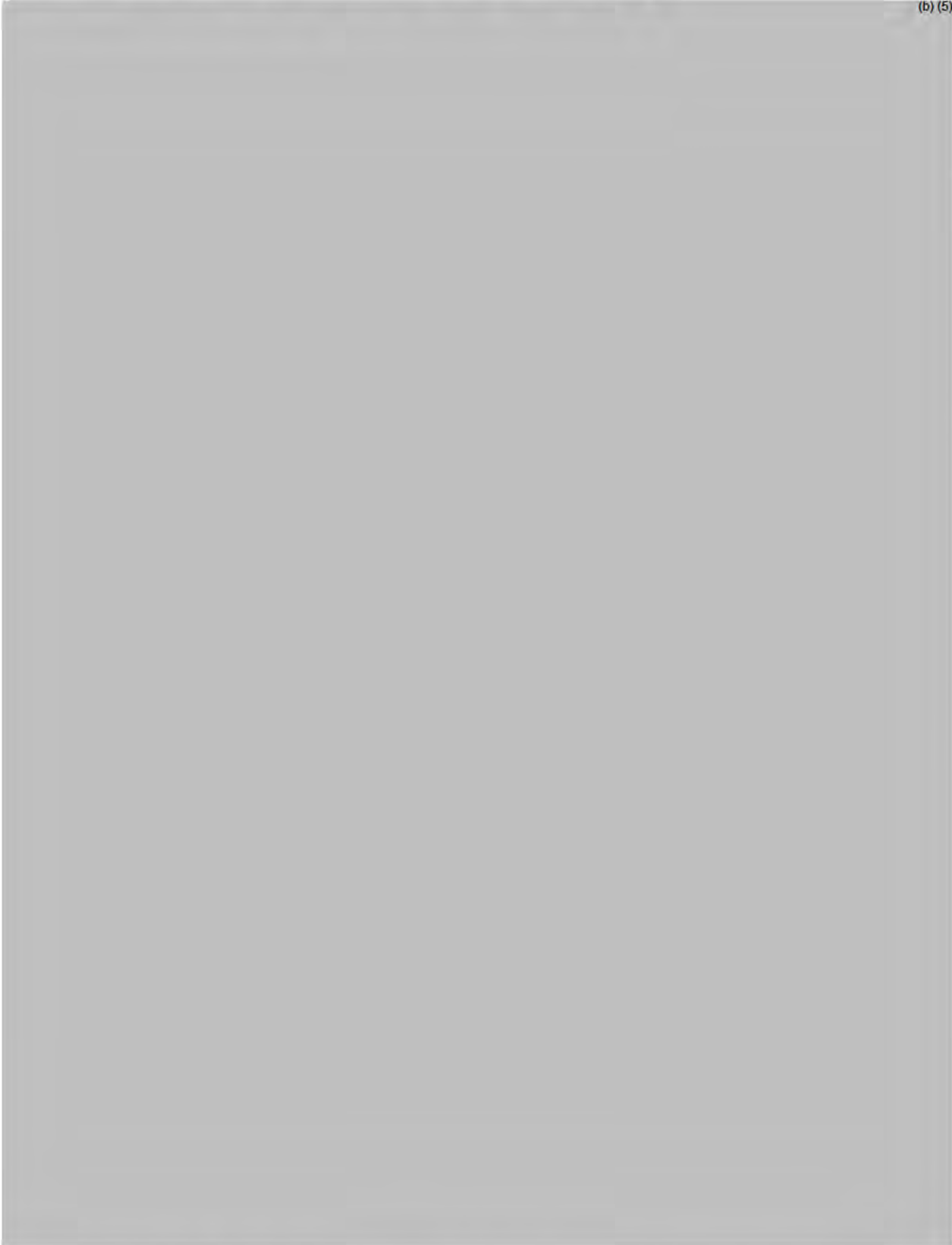
At the today's CD briefing, Dr. Woodcock is planning to discuss her draft memo (which the OND folks have already received). See attached.

Thanks, Michelle

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

Center Director Decisional Memo DRAFT

(b) (5)



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

FDACDER0005437

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 5:16 PM
To: DeMarco, Devota R
Subject: RM
Attachments: NDA 206488 Inspection Summary_v3.docx

From: Rao, Ashutosh
Sent: Wednesday, June 29, 2016 5:34 PM
To: Woodcock, Janet; Moscicki, Richard
Cc: Kozlowski, Steven; Rosenberg, Amy
Subject: Sarepta inspection - draft memo

Dear Janet and Rich,

I have attached a draft memo based on the inspection of Sarepta's laboratory site visit for your review and feedback. I welcome any suggested edits or comments. Please let me know if there are any questions.

A more comprehensive EIR (inspection report) with OSIS and ORA portions will take a bit longer to put together but I can share with you any of the exhibits (raw data files, notebooks, screenshots, photographs) now for additional clarification if needed. OSIS covered the blinding and shipping. ORA is putting everything together as per their requirements.

Thanks
Ash



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

(b) (5)

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

FDACDER0005451

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 10:02 AM
To: DeMarco, Devota R
Subject: RM: FYI Sarepta statement

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: 301-795-4669 / Cell: 240-328-7088
sandy.walsh@fda.hhs.gov



Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 1:35 PM
To: DeMarco, Devota R
Subject: RM FW: Written statement regarding Eteplirsen NDA review and Adcom
Attachments: Accompanying Slides Regarding Eteplirsen Data.pptx; Letter to FDA Regarding Eteplirsen.docx

From: Woodcock, Janet
Sent: Tuesday, May 24, 2016 2:49 PM
To: Throckmorton, Douglas C; Moscicki, Richard
Subject: FW: Written statement regarding Eteplirsen NDA review and Adcom

Crowd sourcing analysis. Very thorough! jw

From: William Markis [mailto: (b) (6)]
Sent: Tuesday, May 24, 2016 2:46 PM
To: Woodcock, Janet; Jenkins, John K
Subject: Written statement regarding Eteplirsen NDA review and Adcom

Dear Dr. Janet Woodcock and Dr. John Jenkins,

Please see my attached letter and slides with comments and novel analyses of Eteplirsen data. These are my personal views as a citizen and researcher with interest in this particular drug application and DMD but without professional ties to this field or the sponsor. The last 4 slides may be of particular interest to you.

Thank you for your time,

William Markis

Dear Janet Woodcock

My name is William Markis and I am writing to you as a researcher and a concerned citizen regarding the Sarepta NDA application for Eteplirsen. By trade, I am a researcher in the biotechnology industry specializing in molecular characterization of protein therapeutics, not currently operating in the DMD space; I am also a published author with nearly 10 years of lab research experience, and these are my personal views. They do not reflect the views of my employer, I wrote this independently, and I was not compensated by anyone for this. I have no conflicts of interest as per "FDA Guidance for Clinical Investigators, Industry, and FDA Staff." I wish to address some of the key points of discussion that were raised in the adcom on April 25th regarding production of dystrophin by eteplirsen, clinical benefit, and patient reported outcomes. I believe there were some critical points which were overlooked in the discussion of the data and their lack of "air time" within agency presentations relative to the contrary point of view resulted in an overly negative discussion and led to a less than fully-informed vote. I have also included a novel analysis of the dystrophin data in comparison with walk benefit and have attached a slide deck which highlights each of the major points I will make below. Based on all the available information including the points I will discuss in this letter, I believe it is critical to approve this drug under the accelerated approval pathway, and I respectfully ask that you do so by using your authority to override the split panel vote.

Dystrophin Quantification

Dr. Rao pointed out problems with the assays used to measure the first 3 biopsies and described the improved methodologies used for biopsy 4 at 180 weeks. Notably, **after** pointing out relevant caveats regarding the controls, Dr. Rao ultimately concludes regarding the 4th biopsy, "Overall a combination of the applicant's methods, immunofluorescence and western blotting, was considered reasonably capable of demonstrating an increase in dystrophin by eteplirsen." (3:26:28 in the archived webcast). But Dr. Farkas contradicted this conclusion in his slides particularly in slide 75 of 178 in the posted FDA presentation slides, and he spent about the first 30 minutes of his presentation casting doubt upon Dr. Rao's conclusion. The two presentations thus seemed to contradict each other, and evidently the applied biochemistry team did not share the conclusions of the clinical review team. Dr. Bastings in his discussion of slide 157 stated a similar conclusion to Dr. Farkas, both in contradiction to Dr. Rao. Several hours of the adcom presented by FDA were devoted to only one side of this debate over dystrophin measurement and the points raised heavily influenced the voting, but I believe there are reasons to dispel the air of uncertainty that was promoted by the clinical review team.

Dystrophin Control Samples

Dr. Farkas stated, "unless there was a substantial change in dystrophin levels" it could be confounded by using different muscle groups, despite admitting there is no evidence to date that different muscle groups in the same DMD patient from the same limb/body region result in meaningfully differing levels of dystrophin. Given this hypothetical concern regarding a possible difference between baseline dystrophin levels in deltoid and biceps, it is very important to analyze the individual patient level data since 1 patient sample used for the baseline control (DMD#1 from study 301) did in fact provide a

deltoid sample. Rather than buck the trend of all the other baseline control samples, which could have confirmed the fear alluded to by Dr. Farkas, instead it was in fact consistent with the trend by exhibiting 0 or BLOQ dystrophin level. While this is only an n of 1, it should be taken as circumstantial evidence which helps alleviate the hypothetical concern, itself lacking evidence to support it, but regrettably this point was not raised or discussed during the adcom. I note that several of the voting members who voted no on question 2 regarding dystrophin and accelerated approval, did so on the basis of the control group being sampled from a different muscle group than the treated patients. This includes Dr. Nuckalls who mentioned this explicitly as the sole reasoning for his no vote while Dr. Kryscio and Dr. Kesselheim voted no in part due the "sampling issues." I question whether those who voted in this manner would have moderated their stance if the single reference point of evidence disputing the hypothetical concern would have been highlighted or addressed in the discussion. Due to the result observed in patient DMD#1, I believe the concern about confounding from alternate muscle groups was overstated.

Despite the fact that there appears no evidence to support the idea that different muscle groups should confound the analysis, still a closer look at Dr. Farkas's aforementioned statement in any case suggests that he overstated this concern in light of the dramatic change from baseline observed in the eteplirsen-treated patients. To quote him again, "unless there was a substantial change in dystrophin levels [it could be confounded by using different muscle groups]." In this case, there **was** a substantial change. There was an 11.6-fold increase from mean baseline levels with a p-value of 0.007 reported by the sponsor. Sticking strictly to the lower limit of quantitation definition, as suggested rightly by Dr. Farkas, it would be a >3.7 fold increase. If we adjust all BLOQ measures in controls and treated samples upward to .25% it results in a new mean treated value of .989%. 0.989 is >3.7-fold increase over the baseline mean of <0.26). The unpaired t-test including all samples and controls, with the adjustments up to .25% where necessary, resulted in a p-value of 0.01 indicating statistical significance between the groups. A statistically significantly change from baseline should be considered a substantial increase in dystrophin. In whichever way one examines this data, the change from baseline is substantial and therefore is unlikely to be confounded by differences in muscle group, even assuming there was such a difference (although no evidence has been shown that there is).

An on-average four-fold increase from baseline in dystrophin (based on lower limits of this assay) should not be denied to eligible patients. An overwhelming number of DMD clinicians, researchers, and experts testified in the OPH and elsewhere that increases on average of 1% of normal (non-diseased) dystrophin levels would be expected to impact the clinical outcomes of the disease for a patient starting at near-zero% without drug. That 1% on average also includes a subset of patients whose dystrophin increased to greater than 2% of normal. I believe the opinions of the DMD clinicians should be most heavily weighed in the consideration of that question, and it is clear from the comments of voters that they did not necessarily take the OPH testimonies into account, resulting in this split negative vote.

There is also evidence from the few paired controls that should alleviate concerns regarding the "before and after" (example: 3:42:50) and build confidence surrounding the dystrophin evidence. (See my accompanying slide 1). Dr. Farkas points out that no western blot data from 9 of 11 prior to treatment were obtained for the 180-week biopsy comparison which he suggests is a limitation on the reliability of the data (and this was echoed in both Dr. Kesselheim's and Dr. Alexander's post-no-vote explanations).

Obviously this situation is not ideal, and practical limitations of remaining tissue prevented re-analyses for all the samples with the improved 4th biopsy methodology. More importantly, there are mitigating factors within these data which must be considered but which were regrettably not pointed out or discussed at the adcom. For the sponsor **does** include 2 paired samples in this control cohort where western blot data was obtained from the eteplirsen-treated patients at baseline and at week 180, run in the new WB assay, and in each of those cases, patient 013 went from 0 (or call it <0.25) (BLOQ) at baseline to 1.15% at 180 weeks, and patient 015 went from 0 (or call it <.25) (BLOQ) at baseline to 2.05% at 180 weeks. This is a remarkable increase and note that not a single baseline measure, neither from 3 patients in the 201/202 study, nor from 6 additional patients from study 301, were anywhere near this level of dystrophin as measured by western blot. These paired data once again confirm the overall trend rather than contradicting it. The statistical analysis on these two groups of samples directly contradicts Dr. Farkas's speculation that the dystrophin in Eteplirsen-treated patients at week 180 may have been present at baseline because had that been true, there is no reason why a random sampling of baseline patients from study 301 would not also show these levels of dystrophin, and yet we observe that they do not. The 2 paired samples only add to the confidence we should have in these measurements. Again, these points were not highlighted during the discussion but should have been.

These subsets are small sample sizes but they still blunt the potential limitations in the overall dataset as raised by the review team, by confirming the overall trend, while several voters cited the controls as reason behind their no votes. Perhaps beyond blunting these concerns, in my view, they largely refute them and need not stand in the way of serving these patients, given the assertion by so many DMD clinicians that they expect these levels of dystrophin to benefit their patients in clinical outcomes and quality of life.

Percent Dystrophin Positive Fibers via IF

There were other seemingly confounding issues raised regarding dystrophin which may have influenced voting members but which lacked scientific rigor or rationale. The question (FDA Slide 83) of why baseline biopsy levels were 1% for the 180-week biopsy PDPF comparison vs. 10-15% at baseline for 12-, 24-, and 48-week biopsies and PDPF comparison was posed in a misleading way and is probably best answered by the points raised by Dr. Rao. The change from baseline is the relevant measure, and the baseline measure can only be compared with the corresponding timepoint measure within the context of a concurrently and identically run assay, including all the factors as listed by Dr. Rao in his slide 55 of 178, including image sampling procedure, independent rescoring, inclusion of low intermediate and high level controls, etc. In Slide 55 of 178 Dr. Rao indicated the necessary characteristics of a well-controlled immunofluorescence assay and indicates the first 3 biopsy readings for study 201-202 were **not** consistent with all of the proposed qualifications. Slide 56 indicates FDA advice to sponsor for conduct of week-180 biopsy for greater reliability consistent with these stated criteria, and in slide 57 Dr. Rao indicates that indeed, technically satisfactory methods were utilized for the week 180 measurements, characteristics of which he lists with bullet points. This evidence suggests biopsy 4 is an entirely different assay than was conducted for biopsies 1 through 3, and obviously one should not expect the baseline readings to be the same utilizing two different methods. Dr. Farkas also suggested the difference of baseline values from the two different assays could be because of "later controls which

weren't matched" but he did not point to evidence as to how these controls lacked matching. He likewise omitted mention that the 201/202 study patients whose data **was** reassessed at baseline for the 180-week analysis with the new assay (and therefore were directly matched) did in fact show much different baseline levels (lower) compared to what was measured in the original 3 biopsies (with unsatisfactory assay), confirming the same trend observed for the newly obtained samples run in the improved assay. For example, for the 180-week PDPF comparison using the newer assay, patient 01008 measured 1.09% PDPF at baseline (12.75% in week 180 sample) patient 01013 measured 2.58% baseline (19.14% in week 180 sample), and patient 01015 measured 0.19% at baseline (increased to 18.48% in week 180 sample). Examining these matched controls repeated in both assays and showing different results in each assay only confirms a **difference in methodology** for each assay. As a researcher with close to a decade of experience running many types of biochemical assays in academic and industry labs, I understand as a basic fundamental principle that the same tissue sample could result in disparate readings using two different assay methods, and this should have been clear to the review team. The review team's use of baseline readings paired with biopsies 1-3, to call into question the baseline reading for biopsy 4 at week 180 using a different method, is an apples to oranges comparison producing undue skepticism. Likewise, the comparison of **treated** 180-week data in Assay 2 with "original" **Baseline Data** in Assay 1 (Slide 84) is a meaningless comparison. Thus when Dr. Bastings in his talk on slide 157 disputes whether 17% PDPF at week 180 even constitutes a change from baseline, citing the argument of Dr. Farkas, this similarly ignores that 17% is only questionable based on cross-comparisons to an assay which is performed with a different method. The baseline mean was around 1% using the apples to apples comparison within the same assay method and the statistics indicated 17% was significantly different. This series of slides cast unnecessary doubt on the IF data in the minds of the voters. I believe that based on Dr. Rao's comments there is reason to have confidence in the newly developed IF method (following much-needed critical help from FDA) as a supplementary measure of dystrophin changes that can (and does) corroborate the western blot data. Therefore, the objections raised on FDA slides 83, 84, and 157 were not scientifically valid. The IF PDPF data, together with percent intensity data, serve as a strong corroboration of changes observed via western blot. The presence of additional paired samples within the IF data also further confirm the overall trends and corroborate the differences from baseline observed across all 3 methods, resulting in increased confidence in the western blot, negating the concern over lack of pairing (Please see my slides 1 and 2, Figures A and B).

In my opinion there is no doubt eteplirsen increases dystrophin levels, and increasing upwards of 2% of non-disease levels in a subset of patients is extremely promising to moderate the disease course.

Walking data:

There were 4 main approaches presented by FDA clinical review team in its discussion regarding the walking benefit produced by eteplirsen, the latter 3 all contradicting the first approach. Namely these approaches were: 1. The groups (Eteplirsen-treated and multiple historical control groups) are not really different; 2. The groups are performing differently but known and unknown factors distinguishing the groups at baseline are the reason why they perform differently; 3. The groups perform differently but do not **exceed the outer range/limits** of natural history; and 4. The walking benefit in those eteplirsen

patients performing best did not appear to correlate with induced dystrophin levels as measured by western blot. I believe all 4 of these claims should be addressed and based on my understanding of the data, I believe they are all incorrect.

1. The review team asserted that when matched for baseline age (slide 112), changes in 6mwt plotted over 4+ years of increase in age show similar or the same disease trajectory, in contrast to the same data plotted by time on observation, (for example sponsor slide 79). The problem with slide 112 is there are too many lines drawn on the same image and it muddies any discernible difference to the naked eye. Even despite this confusing visualization, there are at least 5 eteplirsen patients circled on slide 118 which appear to differ in trajectory from neighboring control arm plots and for which the reviewers offered no explanation. Please see my slides 3 and 4, where I separated the eteplirsen-treated and natural history control (NHC) cohorts into groupings by baseline age and pooled the 6mwt data for each age group as a mean showing the change from baseline age over time. Figure C shows age 7+ and 8+ patients at baseline while figure D shows age 9+ and 10+ year old patients at baseline, in each case showing a clear visual difference in trajectory for the eteplirsen group which appears to outperform the natural history group.

2. A comparison to a natural history control in the context of any trial will have “known and unknown” differences at baseline which distinguish the groups and complicate the comparison. The so-called “unknown differences” are irrelevant because that would otherwise preclude the use of a natural history control under any circumstance, where there will always be something unknown. The statutes do permit analysis with natural history controls and, as Dr. Temple’s presentation made clear, have been used before. Therefore, only known differences are noteworthy.

As for known differences at baseline, the two groups were highly matched for relevant factors such as baseline 6mwt, age, steroid use, and exon 51 skip-amenable mutation which are known to significantly impact 6mwt outcome¹. The sponsor slide 77 of 133 appears to negate concern regarding steroid dosing differences (92% received continuous dosing in eteplirsen-treated vs. only 62% in NHC), showing no meaningful difference in 6mwt trajectory due to type of steroid dosing. The review team pointed out the difference in mean age of steroid start (5.2 years Etep vs. 6.4 years NHC), which the panel dwelled upon, but this was mostly due to a single outlier from the NHC group who did not begin steroids until age 10.7. Excluding this outlier brings the mean to 6.0 which is closer to the mean of Eteplirsen group. It was assumed in the discussion that a higher mean age of steroid start would negatively bias 6mwt result, but in reality, a patient who did not begin steroids until age 10.7 is probably more likely to be a high-performing outlier who for that reason in particular did not **need** to begin steroid treatment until a later age, as determined by his clinician. At baseline only 3 NHC patients are above age 10.7, so this patient must be either ECG1, ECG2, or ECM1. The individual level data on this factor is not available to me, but I would note that out of these 3 patients, two of them (ECG1 and ECG2) have somewhat high baseline 6mwt for age >11.5 at baseline, which could indicate milder disease course, and ECG2 maintains ambulation out to 3 years (age >14.5 at LOA), which is well beyond the median LOA for the NHC. I cannot confirm whether ECG2 was this outlier who began steroids at age 10.7, but whether that is the case or not, the sponsor performed sensitivity analyses which removed outliers and showed the difference between the groups remained statistically significant. My point ultimately is that while a

patient with later starting age of steroid treatment brings the average age of steroid start for the group up, making it **appear** to be unfavorable compared to the mean for eteplirsen treated group, it could in actuality be biasing the 6mwt performance in the opposite direction, **higher** than the eteplirsen-treated group, by nature of his slower disease course as determined by clinicians who could have delayed onset of steroid dosing for the very reason that he was a high-performing outlier and did not yet need to begin steroid dosing until an older age. So the discussion assuming this as a definite bias against the NHC was not accurate.

Given the limited patient supply and historical data these two groups are about as closely matched as possible on the important parameters known to significantly impact 6mwt. At each individual patient level it simply is not possible to have perfectly exact matches, which is why the pooled data and pooled outcome differences are so important.

3. It was apparent from multiple slides (for a brief single example see FDA slide 133) and statements that the review team set entirely "outside the range" of natural history as a threshold for approvability via historical control rather than simply outperformance of age-matched natural history patients as a group. This also seems likely to be the reason they chose not to overlap the Eteplirsen LOA curve onto the CINRG Kaplan-Meier chart, an otherwise inexplicable omission, but instead simply used that chart to prove that a few boys walk to age 18. Importantly, the endpoint for the CINRG curve is also not the same as that used in the NHC and Eteplirsen trials, which Dr. MacDonald clarified in his comments. The CINRG LOA is a more relaxed endpoint which includes as still ambulant those patients who are unable to perform 6mwt even though they would be declared non-ambulant in the other studies. Moreover, the characteristics of the patients at baseline used to generate the Kaplan-meier curve were not even remotely properly matched, based on Dr. Farkas's description (repeated relaxing of criteria to arrive at a group for comparison, but details not specified (5:05:58). Ignoring these obvious comparability hurdles, it is difficult to reconcile how a requirement to assess Eteplirsen patients of age 8-10 at trial start out to 19 years old, to see if all patients outperform the **outer bound** of natural history, would be in any way consistent with FDASIA or the statements of FDA provided to the public². Isn't accelerated approval supposed to accelerate approval? Framed in these terms, the trial would be impractical and unfeasible, precisely the opposite of the intention of FDASIA's precepts regarding speeding development of drugs for rare diseases. Maintaining the outer bound of natural history as approvability threshold would suggest to me an "openness" to historical controls in the purely theoretical sense but not in the real-world sense.

The realistic comparison for this dataset is the assessment of important prognostic indicators and endpoints in the age-matched and relevant controls of NHC group. This showed remarkable difference in 6mwt performance even after the first year of performance was essentially the same between these essentially matched comparator groups. The group collectively outperformed the natural history at 3 and 4 years, which strongly suggests benefit from eteplirsen. They had dramatically different 6mwt mean (Sponsor slide 84), %LOA (Sponsor slide 86) and maintenance of independent rise time ability (Sponsor slide 90). FDA slides 142-144 all show a loss of ability to perform various tests at younger ages and sooner into the observation period than the Eteplirsen patients. In my opinion, the fact that data is not available to age 18 or that 1 cherry-picked patient measure out of the entire NHC cohort might

outperform an Eteplirsen patient (or many patients) on this or that functional test are not valid reasons to ignore these results for the groups collectively which show clear differences. Even despite all the aforementioned problems of lack of comparability of the chosen CINRG cohort due to the more relaxed endpoint favoring longer "ambulation" (via 10m w/r, rather than 6mwt) in that group, the sponsor presented a slide with the Eteplirsen-treated group overlaid on the Kaplan-Meier chart and showed a strong LOA benefit vs. CINRG and NHC. However, there was some dispute during the proceedings about the average age of Study 201/202 participants as shown on their figure. I do not know out to what age Sarepta collected data from these patients but their slide indicated greater than 14.5 years average age based on scale measurements. Either that was a mistake or that is utilizing data beyond the 4 year cutoff point that I am not privy to. I did see that some FDA slides also had data beyond 4 years, but to be conservative I edited the sponsor's slide to show the Eteplirsen curve at the 4 year mark (My Slide 5) (red line, Avg age approximately 13.3 years). **Even with all the relaxed criteria, including the relaxed CINRG basis for declaring patients still ambulatory, the CINRG cohort far underperforms the Eteplirsen group at equivalent ages.**

Even if a drug does not cause the majority of patients to exceed the known outer range of natural history, (we do not have data to age 15-16 yet for the true 6mwt LOA range assessment), it would be very meaningful if a drug causes more of the patients to perform like highest-performing outliers than they otherwise would have without treatment and if the treatment delays LOA, extending median LOA.

4. Reasonably likely to confer clinical benefit

FDA slide 126 claims there was no correlation between dystrophin and function on the 6mwt. But I performed some deeper analysis. The raw data used for FDA slide 126 was not available in the documents, and it seemed to differ from the sponsor reported 4-year 6mwt data, but I was able to estimate with scaling and reproduce the figure using the numbers shown in my slides 7 and 8, Figure G. With these raw data in hand, I now excluded all eteplirsen patients who produced < 0.5% of normal dystrophin on Eteplirsen as so-called non-responders. 0.5% would be twice the LLOQ of the western blot assay, could be reliably considered a significant increase and could represent a threshold level, beyond which benefit on 6mwt measurement would manifest itself. Slide 10 Figure H shows a strong linear correlation of walking benefit with amount of dystrophin for those subset of "responders" that achieved >0.5% of normal dystrophin levels. (FDA can input real values in place of my approximations taken from FDA slide and confirm correlation). This occurred in 56% of treated ambulant patients and 64% of treated patients in total who consented to a 4th biopsy. Once again, not every patient showed an increase of dystrophin and like most FDA-approved drugs, not every patient will benefit from the drug, or at least will not benefit on the measurable clinical endpoint. Within the framework set forth by the clinical review team, this data shows a strong correlation of dystrophin produced to clinical benefit and therefore warrants accelerated approval. This is using (approximations of) the review team's data and the review team's conceptual framework. This also leads me to believe that the 2 boys who lost ambulation before dystrophin was produced have likely benefitted significantly from the drug in ways not measured by walking ability (for example, upper body strength, maintained lung function, etc), since their dystrophin levels at week 180 were 0.52% and 1.62% respectively.

I note that many of the voters voted no with a rationale citing a lack of correlation between dystrophin and walk benefit. Importantly, I believe the premise of the review team is flawed, and I do not believe the 0.5% level is a true threshold required to achieve clinical benefit from the increased dystrophin even if it **could** be the threshold to achieve observable 6mwt benefit. Animal data strongly suggests increasing from patient baseline will have benefit, potentially life-extending, even in small amounts³. In addition, there can be benefit from the drug that doesn't necessarily change the 6mwt measure but impacts other parameters of the disease. The flaw in the premise of the review team is that we know this is a heterogeneous disease and cannot predict the disease course at an individual level, so expecting the direct linear correlation in the first place was not realistic. This is exactly why the pooled data is so important. We already know there may not be a straight numerical correlation between amount of dystrophin and mildness of disease course, for example as seen in Becker's patients, but only a qualitative correlation that in general more dystrophin is better and **in general** results in milder course of disease. In a hypothetical patient X, by inducing 0.4% dystrophin and measuring his walk distance over time, we cannot know with certainty how that walk distance would have performed without the 0.4% dystrophin which is the real assessment of whether that patient benefitted, since at baseline and without treatment, individual patients already vary. (And perhaps in ways we cannot predict, inducing <0.5% will impact 6mwt in certain patients). Only the pooled data becomes predictive and this is why the work of Dr. MacDonald and other clinicians characterizing the 6mwt endpoint is so crucial. There was a great deal of effort in the adcom to foment doubt about the reproducibility of this key endpoint, but Dr. Craig MacDonald pointed out years of work which has definitively characterized it as referenced on the Sponsor's supplemental slide ED-28. The doctor who ran the 6mw test in Sarepta's trials also testified that she led an international consortium to standardize the measure and personally trained clinicians from all over the world to carry out the test according to the strict parameters used in this study and the NHC. The 6mwt endpoint is the gold standard for DMD walking functionality assessment despite whatever limitations it may have.

The true correlation between dystrophin and clinical benefit is that in the Eteplirsen-treated group there was statistically significant dystrophin produced in sum, and in the NHC there was not, while in the Eteplirsen-treated group there was statistically significant 6mwt benefit, LOA benefit, time to loss of independent rise time benefit, and in the NHC there was not. This is the correlation that truly warrants accelerated approval.

Patient-Reported Outcomes

The PRO's reported by Christine McSherry during her guest presentation were striking. I found the prevention of spontaneous falls data very compelling and indicative that patients are also benefitting in ways not measured by the clinical endpoints. This in addition to all the patient testimony gave me further confidence in the data presented by the sponsor that this drug is working.

FDA stated in briefing documents (page 58) "preservation of ambulation and other skills is affected by the value that families and caregivers put on maintaining those skills, with such factors as risk of falls and injury from continued ambulation weighed against the safety and speed of allowing patients to use a wheelchair."

But if the drug prevents falls, then by changing this risk equation it prolongs non-use of wheelchair and maintains physical activity – very important to patients and the disease course. As FDA also stated, “Regular physical activity is necessary to maintain function in DMD and to avoid disuse atrophy. Gentle exercise appears to provide additional benefit, including delay of functional deterioration.” (page 57 FDA briefing documents). This is all the more reason to approve the drug.

The assertions of Dr. Farkas regarding subjectivity of LOA have been vigorously disputed by patients and caregivers, but even if we assumed for argument’s sake his speculation true and took it even further and assumed that the end of ambulation was a **completely** subjective measure, nonetheless somehow eteplirsen is delaying that subjective decision considering only 17% LOA at the 4-year mark, and based on the above statements, delaying this decision, no matter the reason, benefits the patient. (See above quote reference from page 58 FDA Briefing documents). Even by this logic the drug is having an impact. (In reality we should note that the hope and expectations and close attention of trial participation did not prevent LOA in the two rapidly declining patients early in the trial).

Placebo effect

If the NHC result were negatively biased by the fact that they were not trial participants, as suggested by the clinical review team, then they need to explain Sponsor slide 132 which shows the drisapersen placebo-delayed arm with over 3 years of 6mwt data plotted together with the NHC and showing clear similarity. Why didn’t the drisapersen placebo group outperform due to hope and motivation, better care due to trial enrollment, and all the other confounding factors Dr. Farkas indicated would impact the results? That slide refutes all the doubt and uncertainty fomented at the adcom regarding the 6mwt. It only confirms the reliability of this endpoint and the fact that only a dramatic change can really impact it when plotted in grouped, matched patients over a several-year time course. The divergence between Eteplirsen-treated and NHC after the 1-year mark is dramatic (Sponsor slide 84).

Summation

In summary, all the available information leads me to believe that this drug is working at its intended affect. It causes significant production of dystrophin and significant 6mwt benefit, as well as independent rise time and LOA benefit, in addition to all the patient-reported outcomes we witnessed in the OPH. The strong DMD clinician and expert backing of this drug speaks volumes for me, and I add my voice to those who urge you to use your authority and regulatory flexibility to prevent a type 2 error by approving this drug under the accelerated approval pathway as the confirmatory trial continues. This is the first therapeutic to demonstrate induction of truncated dystrophin in DMD patients and it is essential to approve it as soon as possible so the greatest possible number of patients can access it. Thank you so much for your time.

1. <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0108205> Pane et al.
2. <http://www.fda.gov/Drugs/DrugSafety/ucm421270.htm>
3. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659351/> Van Putten et al.

Western Blot Control Samples

– Concerns regarding reliability of controls likely overstated

Figure A

Eteplirsen-Treated

Patient ID	Week 180		Baseline	
	Western Blot %	Muscle group	Western Blot %	Muscle group
002	0.14	Deltoid	--	Biceps
003	0 (BLOQ)	Deltoid	--	Biceps
004	0.96	Deltoid	--	Biceps
005	n.a.	Deltoid	0 (BLOQ)	Biceps
006	2.47	Deltoid	--	Biceps
007	0 (BLOQ)	Deltoid	--	Biceps
008	0.98	Deltoid	--	Biceps
009	0.52	Deltoid	--	Biceps
010	1.62	Deltoid	--	Biceps
012	0.38	Deltoid	--	Biceps
013	1.15	Deltoid	0 (BLOQ)	Biceps
015	2.05	Deltoid	0 (BLOQ)	Biceps

* Individual values in two available paired patient analyses trend in line with large (~4-fold) increase from baseline observed for overall cohort.

Study 301 Baseline

Patient ID	Western Blot% Untreated	Muscle group
DMD1	0 (BLOQ)	Deltoid
DMD2	0 (BLOQ)	Biceps
DMD3	0.37	Biceps
DMD7	0.15	Biceps
DMD8	0 (BLOQ)	Biceps
DMD9	0.2	Biceps

* Solitary deltoid baseline biopsy trends in line with biceps baseline measurements as BLOQ or very close to LLOQ. Coupled with no evidence that DMD deltoids contain meaningfully more dystrophin than biceps, the potential concern is mitigated.

These data, although sparse, contradict the suggestion that unknown differences between muscle groups or baseline control patients would confound results. They confirm overall trends.

Dystrophin IF Data

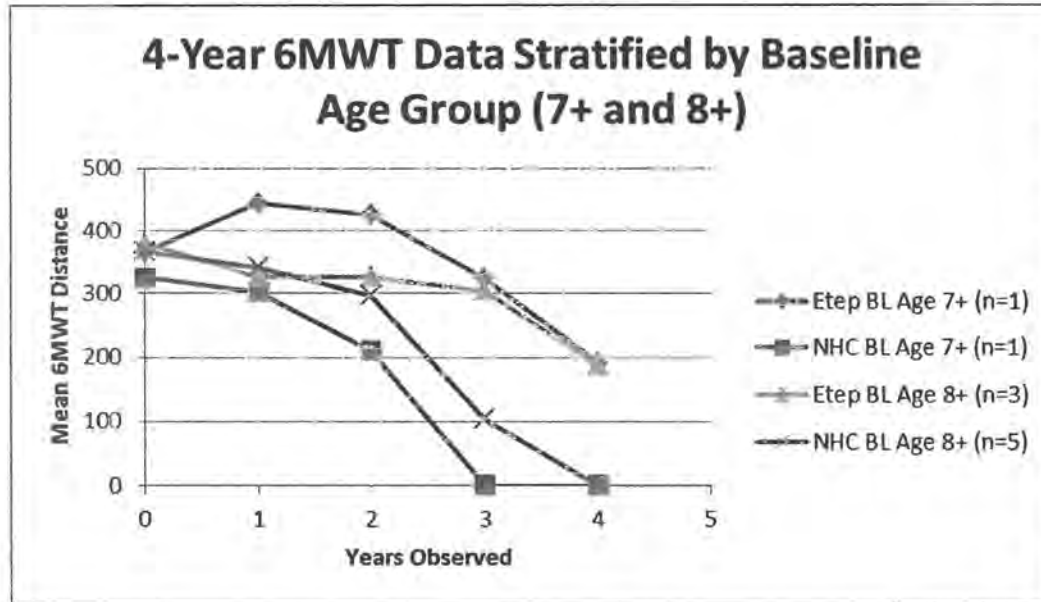
– Concerns regarding reliability of IF Data Unfounded

	180-wk PDPF	BL PDPF	180-wk Intensity	BL Intensity	180-wk WB%	BL WB%
2	4.54				0.14 (BLOQ)	
3	1.42		7		0 (BLOQ)	
4	28.2		28.8		0.96	
6	20.72		28.7		2.47	
7	7.08		12		0 (BLOQ)	
8	12.75	1.09	26.7	11.6	0.98	
9	21.48		23		0.52	
10	23.96		21.4		1.62	
12	33.5		26.1		0.38	
13	19.14	2.58	32.5	16.3	1.15	0 (BLOQ)
15	18.48	0.19	30.7	7.4	2.05	0 (BLOQ)

Figure B: All negative reads (highlighted in green) for 180-wk western blot data consistently show <20% Intensity reading, < 10% PDPF, in contrast to all positive WB samples (greater than BLOQ) which read out above those thresholds for Intensity and PDPF. IF data corroborates WB data. Meaningful increases in IF readings are observed for those samples which were paired (patient 8, 13, 15) and which also have increased dystrophin at 180 weeks by WB.

The corroborating IF data for Patient 12, coupled to strong walk performance, could indicate that 0.38% dystrophin by western blot was a meaningful increase, or the patient is simply an outlier, or both.

Walk Benefit vs. NHC Stratified by Baseline Age



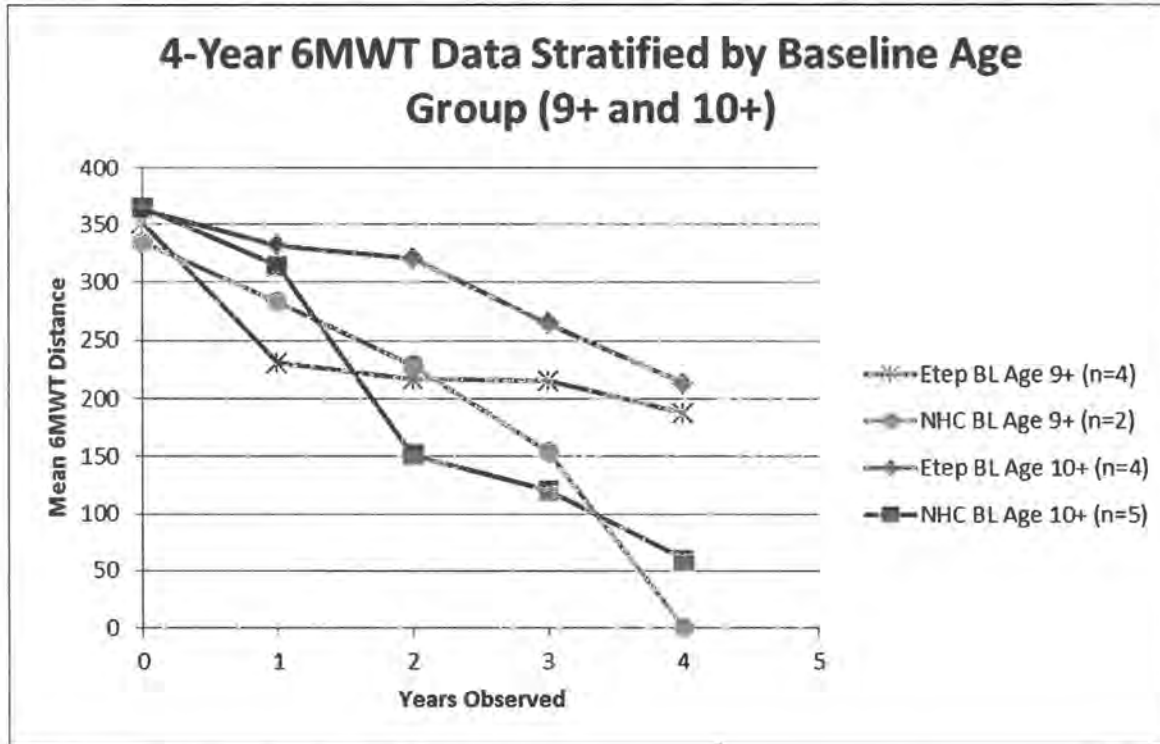
	Mean 6mwt values					Baseline Age (Group Mean)
	0	1	2	3	4	
Etep	366	444	425	324	192	7.29
NHC	325	301.8	210	0	0	7.33
Etep	379	325.6667	326	304.6667	187	8.27
NHC	366.4	341.088	296.4	103.25	0	8.43
Etep	350.75	230.5	216.5	215.25	187.25	9.55
NHC	334.15	283	229	154	0	9.00
Etep	363	331.75	320.5	264.5	213.5	10.64
NHC	364.8	313.6	151	120.4	60	11.02

*ECG3 excluded for missing data points, ECM2 excluded for missing 4-yr data point, so 3-yr and 4-yr NHC (Age 8+) are n=4, n=3 respectively. (They were not counted as 0 which would have made NHC performance worse).

Figure C: 6MWT over 4-year observation period separated by age and treatment group in 7+ and 8+ year-old patients at baseline.

Clear outperformance by Eteplirsen-treated patients when adjusted for age at baseline.

Walk Benefit vs. NHC Stratified by Baseline Age



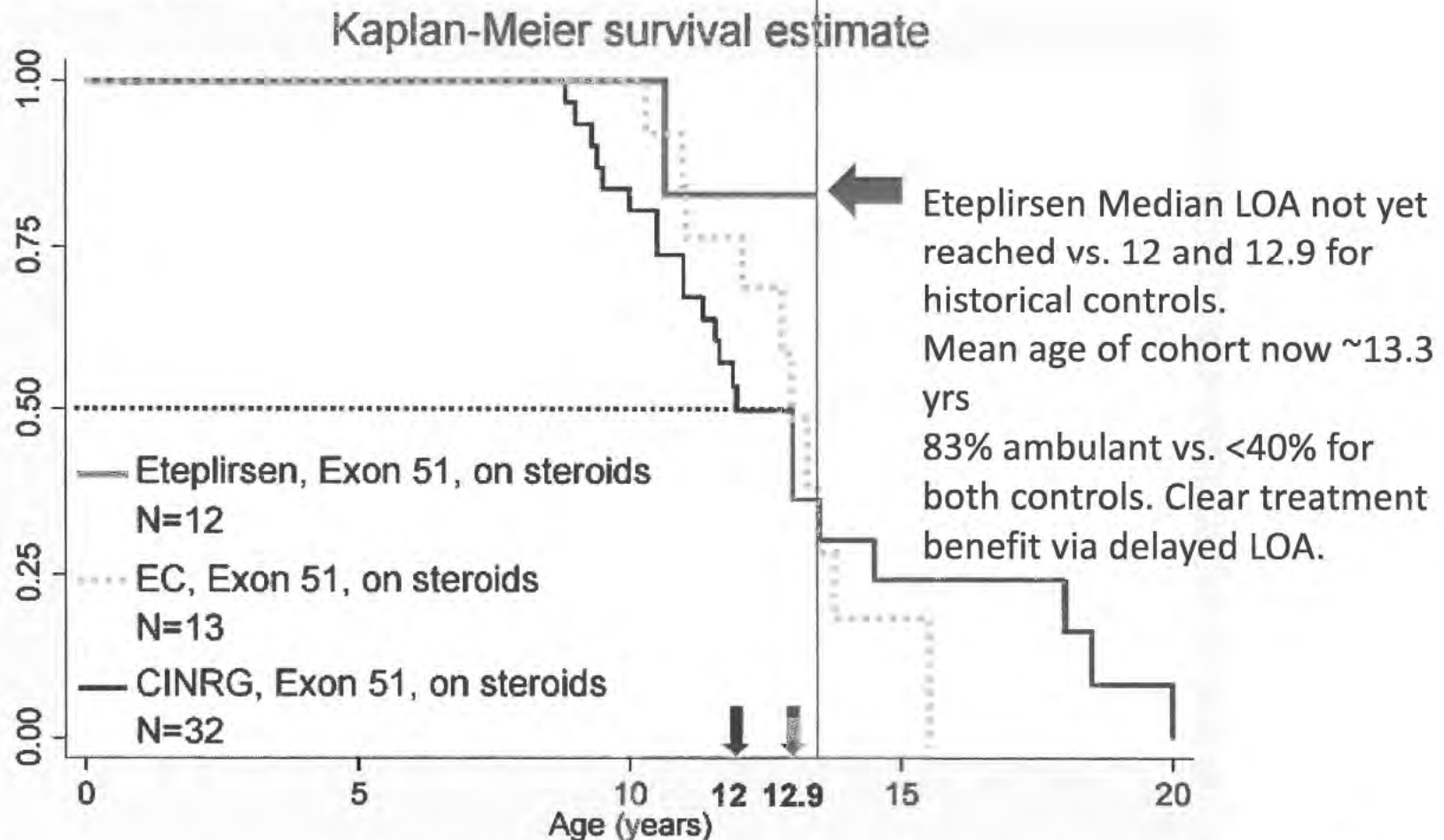
	Mean 6mwt values					Baseline Age (Group Mean)
	0	1	2	3	4	
Eteplirsen	366	444	425	324	192	7.29
NHC	325	301.8	210	0	0	7.33
Eteplirsen	379	325.6667	326	304.6667	187	8.27
NHC	366.4	341.088	296.4	103.25	0	8.43
Eteplirsen	350.75	230.5	216.5	215.25	187.25	9.55
NHC	334.15	283	229	154	0	9.00
Eteplirsen	363	331.75	320.5	264.5	213.5	10.64
NHC	364.8	313.6	151	120.4	60	11.02

Figure D: 6MWT over 4-year observation period separated by age and treatment group in 9+ and 10+ year-old patients at baseline.

Clear outperformance by Eteplirsen-treated patients when adjusted for age at baseline.

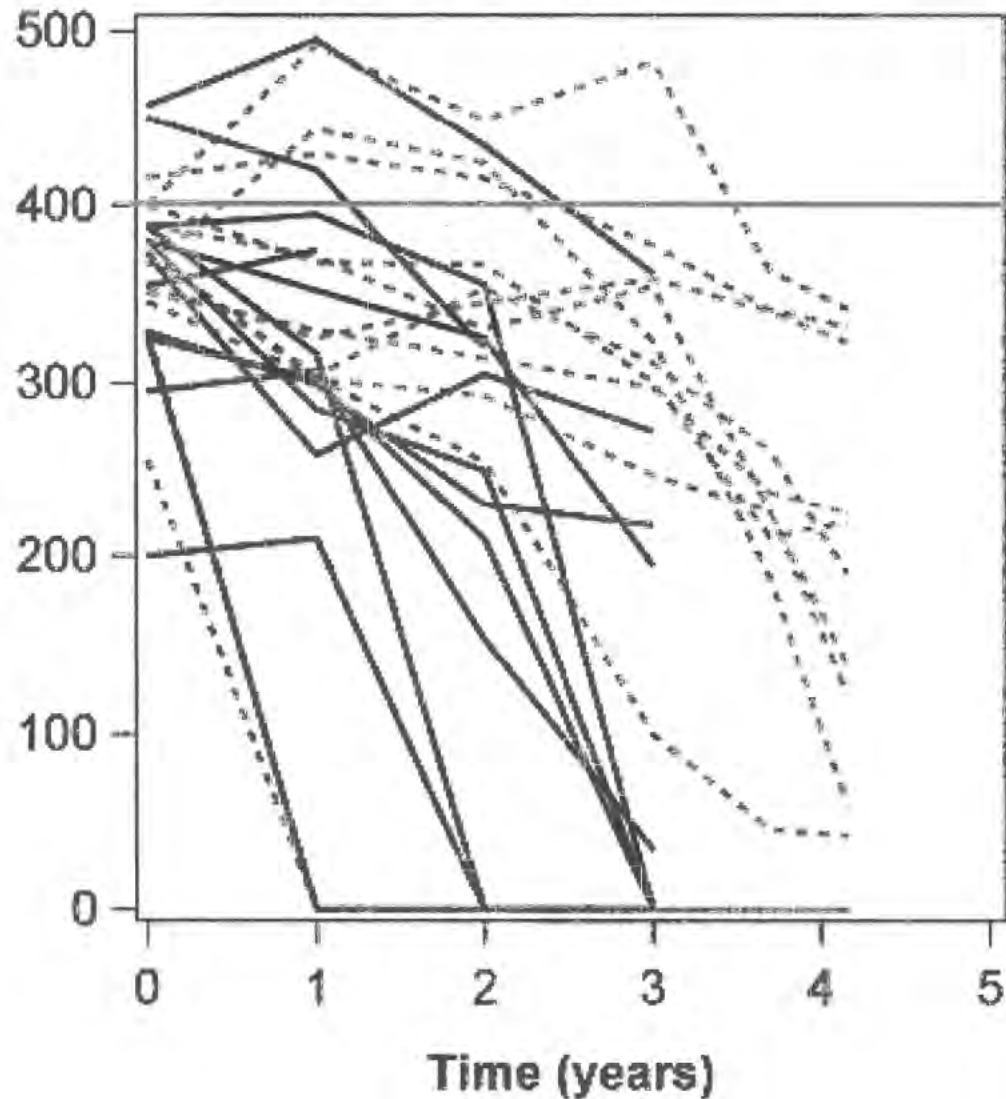
Eteplirsen Preserves Ambulation: Comparison to EC and CINRG Exon 51

Figure E: Eteplirsen preserves ambulation
Slide edited to correct presumed sponsor error within figure



"Presumed error" because I do not know what mean age sponsor has collected data out to, potentially well beyond the 4yr cutoff for NDA filing⁵

Unclear where data for this FDA figure (From Briefing Docs) came from



Unclear where these data taken from.

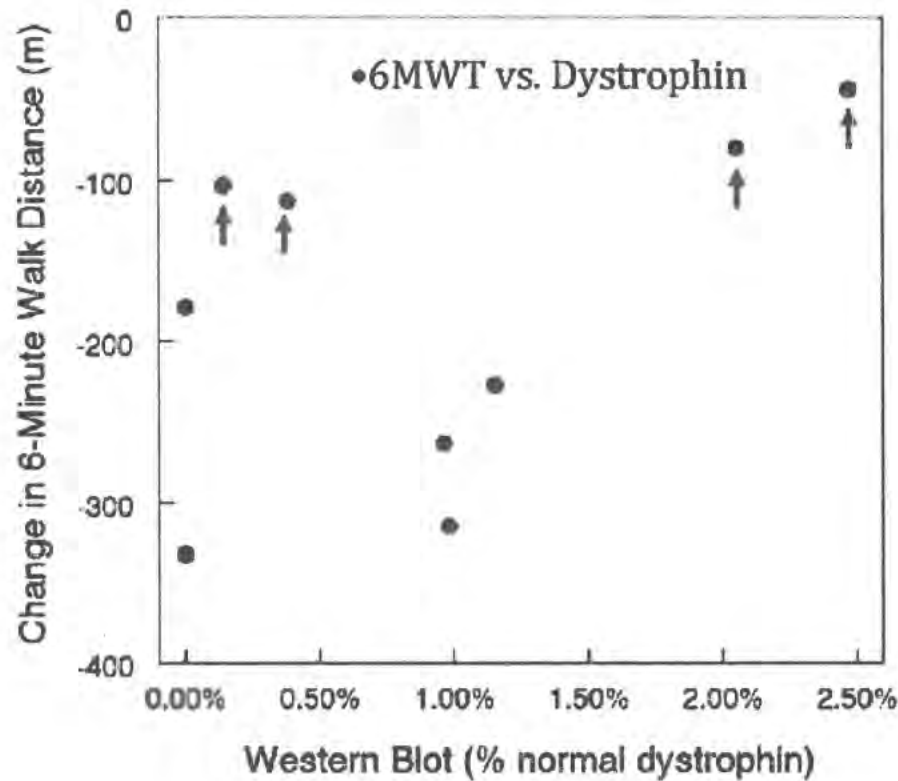
Every Etep line is below 400m at year 4, but patient 015 reported by sponsor as 401 baseline 6mwt and 400 at Year 4.

Approximate changes from 0 to year 4 determined with gridlines and comparison to Figure from FDA slide 126

Figure F

Analysis of Figure from FDA Slide 126 – A Key factor in the “reasonably likely” question

FDA SLIDE 126



Attempted replication using estimated assessment of FDA values results in nearly identical chart. Raw data on next slide

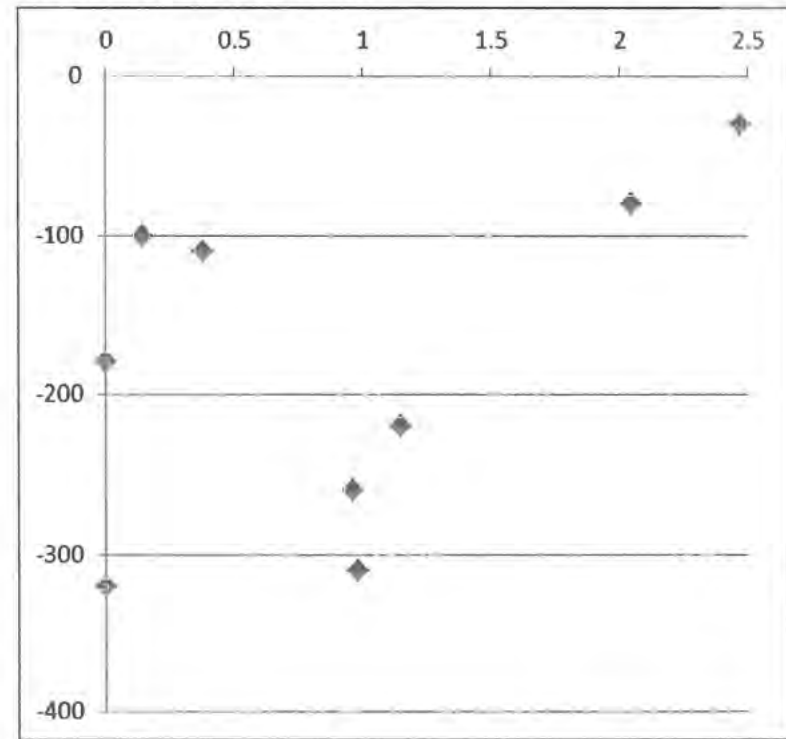
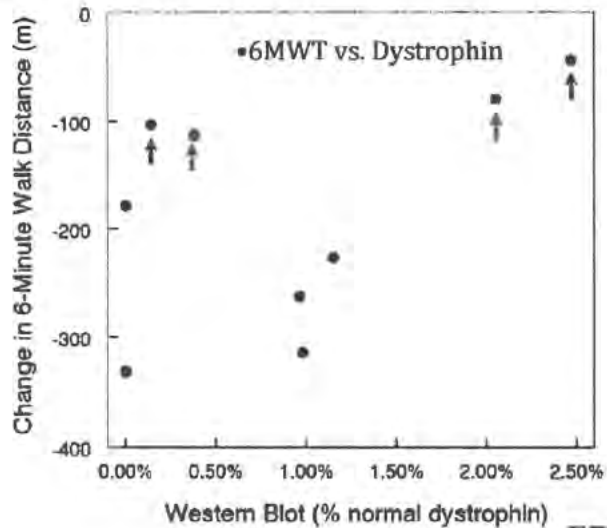


Figure G: Recapitulation of FDA slide 126

Raw Data for Slide 159 Analysis

FDA SLIDE 159



Western Blot (% normal dystrophin)

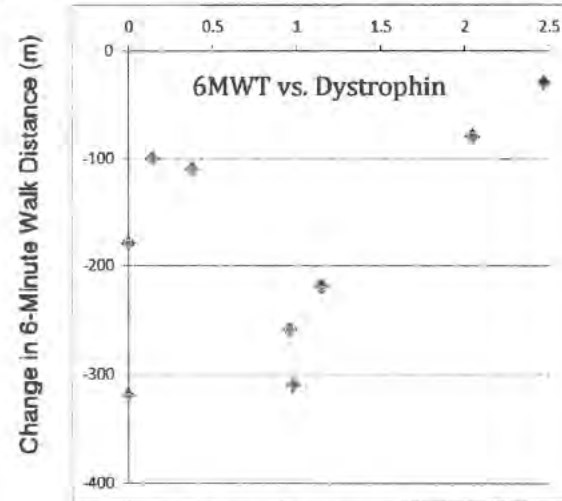


Figure G: Recapitulation of FDA slide 126

FDA Values determined from chart
(estimations; raw data not provided)

Patient	WB %Dystrophin	6mwt Change
15	2.05	-80
13	1.15	-220
12	0.38	-110
8	0.98	-310
7 or 3?	0	-320
6	2.47	-30
4	0.96	-260
3 or 7?	0	-180
2	0.14	-100

***These estimated data values require correction with real values from raw data source utilized by FDA. Approximations produce nearly identical chart at top right.

What happens when we exclude patients with low dystrophin measurements which may not be meaningful enough increases from baseline to impact 6mwt?

If we are to assess the effect of the induced truncated dystrophin on walking benefit, then surely patients in whom dystrophin was not induced should be excluded.

(See next slide)

There is a correlation between % Dystrophin expressed by WB and clinical effect on 6mwt at levels >0.5% of normal

This could indicate the threshold dystrophin level needed to impact 6mwt performance is 0.5% of normal.

$R^2 = 0.96$

Four excluded patients with low WB % highlighted in bold and red.

Patient	WB %Dystrophin	6mwt Change
15	2.05	-80
13	1.15	-220
12	0.38	
8	0.98	-310
7 or 3?	0	
6	2.47	-30
4	0.96	-260
3 or 7?	0	
2	0.14	

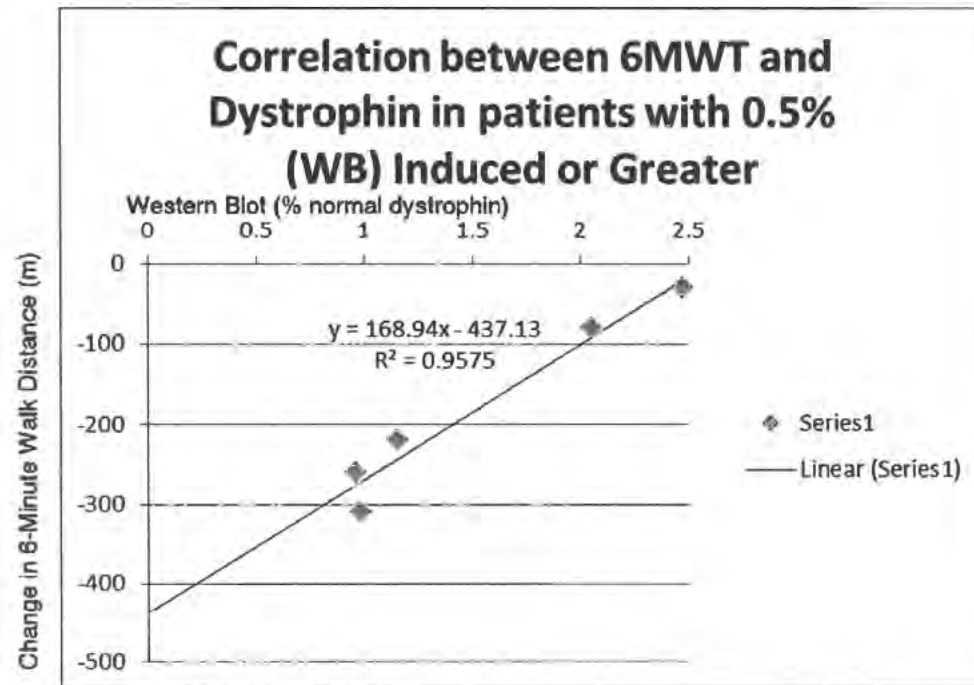


Figure H: >0.5% Induced Dystrophin linear correlation with 6mwt(Reasonably likely to predict clinical benefit).

***Again, these are estimated “6mwt change” values and need to be corrected with true raw data values, but these values replicated FDA figure nearly identically.

Dystrophin produced by eteplirsen, when >0.5% of normal is reasonably likely to predict clinical benefit in DMD patients amenable to exon-51 skipping.

- Occurred in 55% of Still-ambulant patients, and 63% of all patients, at week 180
- Does not preclude other benefits from increases of <0.5% that will not show up in 6mwt measure such as those mentioned by sponsor or PRO's
 - grip strength maintenance, independent rise ability
 - potentially slowed pulmonary function loss
 - reported PRO's: decrease in spontaneous Duchenne falls, less fatigue etc.

What about patients who had low or no dystrophin increase but still performed relatively well on 6mwt? It is a heterogeneous disease with outliers for many reasons and due to many unknown factors and at least one of these patients may have been right at the cusp of meaningful levels of dystrophin increase. I would not expect a precise correlation, and yet in this subset at >0.5% we do observe one anyway.

To quote Dr. Bastings: "There are some aspects of the data that can be considered that if positive would support the reasonably likely question. If there were a correlation between the amount of dystrophin detected in the muscles of individual boys and preservation of their physical abilities, such a link would help support the concept that the amount of dystrophin detected was reasonably likely to predict clinical benefit." 11

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 1:35 PM
To: DeMarco, Devota R
Subject: RM FW: dystrophin slides to dr temple (and dr. unger too)

From: Woodcock, Janet
Sent: Friday, May 20, 2016 8:01 AM
To: Frank J. Sasinowski; Moscicki, Richard
Subject: RE: dystrophin slides to dr temple (and dr. unger too)

Frank, were these "Promovi" results submitted? jw

From: Frank J. Sasinowski [<mailto:FSasinowski@hpm.com>]
Sent: Thursday, May 19, 2016 6:26 PM
To: Woodcock, Janet; Moscicki, Richard
Cc: Frank J. Sasinowski
Subject: FW: dystrophin slides to dr temple (and dr. unger too)

greetings, drs. woodcock and moscicki!

ms. christine mcsherry, her daughter jordan and i just met.

based on my understandings of your concerns over the measurement of dystrophin at nationwide children's (both you, dr. moscicki, and i were there with dr. unger), i thought that it may be productive to have the slide deck i prepared earlier this week and shared with drs. temple and unger on dystrophin.

from my memo below and the slide deck you will see that i was following from dr. temple's explanation to me of his understanding of the week 180 (aka 4th biopsy) measurement of dystrophin by immunohistochemistry (ihc).

in a nutshell, dr. temple said that FDA believes that there was little difference between the baseline results and week 180 results as seen on FDA slide #35.

the slide deck "walks" through that slide and breaks it down, step by step, and provides an explanation for week 180 dystrophin measurement and comparator.

essentially, the baseline % can not be compared to the week 180 % because the techniques and analyses were completely different and not done at the same time.

therefore, it may be inappropriate to compare, as slide #35 shows, the approx. 13% baseline dystrophin with the 17% dystrophin at week 180.

well, then is there anyway to have a valid comparator for the week 180% biopsy?

before the 4th biopsy was surgically excised, the sponsor worked with FDA on figuring out mutually agreeable techniques to be used on the 4th biopsy,

which could also be used on the samples from 3 of the 12 boys for which adequate material remained.

dr. temple said that FDA would be ok with using the baseline biopsy samples from the first exon 51 boys in the promovi trial so long as same disease (exon 51 dmd) and same inclusion criteria.

slide #10 in the attached deck shows the results of the 3 study 201 boys as well as the 6 promovi boys for a total of 9 boys, whose samples were handled the same way using the same techniques and analysis methods that FDA had agreed to for the 11 boys who agreed to a 4th biopsy at week 180. slide #11 shows those results, which were all analyzed at the same time and all using the same FDA directed techniques.

these results are: baseline dystrophin at about 1% (n=9) compared to week 180 dystrophin of about 17% (n=11).

hope this addresses the concerns that ms. mcsherry explained to me that you, dr. woodcock, had conveyed to her about

the possible lack of appropriate comparator for interpreting the week 180 dystrophin biopsies as well as

any concern over the appropriateness of the techniques and analytical methods used for these samples, both baseline and week 180 biopsy samples.

onward.

frank

From: Frank J. Sasinowski
Sent: Wednesday, May 18, 2016 9:01 AM
To: Temple, Robert; Dr. Ellis Unger (ellis.unger@fda.hhs.gov)
Cc: Frank J. Sasinowski
Subject: dystrophin slides to dr temple (and dr. unger too)

greetings, dr. temple!

recently we had a discussion about the dystrophin findings in the eteplirsen development program.

after we discussed the rt-pcr assessment of exon 51 skipping (as indicia of putative pharmacological mechanism of action),

we then spoke of the amount of dystrophin shown by immunohistochemistry (ihc). you and I had a difference of opinion as to whether the 4th biopsy results at week 180 showed dystrophin.

you referred me to the FDA slide at the adcom that showed 17% at week 180 by 3 blinded readers using FDA approved techniques

as not different than the baseline dystrophin values.

I said I would go back and review that slide.

I did...and it is the first slide in the attached deck of 11 slides, FDA slide #35. and, you were and are right: that slide shows 17% at week 180 which is not that dissimilar from the baseline values on that slide.

now, follow the slide deck (I could only scan as is, hit “view” and then, “rotate clockwise”—sorry).

slide #1 is FDA slide #35 from the adccom that you referred me to the other day.

slide #2 is just the FDA slide excluding the results from nationwide children’s (which is the site that dr. unger and I visited, and given dr. unger’s involvement, am copying dr. unger too on this).

slide #3 clarifies that dystrophin ihc samples have to be processed at the same time using the same technique (or not valid comparison).

slide #4 shows that the 8 samples from boys treated for 2 weeks failed to separate from their baseline values,

while the 4 samples from those treated for 24 weeks showed a doubling of dystrophin by ihc.

slide #5 displays these results in histograms, and this finding was the prespecified primary endpoint

of the controlled study, study 201, and was statistically significant.

slide #6 shows that there were no baseline or untreated samples processed at same time of the week 48 biopsies.

slide #7 is from the FDA indicating that therefore week 48 biopsy results can not be relied upon.

slide #8 shows the dystrophin ihc results from the week 48 biopsies but there is no comparator, so largely uninterpretable.

slide #9 show both that FDA and the sponsor worked hard to overcome this week 48 deficiency and the consensus agreement that the 4th biopsies at week 180

should be taken and compared against baseline/untreated samples and all processed at the same time, together.

slide #10 shows the 3 study 201/202 samples that had sufficient baseline material to be processed at same time and using same techniques

as the 4th biopsies plus shows the 6 baseline samples from the promovi study. you, dr. temple, instructed the sponsor to use these promovi samples as appropriate additional baseline samples so long as it was the same disease (they were: all exon 51 skips) and same inclusion criteria.

slide #11 displays the 17.39% dystrophin by ihc from the 3 blinded readers using FDA specified techniques compared to the appropriate baseline results with 1.12% dystrophin.

so, you were right that the FDA slide #35 did show exactly as you recalled: 17% dystrophin from the 4th biopsy at week 180, and you also recalled again correctly that this was not that dissimilar from the baseline % (about 13%) shown on that slide.

however, that baseline % was from samples treated and analyzed many years ago using different techniques.

when the % dystrophin from the 4th biopsies is compared to appropriate samples using appropriate techniques and contemporaneously treated and analyzed, then there is a wide difference from the 1% baseline to 17% at week 180.

onward.

frank

This e-mail is sent by a law firm and may contain information that is privileged or confidential. If you are not the intended recipient, please delete the e-mail and any attachments and notify us immediately.

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 10:15 AM
To: DeMarco, Devota R
Subject: RM: IMPORTANT
Attachments: NCHR letter to Commissioner re FDA approval standards for rare diseases.pdf
Importance: High

From: Guidos, Robert
Sent: Wednesday, May 18, 2016 1:42 PM
To: Moscicki, Richard
Subject: FW: IMPORTANT
Importance: High

FYI.

From: Guidos, Robert
Sent: Wednesday, May 18, 2016 1:34 PM
To: Woodcock, Janet
Subject: IMPORTANT
Importance: High

Janet, see below and attached.
Bob

From: Sher, Rachel
Sent: Wednesday, May 18, 2016 1:26 PM
To: Guidos, Robert
Subject: FW: Concerns about upcoming FDA decision
Importance: High

Can you route this to whoever should get it in CDER?

From: Diana Zuckerman [<mailto:dz@center4research.org>]
Sent: Thursday, May 12, 2016 6:13 PM
To: FDA Commissioner
Cc: Sher, Rachel
Subject: Concerns about upcoming FDA decision
Importance: High

Dear Commissioner Califf,

Since you suggested I contact you by email, I am taking this opportunity to do so. I don't plan on making it a habit to send you letters regarding specific medical products, but this one FDA decision will send a very clear message about whether FDA is making decisions based on science or not, as well as whether FDA respects the analyses of its scientists and Advisory Committees. The letter is below and attached. I bolded some points to make it easier to skim.

Thank you for considering our views on this important precedent.

Sincerely,
Diana Zuckerman, Ph.D.
President
National Center for Health Research
Cancer Prevention and Treatment Fund
1001 Connecticut Ave, NW, Ste. 1100
Washington, DC 20036
(202) 223-4000
www.center4research.org
www.stopcancerfund.org

May 12, 2016

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Commissioner Califf,

I am writing to express our concerns about the April 25th meeting of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee to discuss the approval of Sarepta's eteplirsen for the treatment of Duchenne muscular dystrophy.

One of our Center's Senior Fellows, Dr. Laura Gottschalk, spoke during the public comment period in support of the FDA scientists' views regarding the poor quality of the eteplirsen study design and data. She was the only one of 52 public speakers to do so. She pointed out that with only 12 patients, inadequate control groups, and variations in natural disease progression in historical controls as well as the patients in the study, approval of eteplirsen would only be appropriate if there is a very clear benefit to its use. Unfortunately, Sarepta failed to prove that eteplirsen meets a scientific standard of effectiveness. **FDA approval of eteplirsen on such insufficient data would set a dangerously low bar for approval of drugs in the future.**

We have great empathy for the parents of children with Duchenne Muscular Dystrophy who participated in the Sarepta trial, one of whom we know and respect. We also know that **Sarepta has misled the parents about their data, misrepresented FDA's previous warnings about the inadequacy of the Sarepta trial, and threatened parents that if eteplirsen isn't approved soon, the children will no longer have any access to the drug.** As a result of these misstatements and threats, the patient advocates at the meeting were extremely well-organized and determined.

We understand that Dr. Janet Woodcock wanted to assure patients that she understood their point of view, but we were appalled when she implied that the Advisory Committee should ignore the inadequacy of the science and approve the drug through the accelerated approval pathway despite no scientific evidence that it works. **We have never seen any CDER or CDRH Director so inappropriately try to influence an FDA Advisory Committee at the more than 200 FDA meetings that I and my staff have attended or analyzed.** Despite the hostile and inappropriate behavior of the audience (as described below), Dr. Woodcock repeatedly expressed her sympathy with the audience and reinforced their behavior by making herself available for photographs with the advocates (see Facebook for one example: <https://www.facebook.com/terri.weslevellsworth/posts/1024837964220051>).

We are especially concerned that **Sarepta justified their lack of a randomized control group based on their “ethical concerns” about depriving patients of an effective treatment, given that there was no clear evidence that eteplirsen is effective.** The company used that justification to explain why they disregarded FDA’s repeated warnings that their sample size was too small and that the lack of an adequately sized control group would make approval unlikely. If the FDA were to approve eteplirsen despite the Advisory Committee’s recommendation to reject it, it would send a **clear message to companies that they can ignore FDA’s repeated warnings about the need for an adequate control group based on questionable claims that a control group is unethical.**

Since the FDA’s goal is to approve a new drug if it is effective, and require more research if the results are ambiguous, **we strongly urge the FDA to defer a decision until it carefully reviews the existing data on the effectiveness of eteplirsen in the approximately 21-48 new patients who have been taking the drug for almost a year.** At the FDA’s urging, the company began enrolling more than 100 patients in a larger confirmatory trial, PROMOVI (unfortunately, also without an appropriate control group). It should be unacceptable to the FDA that Sarepta did not discuss their preliminary efficacy results from the PROMOVI trial, even though they provided safety data for those patients during the meeting that was not included in the materials provided to the Advisory Committee. Based on the slides that Sarepta presented, they should have had data on 21-48 new patients who had been taking eteplirsen for approximately 11 months at the time of the FDA meeting, and presumably even more patients who have taken the drug for at least 6 months. Rather than basing a decision on the efficacy data for only 12 patients, FDA should insist on reviewing efficacy and safety data on any PROMOVI patients who have been enrolled in the study for at least 6 months.

A related concern is that the April 25th Advisory Committee **meeting created a hostile environment for scientists who questioned whether eteplirsen was proven effective.** During the FDA presentation, the **audience repeatedly and loudly scoffed or laughed at the clinical team leader of the Division of Neurology Products** as he presented his data. The **audience booed the Deputy Director of the Division of Neurology Products** during his concluding remarks. In contrast, the speaker representing the Jett Foundation received a standing ovation after her comments on behalf of Sarepta. During the open public hearing, there was raucous applause after each of the 51 speakers in favor of eteplirsen.

By law, FDA Advisory Committee meetings should be a place for Committee members to openly discuss the drug or device under consideration. Although stakeholders may have differing goals and perspectives, the meeting as a whole should be an unbiased forum to discuss scientific and clinical data, providing the FDA and the public with the **unbiased opinions of Committee members.** Our two staff members, Dr. Laura Gottschalk and Mr. Paul Brown, have each attended many FDA Advisory Committee meetings, and usually if audience members respond positively or negatively to presentations, they are sternly warned that they will be removed if they do not obey the rules, including no applause or booing. In contrast, at the Sarepta meeting, the moderator made a few weak attempts to ask the audience to hold their applause until all the speakers had presented, but to no avail.

This out-of-control atmosphere had a clear impact on Advisory Committee members who had concerns about the drug. They quickly realized that any tough questions would be met with hostility, whereas positive comments about eteplirsen would be applauded. There is a natural urge to please a crowd that is cheering and booing in response to what is being said. Under the circumstances, it is nothing short of miraculous that most Advisory Committee members voted against approval. Even so, there were three abstentions. Based on our experience evaluating more than 200 FDA Advisory Committee meetings, **three abstentions is extremely rare** and suggests a reluctance to displease the audience.

Due to the frightening atmosphere, our staff decided to leave immediately after our public comment. We were particularly worried because the only guards at the meeting were protecting the panel members and FDA staff, not anyone in the audience. There were no metal detectors or other safeguards at the hotel, as there are for meetings held at FDA. As we left the room after our statement, people from the audience **swore loudly at our staff** and “gave us the

finger.” One of the men in the audience followed us out of the building while swearing at us, and **threatened to punch Mr. Brown in the face.**

We have been told by panel members, that after the meeting was over, some (if not all) of the **panel members who had voted against approval were escorted out by an armed guard**, in response to their request.

We support FDA’s efforts to include patients’ perspectives at public meetings, but this **should never be at the expense of the scientific integrity of the process or the safety of panel members.** And, in our experience, the FDA has been much more accommodating to patients who support approval of a product (such as eteplirsen and flibanserin, for example) than for those who have been harmed by one (Essure and breast implants, for example).

By law, the FDA vets its Advisory Committee members to minimize conflicts of interest that could possibly bias their views. However, if the FDA wants honest, unbiased feedback from all panel members, then they need to ensure that the meeting encourages that, rather than discourages it. We strongly urge you to consider the precedent that the FDA will set if the agency approves eteplirsen based on an open label trial of only 12 patients with such ambiguous results that were reviewed at a public meeting that demeaned the agency and its scientists.

Sincerely,

A handwritten signature in cursive script, appearing to read "Diana Zuckerman".

Diana Zuckerman, PhD
President



NATIONAL CENTER FOR HEALTH RESEARCH

The Voice For Prevention, Treatment And Policy

May 12, 2016

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Commissioner Califf,

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Sincerely,



Diana Zuckerman, PhD
President

Philips, Howard

From: Diggs, Felicia
Sent: Friday, May 13, 2016 11:00 AM
To: Moscicki, Richard
Subject: RE: CDER Clearance - Talking Points - Eteplersin PDUFA date

Great thanks Ric!

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: Moscicki, Richard
Sent: Friday, May 13, 2016 10:46 AM
To: Diggs, Felicia
Subject: RE: CDER Clearance - Talking Points - Eteplersin PDUFA date

Hi Felicia it is to the point. I wonder if its worth adding something like. "The FDA is very carefully considering all of the evidence before it." But I would bow to others who may think this too much and would be fine with the current edition. Ric.

From: Diggs, Felicia
Sent: Thursday, May 12, 2016 5:58 PM
To: Moscicki, Richard
Cc: Woodcock, Janet
Subject: CDER Clearance - Talking Points - Eteplersin PDUFA date

Hi Dr. Moscicki,

Please find attached internal talking points for NDA 206488 eteplersin to treat patients with Duchenne Muscular Dystrophy for your clearance. The talking points are in preparation to potential questions concerning FDA missing the PDUFA goal date of 5/26/2016 to decide on the application's approval. FDA intends on notifying the sponsor either the end of this week or the beginning of next week that we will need additional time to review additional data that was requested, presented at the advisory committee and existing data . If you could clear today it would be greatly appreciated. The document has been cleared by DNP, ODE1, OCOMM, OND, and OEP.

<< File: Talking points-etest pdfua date CDER.doc >>

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

Philips, Howard

From: LaVange, Lisa
Sent: Monday, May 09, 2016 9:43 AM
To: Breder, Christopher D; Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Dunn, Billy; Rao, Ashutosh; Bhattaram, Atul; Ligon, Sharnell (CDER); Kozauer, Nicholas; Hung, Hsien Ming J; Ling, Xiang; Jin, Kun; Nevius, S Edward; Rosenberg, Amy
Cc: Rawlings, Kimberly; Bolek, Michelle; Shreeve, Chris; LaVange, Lisa
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

I was not able to attend the briefing last week but noticed the circulation of this article illustrating adaptive randomization in a clinical trial. There have been several publications recently in the statistical literature on the pros and cons of outcome-adaptive randomization, and a general consensus is evolving that these designs are not beneficial in two-arm trials but may be with multiple randomization arms. The article by Hey and Kimmelman (Clinical Trials, 2015) touches on the ethical aspects of adaptive randomization, and no fewer than six commentaries were published with this article, plus a rejoinder from the original authors! The commentary by Don Berry may be of interest, and also that of Korn and Freidlin. See attached.



Lisa

From: Breder, Christopher D
Sent: Friday, May 06, 2016 3:02 PM
To: Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Dunn, Billy; Rao, Ashutosh; Bhattaram, Atul; Ligon, Sharnell (CDER); Kozauer, Nicholas; Hung, Hsien Ming J; Ling, Xiang; LaVange, Lisa; Jin, Kun; Nevius, S Edward; Rosenberg, Amy
Cc: Rawlings, Kimberly; Bolek, Michelle; Shreeve, Chris
Subject: RE: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

Here is the paper using adaptive randomization I had described at the end of our meeting.

<< File: NEJM Adaptive Randomization Paper.pdf >>
Regards,

Chris

Christopher D. Breder, MD PhD

WO22 4218
(301) 796-1365

-----Original Appointment-----
From: Diggs, Felicia

Sent: Monday, February 29, 2016 9:46 AM

To: Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Guidos, Robert; Throckmorton, Douglas C; Jenkins, John K; Temple, Robert; Unger, Ellis; Bastings, Eric; Farkas, Ronald; Tandon, Veneeta; Choy, Fannie (Yuet); Dunn, Billy; Breder, Christopher D; Rao, Ashutosh; Ware, Jacqueline H; Bhattaram, Atul; Ligon, Sharnell (CDER); Blount, Aprile; CDER 120 Calendar; Kozauer, Nicholas; Hung, Hsien Ming J; Ling, Xiang; LaVange, Lisa; Jin, Kun; Nevius, S Edward; Rosenberg, Amy

Cc: Rawlings, Kimberly; Bolek, Michelle; Shreeve, Chris

Subject: CD Briefing - NDA 206488 Eteplirsen/Sarepta Post Advisory Committee Meeting

When: Wednesday, May 04, 2016 3:00 PM-4:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: WO BLDG 51, Rm 6139

Date: Wednesday, May 4, 2016 3:00 p.m. – 4:00 p.m.

WO BLDG, 51, Rm. 6139

Please note, there will not be handouts or presentation materials for this meeting.

Topic: Discuss application eteplirsen, NME (NDA 206488) Post Peripheral and Central Nervous System Advisory Committee Meeting

CDER Staff Contacts: Fannie Choy, RPMS

CDER Executive Operations Staff Contact: Felicia Diggs, DEO liaison

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

Reason for Briefing: The purpose of this meeting is to discuss the outcome and plan of actions for application eteplirsen, NME (NDA 206488) post advisory committee meeting held on April 25, 2016. Eteplirsen proposed indication is for the treatment of patients with Duchene muscular dystrophy due to a deletion in the dystrophin gene that is amenable to exon 51 skipping.

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Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 10:18 AM
To: DeMarco, Devota R
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

From: Woodcock, Janet
Sent: Sunday, May 08, 2016 10:08 AM
To: Jenkins, John K
Cc: Temple, Robert; Dunn, Billy; Jenkins, John K; Unger, Ellis; Moscicki, Richard
Subject: Re: FDA Information Request: re: NDA 206488 / eteplirsen

Glad to hear they are getting these biopsies and sorry they will take some time to read out. Although these would have provided much more certainty one way or another re dystrophin production the fact that they can't be gotten soon means the situation is unchanged from my point of view so I would like to proceed as discussed. Thanks. Jw

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: May 5, 2016 at 8:37:41 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Cc: Unger, Ellis <Ellis.Unger@fda.hhs.gov>, Moscicki, Richard <Richard.Moscicki@fda.hhs.gov>, Dunn, Billy <Billy.Dunn@fda.hhs.gov>, Jenkins, John K <John.Jenkins@fda.hhs.gov>, Temple, Robert <Robert.Temple@fda.hhs.gov>
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

Janet

Attached is Sarepta's response to the question of how many boys have had a baseline and a second biopsy in the ongoing trial. There are 62 boys with baseline biopsies and 10 each with biopsies at week 24 and 48. Sarepta anticipates that we might ask them to do an interim analysis and states:

"Importantly, the protocol does not provide for an interim analysis for clinical or laboratory endpoints, and therefore any analysis prior to the end of study would require an amendment to protocol 4658-301. The estimated timeline for a protocol amendment—including document generation, submission to 37 clinical trial sites, and approval by IRBs—is 3 to 6 months."

Given that these data are significantly more than currently available for assessment of pre/post assay for dystrophin to support AA, the review team believes it would be very important to obtain these data before making a decision on approval. The 62 baseline samples would provide a very solid estimate of untreated patients and the data out to one year exceeds by 24 weeks the time point that Sarepta argues is required for dystrophin production to be observed. We cannot comment on the accuracy of Sarepta's statement about the need for IRB review and approval to perform an interim analysis and the timeline that would be required to obtain such approval.

What are your thoughts?

John

From: Bastings, Eric
Sent: Thursday, May 05, 2016 5:16 PM
To: Jenkins, John K; Unger, Ellis; Temple, Robert
Cc: Dunn, Billy; Farkas, Ronald
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

We have twenty patients with biopsies both at baseline and at a later timepoint (half at 24 weeks and half at 18 weeks).

Sarepta argues that it would take 3-6 months to make protocol changes and get IRB approval to do the analysis. I am not clear they would need IRB approval for that analysis.

Eric

From: Choy, Fannie (Yuet)
Sent: Thursday, May 05, 2016 5:10 PM
To: Bastings, Eric; Farkas, Ronald
Cc: Dunn, Billy; Choy, Fannie (Yuet)
Subject: FW: FDA Information Request: re: NDA 206488 / eteplirsen

Sarepta's response re: # of pts with 2nd biopsy. Thanks

Fannie

From: Matthew Rael [<mailto:MRael@Sarepta.com>]
Sent: Thursday, May 05, 2016 4:59 PM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff
Subject: RE: FDA Information Request: re: NDA 206488 / eteplirsen

Hi Fannie,

Please find attached our response to the information request from this morning.

Regards,

Matt

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



215 First Street, Cambridge, MA 02142 USA

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

Dear Shamim:

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

Please provide the following status update regarding the PROMOTI study:

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

We ask the information by close of business today.

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

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
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Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Thursday, July 13, 2017 10:47 AM
To: DeMarco, Devota R
Subject: RM - Drisapersen
Attachments: drisapprimary.pdf

From: Rao, Ashutosh
Sent: Tuesday, May 03, 2016 1:53 PM
To: Woodcock, Janet; Moscicki, Richard
Subject: Drisapersen memo

Dear Janet and Rich,

As a follow-up to our discussion, the primary clinical review for drisapersen is attached. A summary of the dystrophin-related findings, including western blotting, is on pages 129 (last paragraph)-131.

With regards to differences in tibialis and quadriceps from the DMD samples Prosensa/Biomarin tested, the data in Figure 21 from Study 114044 includes quadriceps data from 3 patients and the rest were from tibialis. The data do not appear to show variation by more than 2-fold from each other.

Table 14 from Study 114117 shows data from the two different muscle groups in the same table. In this case, the quadriceps derived sample (n=1) appears to show some difference from the tibials in the 6 mg/kg drisapersen-treated samples.

Sarepta used either biceps or deltoid muscles.

Best,
Ash

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

CLINICAL REVIEW (EFFICACY)

Application Type	NDA
Application Number(s)	206,031
Priority or Standard	Priority
Submit Date(s)	4/27/15
Received Date(s)	4/27/15
PDUFA Goal Date	12/27/15
Division/Office	DNP/ODE 1
Reviewer Name(s)	Veneeta Tandon Ashutosh Rao (Office of Biotechnology Products-Dystrophin Bioassays)
Review Completion Date	October 1, 2015
Established Name	Drisapersen
(Proposed) Trade Name	KYNDRISA
Applicant	Biomarin
Formulation(s)	Sterile solution in a single use vial for subcutaneous injection
Dosing Regimen	Loading Dose: 6 mg/kg twice weekly subcutaneous injection for first 3 weeks Maintenance Dose: 6 mg/kg once weekly subcutaneous injection
Proposed Indication(s)	Treatment of Duchenne muscular dystrophy with mutations in the dystrophin gene that amenable to treatment with exon 51 skipping
Intended Population(s)	Exon-51 skip amenable DMD boys
Recommendation on Regulatory Action	Complete Response

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

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Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

1

2 **Glossary**

DMD	Duchenne muscular Dystrophy
DAPC	Dystrophin-Associated Glycoprotein Complex
CGH	Comparative Genomic Hybridization
CK	Creatine Kinase
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
GCP	Good Clinical Practices
GSK	Glaxo Smith Kline
H-RMCA	High-Resolution Melting Curve Analysis
ICH	International Conference of Harmonization
ITT	Intent-To-Treat
MLPA	Multiplex Ligation-dependent Probe Amplification
MMRM	Mixed Effect Model Repeated Measure
PP	Per Protocol
SC	Subcutaneous

Clinical Review (Efficacy)
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1 Executive Summary

1.1. Product Introduction

Drug and Indication: KYNDRISA (Drisapersen sodium, also known as GSK2402968 or PRO051) is a new molecular entity that is proposed for the treatment of Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping.

Drisapersen is a chemically-modified antisense oligonucleotide (20-mer) with a sequence specific to bind to exon 51 of the human dystrophin pre-mRNA intended to cause the splicing machinery to skip over exon 51 during splicing of pre-mRNA. This restores the reading frame of the resulting mRNA. Restoration of the open reading frame allows the generation of an internally truncated dystrophin that is partially functional. Skipping exon 51 restores the reading frame in patients that carry a deletion of exons 45–50, 47–50, 48–50, 49–50, 50, 52, or 52–63, which, combined, is 13% of all DMD patients.

Pharmacological Class: The proposed Established Pharmacologic Class (EPC) for drisapersen is: *“exon skipping oligonucleotide inducer of dystrophin synthesis”*

Dosage Form: Drisapersen sodium will be available as a 200mg/mL sterile solution in a single use vial for subcutaneous (SC) injection.

Proposed dosage regimen:

Loading Dose: 6 mg/kg twice weekly subcutaneous injection for first 3 weeks

Maintenance Dose: 6 mg/kg once weekly subcutaneous injection

1.2. Conclusions on the Substantial Evidence of Effectiveness

This review concludes that, while there may be some evidence suggestive of efficacy of drisapersen, the evidence is inconsistent and in some cases contradictory, and does not reach the level of substantial evidence. I recommend a complete response due to inadequate evidence of efficacy.

1.3. Benefit-Risk Assessment

Note: Risk assessments were conducted by Dr. Evelyn Mentari, MD.

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Benefit-Risk Summary and Assessment

KINDRISA or Drisapersen is a chemically-modified antisense oligonucleotide (20-mer) with a sequence specific to bind to exon 51 of the human dystrophin pre-mRNA. It is designed to cause the skipping of exon 51 which results in the generation of an internally truncated dystrophin.

Duchenne muscular dystrophy (DMD) is a severe male pediatric neuromuscular disorder that occurs due to the absence of dystrophin protein. DMD is present at birth, but the disorder becomes apparent between ages 3-5 years. The loss of muscle strength in DMD is progressive, leading to loss of ambulation in the teens. Progressive loss of muscle strength leads to decline in respiratory function, cardiac complications and ultimately death typically in the third decade. Exon 51 skip-amenable DMD constitutes 13% of the DMD population, resulting in a prevalence of 2340 boys in the United States. There are no FDA approved treatments of DMD in the United States, but glucocorticoids have been shown to prolong function and survival by a few years. Similarly, improvements in supportive care, including physical therapy and assisted ventilation, have led to a steady but slow increase in survival over the past few decades. Chronic glucocorticoid use is associated with Cushingoid syndrome and obesity. There is significant need to treatment options that prolong ambulation and are better tolerated than steroids.

The conclusion of this review is that substantial evidence of clinical efficacy was not established for drisapersen in the treatment of exon 51-skip amenable DMD. There is no independent substantiation of the positive findings from a small Phase 2 study based 6MWD as a clinical endpoint. A larger study intended to provide the most reliable evidence of effectiveness was negative.

Similarly, this review concludes that there is no substantial evidence of an effect on a biomarker that is reasonably likely to predict clinical benefit. Drisapersen had little, if any effect on increasing dystrophin expression, the proposed mechanism of action. An unexpected finding was reduction in serum creatine kinase (CK), potentially a marker of muscle cell integrity, but CK levels are well known to change because of many other non-beneficial effects, such as loss of muscle or decrease in use of muscle, such that the clinical meaningfulness remains inconclusive at this time.

Drisapersen is associated with severe and potentially life-threatening adverse effects. Drisapersen causes immune thrombocytopenia, renal toxicity, and skin injury at injection sites.

- **Thrombocytopenia:** Six drisapersen subjects (2%) had thrombocytopenia $<20 \times 10^9/L$, levels at which patients are at risk potentially fatal complications, including spontaneous intracranial or intrapulmonary hemorrhage. Most of these patients had confirmed anti-platelet antibodies. These cases occurred 14-26 months after the first dose of drisapersen, suggesting that risk increases with duration of exposure. Platelet monitoring every 2 weeks, patient education regarding the signs and symptoms of thrombocytopenia, and facilitating prompt medical assessment and treatment can mitigate this risk. However, the decrease in platelets occurred precipitously and unpredictably so that even with intensive monitoring, the risk remains. Concomitant use of with antiplatelet, thrombolytic, or anticoagulant drugs is not recommended.
- **Renal Injury:** Renal toxicity was reported in 61% of drisapersen 6 mg/kg/week subjects, compared to 34% of placebo subjects. Proteinuria was the most common renal abnormality and occurred in 44% of drisapersen 6 mg/kg/week subjects, compared to 23% of placebo subjects. One patient developed multiple life-threatening thromboemboli in the setting of glomerulonephritis with nephrotic syndrome. Renal laboratory monitoring every 2 weeks and cessation of drisapersen according to recommended laboratory criteria can mitigate this risk but will not eliminate the risk of severe and potentially fatal renal toxicity.
- **Injection Site Reactions:** Injection site reactions occurred in 79% of drisapersen patients and included ulceration, irreversible scarring, and atrophy. The risk for first injection site reaction occurred throughout the first 72 weeks of exposure. 21% of reactions were not resolved by the end of the studies. Reactions known to resolve lasted for a mean of 58 days and up to 1217 days. Injection site reactions occurred despite administration by a medical professional and rotation of injection sites. No

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

other strategies to mitigate the risk of injection site reactions are known.

The benefit of drisapersen in exon 51 skip amenable patients is inconclusive at this time. Therefore, the benefit-risk assessments were not made.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Duchenne muscular dystrophy (DMD) is a severe pediatric neuromuscular disorder that occurs exclusively in males. DMD is caused by the absence of functional dystrophin protein that protects muscle fibers against contraction damage. Exon 51 skip-amenable DMD, a subgroup of DMD is defined by the presence of exon 51 in the dystrophin gene and the deletion of one or more exons contiguous with exon 51, resulting in an out-of-frame deletion in which the reading frame is restorable by the skipping (removing) of exon-51. • Lack of dystrophin results, through mechanisms not precisely understood, in degeneration of muscle fibers, attracting inflammatory cells and ultimately replacement by fibrotic tissue and adipose tissue. This leads to subsequent loss of muscle strength and function. • Loss of muscle strength is progressive, leaving the patients wheel chair bound by age 10-14. Progressive scoliosis develops that impairs pulmonary and cardiac function. Patients with DMD usually survive until late adolescence but not more than 20 to 25 percent live beyond the twenty-fifth year. • Mutations that are treatable by skipping exon 51 are thought to make up around 13% of the DMD population, resulting in a prevalence of about 2340 boys in the US.	The loss of muscle strength in DMD is progressive leading to loss of ambulation in the teens. Progressive loss of muscle strength leads to decline in respiratory function, cardiac complications and ultimately death typically in the third decade.
Current Treatment Options	• There are no FDA approved treatments of DMD in the Unites States. • The current standard of care is glucocorticoids (prednisone, prednisolone and deflazacort) administered either daily or intermittently with a modest effect. In addition, supportive care such as assisted ventilation and physiotherapy are used to improve quality of life and survival in DMD. • The risks of chronic use of glucocorticoids include increased infections, diabetes, Cushingoid appearance, delayed puberty, behavioral changes, obesity, osteoporosis, and increased frequency of long bone and vertebral fractures.	There is a specific unmet medical need for treatment of exon 51 skip- amenable DMD that will maintain ambulation as long as possible and slow subsequent scoliosis, respiratory and cardiac failure.
Benefit	• KYNDRISA or Drisapersen is a chemically-modified antisense oligonucleotide (20-mer) with a sequence specific to bind to exon 51 of the human dystrophin pre-mRNA. It is designed to cause the skipping of exon 51 which results in the generation of an internally truncated dystrophin. • The development program for drisapersen was exemplary for a severe rare disease, such that beneficial effects on biomarkers and clinical endpoints could have been detected if present. The efficacy of drisapersen was evaluated in one Phase 3 and two Phase 2 randomized placebo controlled trials in ambulant DMD boys ages >5 years in 290 subjects (195 on drisapersen and 95 on placebo) for 24- 48 weeks duration. In addition, two open label extension trials for a total	Studies with drisapersen were adequate and well controlled with an acceptable clinical endpoint, change from baseline 6MWD. No substantial evidence of efficacy was established for drisapersen in the treatment of exon 51-skip amenable ambulant DMD patients There is no independent substantiation of the positive findings from a

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Dimension	Evidence and Uncertainties	Conclusions and Reasons												
	duration up to 3.5 years intended to provide supportive evidence. Two doses: 3mg/kg/week (n=18) and 6mg/kg/week (n=177) were evaluated in these studies. - The primary endpoint was change from baseline 6-minute walking distance (6MWD), measured 24 or 48 weeks after treatment. 6MWD is an acceptable, potentially clinically meaningful endpoint. Biomarkers at the mechanistic or molecular level such as dystrophin protein expression, MRI and serum creatine kinase (CK) were measured in some subjects. - There is no substantial evidence of efficacy for drisapersen. No precise estimate of treatment benefit at 6 mg/kg/week can be established. Note that positive primary endpoint for study DMD114117 was at 24 weeks. At 48 weeks this study showed a decline in change from baseline 6MWD. Study 876 was only placebo-controlled up to 24 weeks. Results below: <table border="1" data-bbox="479 643 1473 802"> <thead> <tr> <th data-bbox="479 643 745 738">6 mg/kg/week versus placebo</th> <th colspan="3" data-bbox="745 643 1473 675">6MWD</th> </tr> <tr> <th data-bbox="479 738 745 738"></th> <th data-bbox="745 675 987 738">Study DMD114044 (n=186)</th> <th data-bbox="987 675 1229 738">Study DMD114117 (n=53)</th> <th data-bbox="1229 675 1473 738">Study DMD114876 (n=51)</th> </tr> </thead> <tbody> <tr> <td data-bbox="479 738 745 802">Treatment Difference (p-value)</td> <td data-bbox="745 738 987 802">10 m at 48 weeks (0.42)</td> <td data-bbox="987 738 1229 802">35 m at 24 weeks (0.01)</td> <td data-bbox="1229 738 1473 802">27 m at 24 weeks (0.07)</td> </tr> </tbody> </table> - The weakness of the data include: no independent replication of the results obtained in DMD114117, a decline in change from baseline at Week 49 in the same trial, a different regimen of 6mg/kg dose with identical drug exposure not statistically significant with a p-value of 0.80, a p-value of 0.07 from DMD114876 increased to a p-value of 0.21 after removing a single placebo subject that was unblinded during the study. - There were multiple secondary endpoints expected to be correlated with the primary endpoint but these generally were not statistically significant in any of the studies, and increase doubt about the robustness of the result on 6MWT. - Drisapersen was designed to increase dystrophin expression, but any increase in dystrophin protein expression was equivocal. Any effect on dystrophin appears so small as to be unlikely to have resulted in clinical benefit. - There was a 30-40% reduction in CK in the placebo controlled studies based on percent change from baseline CK, but the clinical meaningfulness of this is uncertain due to the presence of cofounders that reduce CK. - A small amount of muscle MRI data was collected, but the data was not reliably collected and the results were equivocal. - The open label studies did not provide evidence of slower progression based on known natural history of DMD patients.	6 mg/kg/week versus placebo	6MWD				Study DMD114044 (n=186)	Study DMD114117 (n=53)	Study DMD114876 (n=51)	Treatment Difference (p-value)	10 m at 48 weeks (0.42)	35 m at 24 weeks (0.01)	27 m at 24 weeks (0.07)	small Phase 2 study. A larger study intended to provide substantiation of effectiveness was negative. One can argue the reduction in serum creatine kinase to be plausibly treatment related, but it remains inconclusive at this time.
6 mg/kg/week versus placebo	6MWD													
	Study DMD114044 (n=186)	Study DMD114117 (n=53)	Study DMD114876 (n=51)											
Treatment Difference (p-value)	10 m at 48 weeks (0.42)	35 m at 24 weeks (0.01)	27 m at 24 weeks (0.07)											

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety database for drisapersen includes all patients from the 3 Phase 2 and Phase 3 placebo controlled trials and from the 3 open label studies. Drug exposure is adequate and reflects the intended population for use. • The most common AEs were: Injection site erythema (52%), Proteinuria (44%); injection site discoloration (36%). • Six drisapersen subjects (2%) had thrombocytopenia $<20 \times 10^9/L$, levels at which patients are at risk potentially fatal complications, including spontaneous intracranial or intrapulmonary hemorrhage. These cases occurred 14-26 months after the first dose of drisapersen. Despite routine monitoring of platelets every 2 weeks, thrombocytopenia occurred precipitously in some cases. • Renal abnormalities occurred in 61% of patients taking drisapersen, and the risk for a renal adverse event existed throughout 72 weeks of exposure. Proteinuria occurred in 44% of drisapersen 6 mg/kg/week patients, compared to 23% of placebo patients. Proteinuria was generally reversible on discontinuation, although one patient had life-threatening glomerulonephritis with nephrotic syndrome and multiple thromboemboli. • Injection site reactions, including discoloration, induration, pain, pruritus, bruising, atrophy, hematoma, and swelling, occurred in 79% of drisapersen patients. In 5% of all drisapersen patients, injection site reactions led to ulceration, fibrosis/sclerosis, or calcification. The risk for first injection site reaction occurred throughout the first 72 weeks of exposure. 21% of reactions were not resolved by the end of the studies. Reactions known to resolve lasted for a mean of 58 days and up to 1217 days. • Concomitant use with antiplatelet, thrombolytic, or anticoagulant drugs is not recommended. Patients taking these drugs were excluded from clinical studies. • Safety in the postmarketing setting: Laboratory values as markers of renal and thrombocytopenia adverse events were closely monitored during the clinical studies, and close monitoring will be necessary in the postmarket setting if the drug is approved. • Other uncertainties: The clinical effects of anti-drisapersen antibodies. The clinical effect of pro-inflammatory activity.	Major safety issues of thrombocytopenia, renal adverse events, and injection site reactions occur at the proposed dose of drisapersen. The safety issues can have life-threatening outcomes; the adverse reactions can be mitigated but not completely prevented with monitoring. The magnitude of the potential for serious harm after approval is unknown. Adherence to monitoring of platelets and renal laboratory parameters every two weeks is necessary, and failure to adequately monitor, recognize signs and symptoms, and provide prompt medical treatment in the postmarketing setting would increase the risk of adverse and potentially life-threatening outcomes. Injection site reactions occurred despite administration by a medical professional and rotation of injection sites. No other strategies to mitigate the risk of injection site reactions are known. Based on nonclinical findings and because of limitations due to the small number of patients exposed and duration of exposure in the clinical trials it is likely that adverse reactions not identified to date will occur in the postmarketing setting.
Risk Management	If drisapersen is approved, the following risk management approaches are recommended: • A patient registry as a post-marketing requirement will help to evaluate the main safety risks of drisapersen in the postmarketing setting. • Strong product labeling including a boxed warning and a Medication Guide with recommendations for monitoring of laboratory parameters and for rotation of injection	A patient registry as a post-marketing requirement will help to evaluate the main safety risks of drisapersen in the post-marketing setting. A boxed warning should be included in

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	sites is necessary to mitigate the risks of renal and thrombocytopenia adverse events and of injection site reactions. However, even with adequate monitoring, some patients will likely experience serious adverse events.	labeling to describe the risks of renal adverse events and thrombocytopenia and to provide recommendations for monitoring and to warning of the risk for injection site reactions and provide recommendations for rotation of injection sites. A medication guide should be required to describe these risks and symptoms of concern, and to highlight the need for prompt medical attention.

2 Therapeutic Context

Analysis of Condition

Duchenne muscular dystrophy (DMD) is the most frequent of the early onset muscular dystrophies that occur almost exclusively in males (X-linked recessive disorder). A small percentage of female carriers may exhibit a range of muscle symptoms from the full Duchenne phenotype to milder skeletal muscle weakness. Exon 51 skip-amenable DMD, a subgroup of DMD is defined by the presence of dystrophin exon 51 and the deletion of one or more exons contiguous with exon 51, resulting in an out-of-frame deletion in which the reading frame is restorable by the skipping (removing) of exon-51.

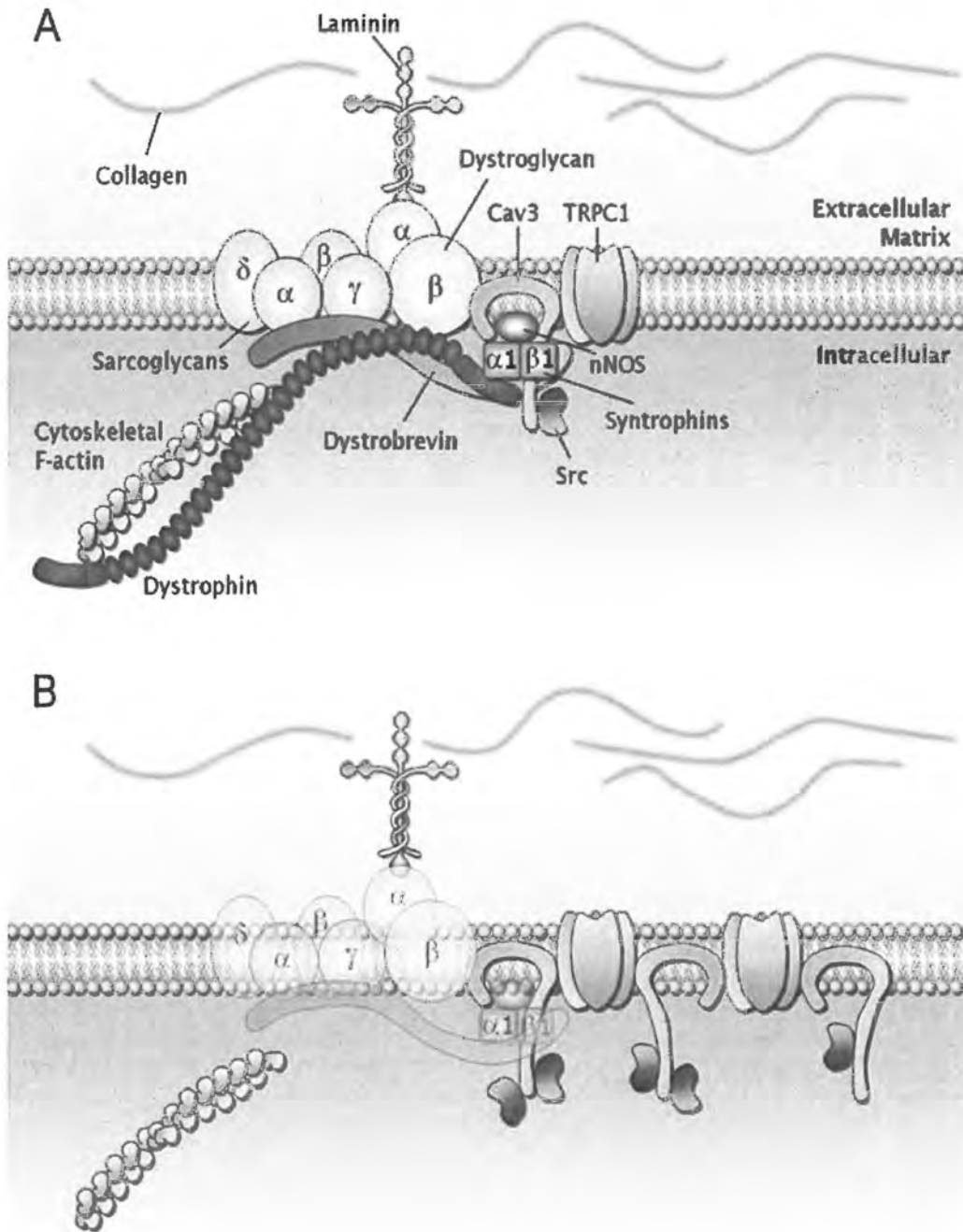
Etiology: DMD is caused by the absence of functional dystrophin protein due to mutations in the DMD gene. Mutations that disrupt the translational reading frame of the dystrophin transcript, lead to a prematurely aborted dystrophin synthesis. The resulting dystrophin deficiency at the muscle fiber membranes leads to progressive fiber degeneration. The most common mutation is exon deletions (~60%) (Aartsma-Rus 2002). Dystrophin provides structural stability to the dystroglycan complex on the muscle cell membranes, protecting muscle fibers against contraction induced damage. In addition, the association of dystrophin with catalyzing enzymes (nitric oxide synthases) completes the link between the extracellular matrix and intracellular signal transduction enzymes (Brenman 1995, Allen 2011) (Figure 1). Dystrophin is expressed in the skeletal, cardiac, and smooth muscle, as well as in the brain.

Lack of dystrophin results, through mechanisms not precisely understood, in degeneration of muscle fibers, attracting inflammatory cells and ultimately replacement by fibrotic tissue and adipose tissue. Dystrophin deficiency results in loss of neuronal nitric oxide synthase, which normally is localized to the sarcolemma as part of the dystrophin–glycoprotein complex. The absence of functional dystrophin in DMD results in deterioration of the skeletal musculature with subsequent loss of strength and function (Bushby 2010).

Clinical Features: DMD is present at birth, but the disorder usually becomes apparent between ages 3 and 5 years. There is a proximal-to-distal progression of muscle weakness. The boys fall frequently. Running, jumping, and hopping are invariably abnormal. By age 5 years, muscle weakness is obvious by muscle testing. On getting up from the floor, the patient uses his hands to climb up himself. Contractures of the heel cords and iliotibial bands become apparent by age 6 years, when toe walking is associated with a lordotic posture. Loss of muscle strength is progressive, with predilection for proximal limb muscles and the neck flexors; leg involvement is more severe than arm involvement. Between ages 8 and 10 years, walking may require the use of braces. By age 10-14, patients become wheel chair bound. Contractures become fixed, and a progressive scoliosis often develops. The chest deformity with scoliosis impairs pulmonary function, which is already diminished by muscle weakness. By age 16–18 years, patients are predisposed to serious, sometimes fatal pulmonary infections. In the last years of life the patient becomes bedfast. In general, there is a wide range of functional ability at a given age.

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Figure 1 (A) Dystrophin-Associated Glycoprotein Complex (DAPC); (B) Protein changes in dystrophic muscle



Source: Allen 2011

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The use of glucocorticoids and the management of spine deformity, pulmonary and cardiac dysfunctions have altered the timing of some of the clinical milestones of the disease.

Life Span: Patients with DMD usually survive until late adolescence but not more than 20 to 25 percent live beyond the twenty-fifth year. Respiratory, orthopedic and cardiac complications emerge, and without intervention the mean age at death is around 19 years (Bushby 2010). Following the introduction in the 1990s of assisted ventilation in the later stages of the disease, the mean age of survival (for those ventilated patients who do not develop early and severe cardiomyopathy) shifted to 24 years, with some surviving to the early thirties (Rall 2012, Eagle 2002).

Incidence: The incidence of DMD is 13 to 35 per 100,000 yearly or about 1 in 3,500 live male births globally. The estimated prevalence in the US is 18,000, with an additional 15,000 cases in EU (McNeil 2009). Mutations that are correctable by skipping exon 51 are thought to make up around 13% of the DMD population, resulting in a prevalence of 2340 boys in the US and 1950 boys in the EU.

Diagnostic Criteria: All boys with a clinical suspicion of a DMD diagnosis are subjected to molecular analysis of their dystrophin gene. Molecular methods that assess DNA copy number are used as the initial step in the diagnosis of DMD. If no deletions are identified, then DNA sequencing is performed to identify point mutations or small insertions or deletions. Three commonly used tests to determine a patient's mutation in the dystrophin gene include Multiplex Ligation-dependent Probe Amplification (MLPA), High-density Array Comparative Genomic Hybridization, and Single-Condition Amplification Internal Primer Sequencing.

Serum CK levels are invariably elevated to between 20 and 100 times normal. The levels are abnormal at birth but decline late in the disease because of inactivity and loss of muscle mass. EMG demonstrates features typical of myopathy.

2.2. Analysis of Current Treatment Options

There are no FDA approved treatments of DMD in the US that will prevent or slow muscle weakness in DMD. The current goals of treatment are to maintain function for as long as possible and to manage associated complications, such as joint contractures, scoliosis, cardiomyopathy, respiratory insufficiency, and weight gain.

The current standard of care is glucocorticoids (prednisone, prednisolone and deflazacort) administered either daily or intermittently. There is no consensus of the dosing regimen of these glucocorticoids globally. Most frequent regimens include 0.75 mg/kg/day prednisone, 10 days on/10 days off, 0.9 mg/kg/day deflazacort, and 5 mg/kg/day on weekends (Griggs 2013). The recent natural history studies have shown that the use of glucocorticoids have changed the natural progression of the disease. Randomized controlled trials published in literature have shown that glucocorticoids improved muscle strength and function for six months to two years. Data from non-randomized studies suggests functional benefit over a five year period in many treated patients, but the overall long-term benefit remains unclear (Cochrane Review). The risks of chronic use of glucocorticoids include increased infections, diabetes, Cushingoid appearance, delayed puberty, behavioral changes, obesity, osteoporosis, and increased frequency of long bone and vertebral fractures.

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In addition, supportive care such as assisted ventilation and physiotherapy are used to improve quality of life in DMD.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Drisapersen is a new molecular entity and is not currently marketed in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

Drisapersen was initially licensed by Prosensa, who conducted the Phase 1 studies and an open label extension of the Phase 1 study. It was licensed by GSK in 2010. GSK suspended dosing in all studies following the results of the Phase 3 study DMD114044. Subsequently rights were regained by Prosensa and more recently in January 2015 Biomarin acquired Prosensa.

A brief chronology of the regulatory activity with GSK, Prosensa and Biomarin and FDA on the development of drisapersen primarily as it relates to the assessment of efficacy mainly and additional important milestones is tabulated below. The regulatory interactions regarding different review disciplines will be addressed in the respective reviews (i.e. chemistry, nonclinical and safety).

Date	Summary of Regulatory Activity
8 July 2009	Pre-IND meeting with Prosensa; concerns raised by FDA at the meeting were: • 6 mg dose selection based on the 5 week CLIN-02 study may not be adequate, not clear if 6 mg was the MTD. • 6MWD as a primary endpoint acceptable provided 'large enough benefit', supportive data from secondary endpoints will be important due to concerns of unblinding due to injection-site reactions. • Need steps to minimize risk and potential effects of unblinding. • Difficulty in supporting the safety of a 12-month pivotal based on limited human data. • Implementation of adequate safety monitoring for platelet, liver and renal effects. • Need to take confounding factors such as non-invasive ventilation, use of glucocorticoids, scoliosis and surgery into account for randomization scheme or analytical plan.
25 August 2009	FDA grants Orphan Drug Designation to Prosensa
8 April 2010	GSK submitted IND105284 to the FDA Division of Neurology Products, including protocol DMD114118 (single dose PK, safety/tolerability study)

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7 June 2010	FDA puts IND105284 on Partial Clinical Hold (only single dose in study DMD114118 is allowed to proceed, not the open label extension) for following reasons: • AEs in previous human studies not described in sufficient detail based on ICH3 Guidelines • Inadequate monitoring of hematological, hepatic and renal effects • Inadequate information on open label extension part DMD 114348
1 November 2010	GSK provides response to the Partial Clinical Hold, including submission of dose ranging protocol DMD114876
6 December 2010	FDA grants Fast-Track Designation to drisapersen
18 January 2011	FDA continues Partial Clinical Hold as 39 week study in monkey induced vascular injury at all doses. There was thrombus formation at two high doses.
4 May 2011	FDA removes Partial Clinical Hold, multiple dosing in protocol DMD114876 is allowed to proceed; Division proposes exclusion, monitoring and discontinuation rules.
4 January 2012	FDA requests additional safety information regarding recent adverse events of proteinuria
2 March 2012	GSK submits new protocol with new safety criteria to monitor and manage future events of proteinuria that is agreed with FDA
7 March 2013	Teleconference to discuss safety monitoring and managing regarding an adverse event of venous sinus thrombosis
23 May 2013	EOP2 Meeting with GSK. Issues discussed at this meeting were: • Pathway of approval: FDA did not consider "accelerated approval" based on Phase II studies as the regulatory course for drisapersen because 6MWD is a clinically meaningful endpoint. Top lines results of the Phase III study were to be available 4 months after the EOP2 meeting. FDA recommended that NDA based on Phase II (DMD114117, DMD114876) and Phase III (DMD 114044) along with results from DMD114763 appear most appropriate. FDA was open to considering dystrophin expression as supportive along with 6MWD to support filing of NDA, but was unclear with the current data were adequate. • FDA recommended immunogenicity be adequately addressed for both drug product and dystrophin. GSK indicated that there was no risk of immunogenicity with AON product. The FDA recommended that GSK provide supportive data explaining why AONs do not need immunogenicity assessments. • FDA agreed to the possibility of a rolling review of the NDA.
26 June 2013	FDA grants Breakthrough Therapy designation for drisapersen based on the results of Study DMD114117 and the 141 week open label study DMD 114673.
02 June 2014	Prosensa receives FDA communication on regulatory path forward. • FDA expresses reservations about the persuasiveness of the available data, but open to filing an NDA for drisapersen for consideration under an accelerated approval pathway. • FDA advised that the 6MWD could be interpreted as an intermediate clinical endpoint, supplemented by relevant evidence supporting reasonably likelihood

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	of predicting longer term benefits. • FDA advised on types of confirmatory studies.
22 October 2014	Prosensa participates in Type C meeting with FDA to discuss confirmatory trials. FDA recommends a 2-3 year long confirmatory study. Prosensa agreed with conducting a longer 2-3 years study with an interim analysis. No agreement has been reached on the design of the confirmatory study in subsequent interactions with Biomarin.
12 January 2015	Pre-NDA meeting with FDA, Prosensa and Biomarin. The following agreements were reached: • Antibody data from supportive studies to be submitted at the 120-safety update • DMD natural history data collected by CINRG to be included at the time of NDA submission. • FDA disagreed with Biomarin's proposal to submit only Dr Goeman's natural history data for comparisons based on age and 6MWD and CINRG data for interpretation of pulmonary function in Study DMD114673. FDA explained that totality of available natural history data, including Dr Goeman's data and the CINRG data and any other natural history data would need to be provided at the time of NDA submission to enable appropriate review. FDA did not agree that matching would be adequate if based on 6MWD and age alone. Additional data, such as ability to jump and hop and detailed history corticosteroid use would be necessary. The sponsor agreed to include all natural history data available to the sponsor at the time of NDA submission. Note: CINRG natural history data was not submitted in the application, and could not be obtained by FDA from CINRG. Matching was only done based on age and 6MWD. Additional data, such as ability to hop, jump etc. from Goeman's natural history data were not provided in the application.
9 April 2015	FDA did not agree that a 24 week randomized double blind placebo controlled confirmatory study with drisapersen followed by a 72 week open label extension study would provide convincing evidence of benefit given the bias associated with potentially unblinding adverse effects on an effort dependent endpoint.

3.3. Foreign Regulatory Actions and Marketing History

Drisapersen has not been submitted for approval in any other country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The review was pending at the time completion of this review.

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4.2. **Product Quality**

The applicant proposes the to-be marketed Drisapersen sodium injection for subcutaneous use be available as 160mg/0.8 mg ad 100 mg/0.5 mg single use vials. The CMC reviewer recommends eliminating the counterion name from the product and expressing the product strength as drisapersen and not as drisapersen sodium This will change the dosage strength to 150.4 mg (equivalent to 160 mg drisapersen sodium)/0.8 mL and 94 mg (equivalent to 100 mg drisapersen sodium)/0.5 mL in single-use vials.

4.3. **Clinical Microbiology**

Not applicable

4.4. **Nonclinical Pharmacology/Toxicology**

The review was pending at the time of completion of this review.

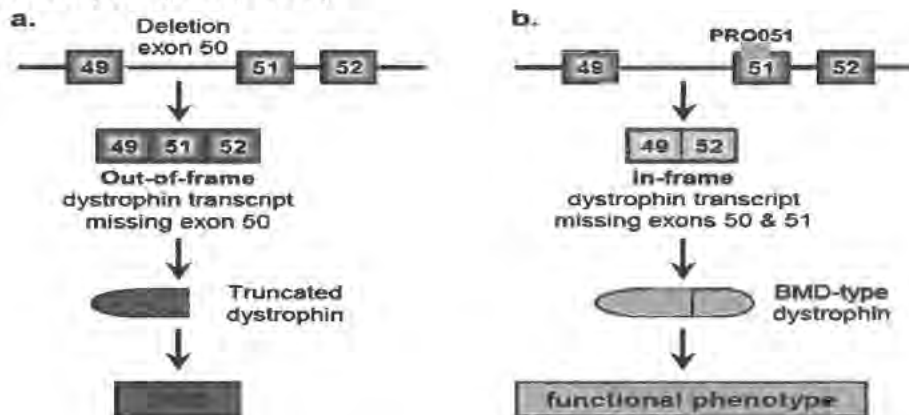
4.5. **Clinical Pharmacology**

4.5.1. **Mechanism of Action**

Drisapersen is a chemically modified oligonucleotide (fully 2'-O-methyl substituted RNA backbone with phosphorothioate linkages) to promote RNA binding and prevent mRNA breakdown after binding. According the Applicant, drisapersen has high sequence specificity to exon 51. The Applicant's proposed mechanism of action involves disruption of secondary structure and/or interference with the binding of splicing regulatory proteins, resulting in skipping of exon 51 during post-transcriptional splicing and a mature mRNA transcript that is internally shorter but capable of dystrophin production in DMD. The truncated dystrophin lacks amino acids in the central rod domain, but retains the N- and C-terminal domains necessary for its structural and signaling roles. Drisapersen-induced exon skipping has a mutation-dependent corrective approach. Skipping of one specific exon applies to a series of different mutations. Skipping exon 51 with drisapersen would restore the reading frame in patients that carry a deletion of exons 45-50, 47-50, 48-50, 49-50, 50, 52, or 52-63, which comprise a total of 13% of all DMD patients. The exon skipping mechanism by drisapersen is shown schematically in Figure 2 in a patient that has exon 50 deletion.

Figure 2: Schematic representation of exon skipping mechanism

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4.5.2. Pharmacodynamics

The results of dystrophin analysis are discussed section 6 of the review for each individual study.

4.5.3. Pharmacokinetics

- In Plasma:
 - Maximum plasma levels are generally reached between 2 to 4 hours after SC administration, after which the plasma levels decline during a rapid initial tissue (re)distribution phase, followed by a slower elimination phase.
 - After 24 weeks of dosing, the trough plasma concentrations at Week 36 (12 weeks after stopping treatment) were approximately half of the trough concentration at Week 23, indicating drisapersen has a long terminal half-life.
 - In DMD subjects the major drug-related component in plasma after repeated SC administrations was unchanged drisapersen.
 - No studies have been performed specifically to evaluate excretion in humans, but mice studies suggest it is mainly through the urinary route.
- In Skeletal Muscle:
 - Drisapersen concentrations in the muscles reach maximum levels after 39 weeks of dosing.
 - Drisapersen is also eliminated slowly from the muscle tissues with concentrations declining 40% after 12 weeks of stopping treatment.

4.6. Devices and Companion Diagnostic Issues

Development of a companion diagnostic was not required because DMD mutation analysis is incorporated in DMD diagnosis, and thus occurs prior to, and separate from, consideration of a therapeutic.

4.7. Consumer Study Reviews

Not applicable.

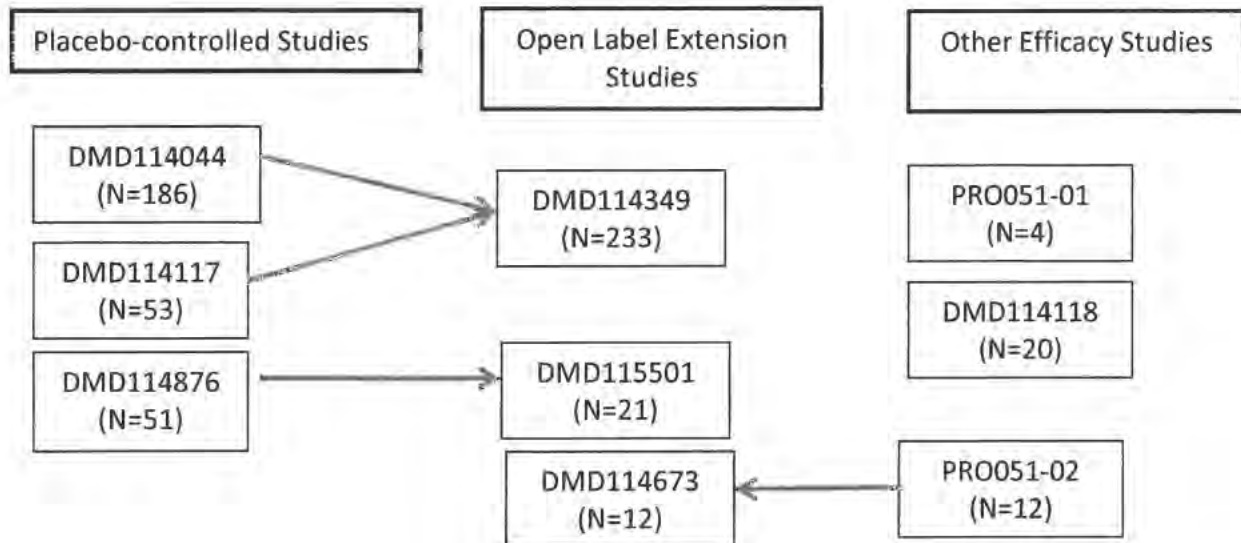
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5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The drisapersen clinical development program consists of nine clinical studies in 326 boys with DMD (Table 1). Of the 326 subjects treated in the clinical development program, 312 received at least one dose of drisapersen. The cut-off date for the NDA submission was 31 August 2014. In September 2013 dosing was halted in all studies after the negative results of the Phase 3 Study DMD114044. No subjects received drisapersen from September 2013 up to the cut-off date. Seven clinical studies were completed by the cut-off date.

A schematic of the development program is shown below:



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Table 1 Summary of clinical studies of drisapersen for the treatment of DMD

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
DMD 114117 Completed	Phase II Randomized, double-blind, placebo-controlled, parallel group	<u>Loading dose:</u> 6mg/kg SC drisapersen twice weekly for 3 weeks, then either: <u>Continuous:</u> SC 6 mg/kg/wk or <u>Intermittent:</u> alternating weeks of SC 6 mg/kg twice weekly and 6 mg/kg/wk for 6 weeks followed by 4 weeks off-dose period Dose-matched placebo	1°: 6MWD at week 24	48 weeks	N=53	ambulant subjects, 6MWD ≥ 75m, able to Rise from floor ≤ 7s	13 centers in 9 countries
DMD 114876 Completed	Phase II Randomized, double-blind, placebo-controlled, parallel group	3 mg/kg/wk or 6 mg/kg/wk Volume-matched placebo	1°: 6MWD at Week 24	24 weeks (followed by 24-week post-treatment period with no treatment)	N=51	ambulant subjects, 6MWD ≥ 75m, able to Rise from floor ≤ 15s	13 centers in 1 country
DMD 114044 Completed	Phase II Randomized, double-blind, placebo-controlled, parallel group	6 mg/kg/wk Dose-matched placebo	1°: 6MWD at Week 48	48 weeks	N=186	ambulant subjects, 6MWD ≥ 75m	44 centers in 19 countries
Short-term Repeat-dose Open Label Study							
PRO051-02 Completed	Phase I/II Open-label, rising dose	0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg, or 6 mg/kg SC once weekly	1°: Dystrophin	5 weeks	N=12	ambulant and non-ambulant subjects	2 centers in 2 countries
Long-Term Extension Studies to Support Efficacy and Safety							
DMD	Phase I/II	6 mg/kg/wk drisapersen SC	6MWD	Ongoing	N=12	ambulant and non-	2 centers in 2

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114673 (Extension to PRO051-02) Ongoing	Open-label uncontrolled extension of PRO051-02	for 72 weeks. After an interval of 8 weeks (Weeks 73-80) off drug, subjects restarted an intermittent treatment regimen of 6 mg/kg/wk drisapersen for 8 weeks, followed by 4 weeks off treatment (12-week cycles) up to 188 weeks. An IV sub study was conducted following Week 188		<u>Planned:</u> Until launch or termination of development. <u>Actual:</u> Dosing in the study was halted in September 2013, but was restarted after the data cut off for this submission (August 31, 2014).	IV sub study N=7	ambulant subjects at start of parent study PRO051-02	countries
DMD 114349 Terminated Completed	Phase III Open-label extension of DMD114117 and DMD114044	6 mg/kg/wk SC drisapersen Subjects with tolerability issues had the option to enter the intermittent arm of 6 mg/kg/wk for 8 weeks followed by 4 weeks off dose. Subjects who did not wish to receive drisapersen or who had to withdraw from both active arms during the study had the option to go into a natural history observation arm.	6MWD	<u>Planned:</u> Until launch or termination of development (minimum 104 weeks). <u>Actual:</u> Up to 101 weeks at time of termination of dosing in September 2013	N=233	ambulant at start of parent study (DMD114044 or DMD114117)	58 centers in 24 countries
DMD 115501 Ongoing (not submitted)	Phase III Open-label extension of DMD114876	6 mg/kg/wk SC drisapersen Subjects with tolerability issues had the option to enter the intermittent arm of 6 mg/kg/wk for 8 weeks followed by 4 weeks off		<u>Planned:</u> Until launch or termination of development <u>Actual:</u> Dosing in the study was halted in	N=21	ambulant at start of parent study (DMD114876)	13 centers in 1 country

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		dose.		September 2013, but was restarted after the data cut off for this submission (August 31, 2014).			
<i>Other studies pertinent to the review of efficacy or safety</i>							
PRO051-01 Completed	Phase1 Open label, single dose	0.8 mg IM	Safety, tolerability Dystrophin	Single dose	N=4	Ambulant and non-ambulant	Single center
DMD 114118 Completed	Phase 1 Randomized, placebo-controlled, rising dose	3, 6, 9, 12 mg/kg SC No subjects received 12 mg/kg	Safety, tolerability, PK	Single dose	N=20	Non ambulant	2 centers in 2 countries

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5.2. Review Strategy

I reviewed all the clinical efficacy data (placebo controlled studies, open label studies and the exploratory Phase I studies) submitted to the NDA along with the published literature and medical text books to evaluate the efficacy of drisapersen in the treatment of DMD with mutations amenable to exon 51 skipping. I conducted my own analyses of the primary data using graphical explorations and descriptive statistics in JMP, JReview and Excel. The applicant's primary statistical MMRM analyses were confirmed by the statistician Dr. Sharon Yan, Ph.D. I reviewed the dystrophin data from each study, but the methodology for the assessment of dystrophin and its reliability in each study was reviewed by Dr. Ashutosh Rao, Ph.D. His comments were incorporated in this review of the dystrophin data. The safety data were reviewed by Dr. Evelyn Mentari, MD in a separate review. The MRI data were reviewed by Dr. Daniel Krainak, Ph.D from CDRH Imaging Division.

6 Review of Relevant Individual Trials Used to Support Efficacy

Study DMD 114117

6.1.1. Study Design

Overview and Objective

Study DMD114117 was a Phase II placebo controlled clinical study to assess two dosing regimens, continuous and intermittent, of 6mg/kg drisapersen. An intermittent regimen was selected to potentially mitigate liver and kidney toxicities. PK/PD modeling predicted that the selected intermittent regimen would provide similar peak concentrations (C_{max}) and total exposure (AUC) over the 48 weeks to the continuous regimen. Both the continuous and the intermittent regimen had comparable total doses administered throughout the study.

Studied period: 01 September 2010 to 12 September 2012

Study center(s): 13 centers in 9 countries in Australia, Belgium, France, Germany, Israel, Netherlands, Spain, Turkey, and the United Kingdom.

Trial Design

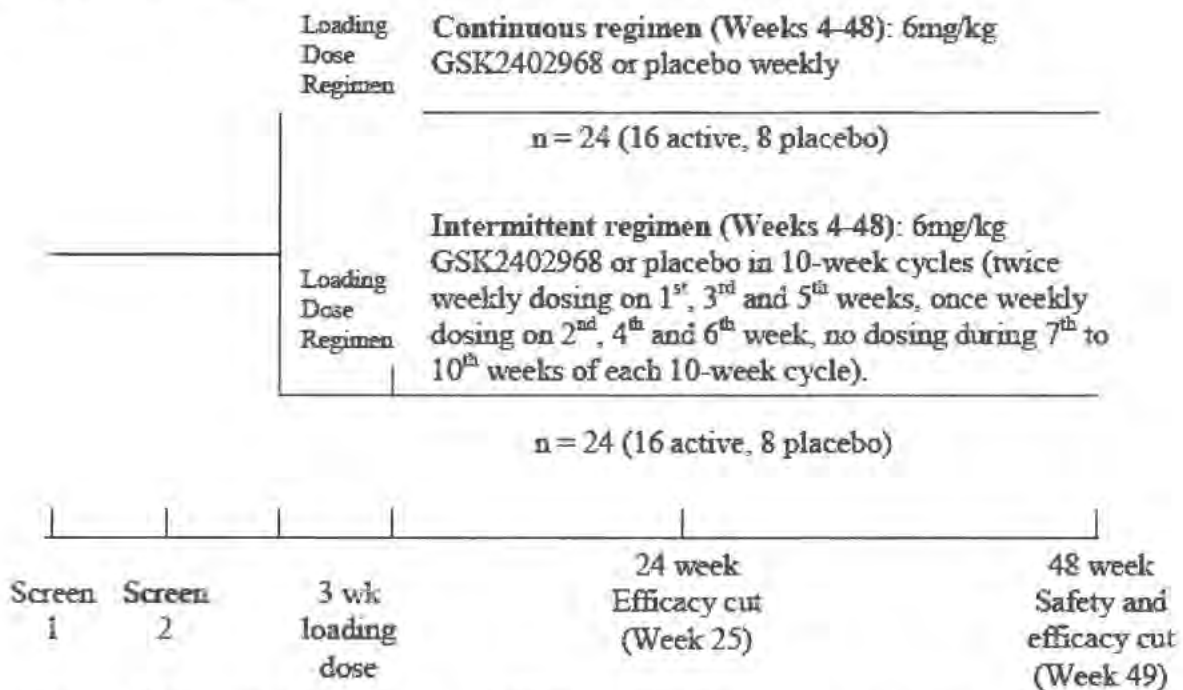
Study DMD114117 was a 48 week double-blind, parallel-group, placebo-controlled clinical study in ambulant DMD boys, with primary efficacy at 24 weeks. The study was fully blinded with respect to active and placebo in each cohort, however the different regimens were not fully blinded, due to the number of dummy doses that would be needed to blind both regimens.

At the end of the treatment period, subjects who completed the study had the option to enter an open-label extension study (Study DMD114349). Additional criteria for entering the open label study are discussed in section 6.4. If subjects did not enter the extension study, they were monitored for a minimum of 20 weeks after the last dose.

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Study Schematic is shown in

Figure 3. Screen 1 and 2 were 4 and 2 weeks prior to randomization, respectively.

Figure 3 Study Design Schematic



Population: N=54 ambulant subjects with DMD resulting from a mutation that can be corrected by exon 51 skipping. The sample size was not based on statistical considerations, but would allow the detection of an effect size of 1.1 with 80% power at significance level of 5%

Key Inclusion Criteria:

- Mutation confirmed by a state-of-the-art DNA diagnostic technique covering all DMD gene exons, including but not limited to MLPA (Multiplex Ligation-dependent Probe Amplification), CGH (Comparative Genomic Hybridization) or H-RMCA (High-Resolution Melting Curve Analysis)
- Male of at least 5 years of age
- Able to rise from floor in ≤ 7 seconds (without aids/orthoses),
- Able to complete the 6MWD test with a distance of at least 75m,
- Results of 6MWD must be reproducible (within 20% for each test) between Screening Visits 1 and 2
- On glucocorticoids for a minimum of 6 months immediately prior to screening, with no significant change in total daily dosage or dosing regimen for a minimum of 3 months immediately prior to screening and a reasonable expectation that total daily dosage and dosing regimen will not change significantly for the duration of the study (unless clinically indicated)
- Life expectancy of at least 1 year

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- QTc <450 (based on single or average QTc value of triplicate ECGs obtained over a brief recording period), or <480 msec for subjects with Bundle Branch Block. Note: QTc could be either QT interval corrected for heart rate by Bazett's formula (QTcB) or QT interval corrected for heart rate by Fridericia's formula (QTcF), and machine read or manual overread.

Key Exclusion Criteria:

- Any additional missing exon for DMD
- Current or history of liver or renal disease
- Use of anticoagulants, antithrombotics or antiplatelet agents, previous treatment with investigational drugs, idebenone or other forms of Coenzyme Q10, within 1 month of treatment initiation.
- Positive hepatitis B surface antigen, hepatitis C antibody test, or human immunodeficiency virus (HIV) test at screening.
- Symptomatic cardiomyopathy, to discuss with medical monitor, if subject has a left ventricular ejection fraction <45% at Screening

Key Withdrawal Criteria:

- AE jeopardizing safety of the subject
- Administration of idebenone or Coenzyme Q10 during study
- New evidence of cardiomyopathy.
- QTc>500, to be discussed with Medical Monitor

Dosing regimen:

After a 2-4 week screening period, all subjects received a loading dosing regimen of twice weekly subcutaneous (SC) dosing with 6 mg/kg driscapersen for the first 3 weeks, which was followed by the following regimen in parallel cohorts for 48 weeks. Each cohort included subjects on driscapersen and matched placebo in a 2:1 ratio. Subject randomization was done using Interactive Voice Response System according to the randomization schedule.

- Continuous regimen; 6 mg/kg SC driscapersen once weekly for 48 weeks
- Intermittent regimen; 6 mg/kg SC driscapersen twice weekly on 1st, 3rd and 5th weeks, once weekly on 2nd, 4th and 6th weeks, and no active drug on 7th to 10th week of each 10 week cycle for 48 weeks

Injection sites were rotated to minimize injection site reactions. Some subjects received multiple injections depending on the weight of the subject. There were no food restrictions with regards to dosing. All study treatment was supplied in identical vials. The appearance of the active and placebo solutions were not identical and hence a blinding label was applied to the syringe to minimize the risk of unblinding the subjects. The volumes were different according to the weight of the subject, and were matched for active and placebo. To maintain the blind, the dose was prepared and administered by appropriately trained and qualified unblinded personnel who were not involved in the study's efficacy assessments.

Reviewer's Comment:

Applicant's study design elements mostly appeared reasonable based on the preclinical and clinical information available at the time of study conduct as discussed below:

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- **Design:**
 - Approaches towards blinding of active and placebo treatment were “less than ideal” by design. The placebo solution had a different appearance from the drisapersen solution. The study, by design, was not blinded for the regimens, with a different schedule of doses for the continuous and intermittent arms. Treatment was administered by personnel who knew if drug or placebo was being administered; while these personnel were not involved in efficacy assessments, direct patient contact (and presumably contact with other study personnel) may have jeopardized blinding.
- **Inclusion/Exclusion Criteria:**
 - Steroids are the standard of care in the treatment of DMD; therefore enrolling subjects on their stable steroid dose was prudent, but there are many factors associated with steroid use that would render heterogeneity to the selected DMD population. The enrollment criteria required subjects on steroid for a minimum of 6 months, hence some subjects were on steroid for much longer and these subjects may have different disease progression trajectories (Kim, 2014). At this time there is no consensus on the optimal dose, regimen (continuous or intermittent) or the type of steroid. The choice of steroids also varies from country to country. Published data suggest that earlier initiation of steroids provide more sustained improvement in clinical function (Moxley RT III, 2005; Manzur, 2008). Recent 36 month data have shown that patients on daily steroids do better than intermittent steroids (Pane 2014). The impact of age of initiation of steroid use on disease progression is not well established, but in general DMD patients receiving steroid treatment increase ambulation from 2-5 years compared to those not on steroid treatment. All these factors were not controlled in the selection of patients for this study. Understandably, the standard of care being different from country to country enrolling patients with regards to consistency with steroid use would considerably limit the patients meeting the enrollment criteria. These factors are likely to impact the disease trajectory of an individual patient.
 - The inclusion criteria required subjects to have no more than 20% difference in 6MWD at the two screening visits 1 and 2 that were separated by 2 weeks. This allows for a lot of variation in the 6MWD that is in fact larger than the difference possibly seen in 1 year in many cases.
 - The inclusion criteria of 75 m 6MWD would include subjects that are likely to lose ambulation in 1 year (Mazzone 2011). This criterion was based on available natural history data at the time of study conduct. Recent published data suggest that patients with 6MWD<325 are more likely to lose ambulation in 1 year (McDonald 2013b).
 - The inclusion criteria of rise of floor of ≤ 7 seconds was included for a more homogenous population, although disease trajectories may vary in subjects with rise from floor of <4 or >4 as well. In addition Rise from Floor in conjunction with 6MWD also appears important in disease progression (Mazzone 2010).
 - The impact of use of idebenone or other forms of Coenzyme Q10 more than 1 month of treatment initiation is not well established, but may add to variation in disease progression. Other enrollment criteria appear reasonable.
- **Dose:**

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- A loading dose appears appropriate. PK modeling had suggested that steady state could be achieved 6 weeks earlier with a loading dosing regimen of twice weekly dosing for 3 weeks, given the long half-life of drisapersen (29 days).
- There is limited human data on a 9mg/kg /week dose in non-ambulant subjects, but decision was based on pre-clinical pro-inflammatory findings. Applicant has not evaluated longer dose interval with higher doses due to limitations in injectable volume by SC administration.
- **Assessments:**
 - Based on what was known at the initiation of this study, efficacy assessments at 24 and 48 week seemed reasonable. PK/PD characteristics of drisapersen had estimated dystrophin protein turnover half-life of 5 weeks. Based on this it was hypothesized that dystrophin expression will reach steady state in 24 weeks, hence a 24 week primary endpoint. Efficacy was also assessed at 48 weeks. (The dystrophin half-life was verified by the sponsor during the review cycle. The Applicant clarified in a response dated June 18, 2015 that this reflected the thought at the time protocol was written. Recent published studies suggest a dystrophin half-life in the range of 2 to 4 months in the skeletal muscle of mdx mice (Verhaart 2014; Wu, 2012). Although, the dystrophin half-life from mice may not predict human dystrophin half-life, but likely is longer in humans than in rodents. Given this, studies longer than 48 weeks may be desirable to achieve optimal results to allow adequate time for the attainment of steady state levels of dystrophin.

Study Endpoints

The following efficacy assessments were done once or twice at screening, baseline, and Weeks 13, 25, 37 and 49, unless specified otherwise.

Primary efficacy endpoint:

- **Muscle function using 6 minute walking distance (6MWD) test:** change from baseline at 25 weeks. Subjects were asked to walk, as quickly but as safely as they could, up and down a fixed distance until they were told to stop after 6 minutes. The subjects were warned of the time and were told that they could stop earlier if they felt unable to continue walking. The total distance walked within 6 minutes (or until the subject stopped in case of early termination of the test) was recorded in meters.

Secondary efficacy endpoints:

- **Timed function tests (times and grading):** These were assessed on a 6-point scale to differentiate those subjects with similarly fast times who may have achieved a ceiling time (Attached to the Appendix A).
 - **Rise from floor**, no aids or orthoses allowed, subjects stood from a standardized supine position as quickly as possible when told to "go". Time was recorded from initiation of movement to upright position.
 - **10m walk/run**, no aids or orthoses allowed: Subject was asked to walk a 10 m measured walkway as quickly as possible. Time was recorded to one tenth of a second. If the subject could not complete the 10-meter walk, the total distance was recorded.
 - **4-stair climb (ascend and descend)**, handrail allowed: subject ascended and descended 4 steps
- **North Star Ambulatory Assessment:** It consists of 17 activities graded 0 (unable to perform), 1 (performs with modifications), 2 (normal movement). NSAA Total Score ranges from 0 to 34, with a

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score of 34 implying normal function. The scale assesses activities required to remain functionally ambulant (e.g. rise from the floor), activities that can be difficult even early in the disease (e.g. standing on heels) and activities that are known to progressively deteriorate over time (stand from a chair, walk). (Scale attached in the Appendix A).

- **Muscle strength (total score):** knee flexors, knee extensors, elbow flexors, elbow extensors, shoulder abductors and hip flexors (as determined by handheld myometry using a microFET2 myometer)
- **Frequency of accidental falls during 6MWD**
- **Time to loss of ambulation**
- **Pulmonary function using non-invasive spirometry** (FEV1, FVC, MIP, MEP, PCF, PF)
- **Creatine kinase serum concentrations:** at Screening, baseline and Weeks 3, 5, 9, 13, 17, 21, 25, 33, 41 and 49.
- **Dystrophin expression** (muscle biopsies from tibialis anterior) including percent change from baseline: at baseline, Week 25 and 49 and mRNA production in muscle tissue

Exploratory endpoints:

Pediatric Quality of Life Neuromuscular module, gait characterization by accelometry during 6MWD, percent predicted 6MWD (the percentage of the predicted 6MWD for a healthy boy of the same age and height that the boy with DMD was able to walk), lean body mass by DEXA scan, were conducted as exploratory endpoints. Pharmacokinetics, drisapersen muscle concentration and DNA samples were also taken.

Reviewer's Comment:

6MWD is an effort dependent endpoint. The results may be affected by bias from unblinding due to adverse events such as injection site reaction, which occurred in most patients administered drisapersen. 6MWD was considered a reasonable clinical endpoint in DMD, as little was known on the natural history data of 6MWD in DMD and most data were published on the validity of 6MWD in DMD.

Like the 6MWD, the Timed Function Tests and NSAA are also effort and motivation dependent and measure similar functional capabilities as the 6MWD. In addition, NSAA scoring may be subjective and susceptible to observer bias.

Statistical Analysis Plan

The intent-to-treat (ITT) population was defined as all subjects who are randomized to the study and received at least one dose of study medication and have at least one efficacy assessment. This is the primary population for evaluation of efficacy parameters. The per protocol (PP) population is defined as all ITT subjects and have no major protocol deviations.

There was no interim analysis, although two main analyses were done (1) at week 25 (primary) and (2) at week 49.

Primary Endpoint Analyses: Primary assessment of efficacy data was conducted using a Mixed Effect Model Repeated Measure (MMRM) at week 25 on the Observed case (OC) data. The model included

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treatment, visit, treatment by visit interaction, country/country grouping, baseline 6MWD and baseline 6MWD by visit as fixed effects. Comparison of each dosing regimen with placebo (combined group pre-specified) was adjusted using Bonferroni-Holm adjustment for multiplicity. The p-values from the two primary analyses (6 mg/kg drisapersen continuous vs. placebo, and 6 mg/kg drisapersen intermittent vs. placebo), were ordered smallest to largest. The smallest p-value was compared to a significance level of $\alpha/2$ (0.025). If the result was demonstrated to be statistically significant at this level, i.e. $p < 0.025$, then the second p-value was compared to a significance level of α (0.05). If the initial comparison shows the result not to reach statistical significance, then the second comparison was also considered not to have reached statistical significance.

If the assumptions of normality were not met, a log-transformation of the data prior to an MMRM analysis was used.

Sensitivity Analyses for primary endpoint: The following sensitivity analyses were performed:

- ANCOVA on OC data for the ITT population
- ANCOVA on LOCF data (missing data for at least 3 months) for the ITT population
- ANCOVA on data imputed via multiple imputations for the ITT population
- MMRM on OC data with PP population

ANCOVA model included fixed terms for treatment, baseline 6MWD and country. The covariates assessed were county, baseline 6MWD, steroid regimen, age, baseline rise time, lean body mass index. MMRM model included terms for Treatment, Visit, Treatment by Visit, Country Grouping, Baseline 6MWD and Baseline 6MWD by Visit.

Secondary endpoint analyses:

- For continuous endpoints MMRM analyses on OC data, with similar fixed terms
- Kaplan-Meier and Log rank test on time to event endpoints such as loss of ambulation (if ≥ 4 subjects in either treatment group experienced a loss of ambulation)
- ANCOVA on %predicted 6MWD on OC data

Protocol Amendments

The protocol amendments related to efficacy assessments are summarized below:

Amendment 1 (20 Jul 2010)	Country specific: To remove DEXA scan due to logistics
Amendment 2 (24 Sep 2010)	Country specific: to add conduct gait characterization collected by accelerometric data to 5 sites (N=20 of 54 subjects) and include 50 healthy control height matched subjects for this.
Amendment 3* (13 Oct 2010)	• Approval of recruitment of healthy control was not granted, hence removed. Intent to enroll in a different protocol. • Removed the inclusion criteria that required reproducibility of Rise From Floor (within 20% at pre-drug visit 1 and 2). • Modified the exclusion criteria regarding concomitant medications: idebenone and Coenzyme Q allowed within 1 month of study administration instead of 6 months • Removed muscle biopsy at 49 weeks • 'Pediatric Quality of Life Neuromuscular module' moved from secondary endpoint to exploratory analyses.
Amendment 4*	• addition of the frequency of accidental falls during the 6MWD and time to

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(19 Jul 2010)	loss of ambulation as 2 ^o endpoint

*Also amended safety monitoring and stopping criteria

Reviewer's Comment: These amendments are unlikely to bias the study results as were done within the first month of study initiation when few subjects were enrolled.

Data Quality and Integrity: Sponsor's Assurance

The study was conducted in accordance with ICH GCP (ICH E3 and E6) and applicable country-specific requirements. Written commitments were obtained from investigators to comply with GCP. Study was conducted with written informed consent from subjects and their parents.

6.1.2. Study Results

Patient Disposition

A total of 53 subjects were randomized (Table 2). No subject withdrew from the study.

Protocol Violations/Deviations

The number of subjects with protocol deviations is summarized in Table 2.

Table 2: Number of subjects (%) with major protocol deviations up to week 25

ITT and Safety Population	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)	Total (N=53)
PP Population	17 (94)	17 (94)	15 (88)	49(92)
Subject with major protocol deviation	1(6)	1(6)	2(12)	4(8)
Failed Inclusion criteria (Able to complete the 6MWD test with a distance of at least 75 m and results of 6MWD within 20% of each other at each pre-drug visit.) ^a	1(6)	1(6)	1(6)	3 (6)
Failed Inclusion criteria (Receiving glucocorticoids for ≥ 6 months prior to screening, with no significant change in total daily dosage or dosing regimen for 3 months prior to screening.) ^b	0	0	1(6)	1(2)

Source: NDA DMD114117 study report, page 58

^aSubject 3055 in the placebo group, Subject 2129 in the 6 mg/kg drisapersen continuous group and Subject 2126 in the 6 mg/kg drisapersen intermittent group. ^bSubject 2103 in the 6 mg/kg drisapersen intermittent

Subject 3055 in the placebo group in addition to not being able to complete the 6MWD test with a distance of at least 75 m at screening also had a single deletion of exon 45 that was not amenable to exon 51 skipping. Given the fact that this subject was on placebo, the applicant included him in the primary analysis with the ITT population. In addition, two placebo subjects on a single visit (week 37 and week 9, respectively) were given active drug based on PK analysis). One subject had lower

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drisapersen concentrations at week 9 and according to the applicant probably missed a dose that was not reported.

Reviewer's Comment:

- The sensitivity analysis (MMRM with the PP population) was also positive with a similar p-value ($p=0.013$); hence the impact of protocol violation of subject 3055 was not a concern.
- Dr. Sharon Yan (Statistician) also conducted an analysis averaging the 2 screening and baseline 6MWD values. A treatment difference over placebo of 30m ($p=0.03$) was obtained from the drisapersen continuous regimen. Hence, the impact of protocol violation in a few subjects with 6MWD for the 2 screening visits not within 20% was not a concern.
- A single missed dose or wrong treatment on a single occasion is unlikely to affect efficacy results, but analysis was done excluding these subjects as well.

Table of Demographic Characteristics

According to the applicant, the demographic characteristics were similar across treatment groups with the intermittent group being older and having slightly higher mean height and weight values. The demographic characteristics for primary analysis are shown in Table 3.

Table 3 Demographic characteristics of the primary efficacy analysis

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)	Total (N=53)
Age (yrs)				
Mean (SD)	6.9 (1.2)	7.2 (1.7)	7.7 (1.5)	7.3 (1.5)
Median	7.0	6.5	8.0	7.0
Min., Max.	5, 9	5, 11	5, 10	5, 11
Ethnicity, n (%)^a				
n	16	17	15	48
Not Hispanic/Latino	16 (100)	17 (100)	14 (93)	47 (98)
Hispanic/Latino	0	0	1 (7)	1 (2)
Race, n (%)^a				
n	16	17	15	48
White - White/Caucasian/ European Heritage	13 (81)	15 (88)	14 (93)	42 (88)
White - Arabic/North African Heritage	0	2 (12)	0	2 (4)
American Indian or Alaska Native	0	0	1 (7)	1 (2)
Asian - South East Asian Heritage	1 (6)	0	0	1 (2)
Native Hawaiian or other Pacific Islander	1 (6)	0	0	1 (2)
Mixed Race	1 (6)	0	0	1 (2)

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Height (cm)				
Mean (SD)	119 (8)	118 (11)	121 (10)	NA
Median	120	120	120	NA
Min., Max.	99, 132	102, 139	106, 139	NA
Weight (kg)				
Mean (SD)	25 (5)	25 (7)	28 (10)	NA
Median	24	23	26	NA
Min., Max.	16, 35	16, 42	18, 51	NA

Source: DMD114117 study report, page 60

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

According to the Applicant, baseline DMD characteristics were relatively balanced across treatment groups (Table 4). The time since first symptoms, diagnosis and first corticosteroid use in the intermittent group were slightly longer than the other two treatment groups which are consistent with the older mean age of this group. Mean baseline values for the 6MWD test were higher in the continuous group (427.61 m) than in the placebo (403.18 m) and intermittent (394.57 m) treatment groups.

Table 4 Baseline disease characteristics

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)	Total (N=53)
Time Since First Symptoms (months)				
Mean (SD)	63 (24)	61 (25)	64 (24)	63 (24)
Median	73	57	63	62
Min, Max	15, 95	27, 112	27, 105	15, 112
Time Since Diagnosis (months)				
Mean (SD)	44 (22)	45 (28)	48 (26)	45 (25)
Median	35	41	47	43
Min, Max	12, 82	3, 96	3, 105	3, 105
Time Since First Corticosteroid Taken (months)				
Mean (SD)	24 (14)	26 (21)	33 (17)	27 (18)
Median	22	14	34	26
Min, Max	7, 60	7, 69	7, 63	7, 69
Corticosteroid Regimen				
Continuous	11 (61)	12 (67)	9 (53)	32 (60)
Intermittent	7 (39)	6 (33)	8 (47)	21 (40)
6MWD (m)				
Mean (SD)	403 (45)	428 (70)	395 (67)	NA
Exon Mutation, n (%)				

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DMD 45-50 deletion	7 (39)	6 (33)	5 (29)	18 (34)
DMD 48-50 deletion	3 (17)	6 (33)	6 (35)	15 (28)
DMD 49-50 deletion	1 (6)	4 (22)	3 (18)	8 (15)
DMD 50 deletion	4 (22)	1 (6)	3 (18)	8 (15)
DMD 52 deletion	3 (17)	1 (6)	0	4 (8)

Source: NDA DMD114117 study report, page 61

Reviewer's Analysis and Comments on Baseline Characteristics:

The heterogeneity in the DMD population is well known (Humbertclaude 2012, McDonald 2013). Some advantage for 6mg/kg/week group was observed. Higher baseline function is almost always associated with slower long term decline (McDonald:

http://www.treatnmd.eu/downloads/file/meetings/2013/workshop/Session1/McDonald_NH.pdf

Subjects in the continuous treatment regimen appeared to have greater number of subjects that were < 7 years, on continuous steroids, higher mean baseline 6 MWD, greater number of subjects with baseline 6MWD of >400m, shortest time since first symptoms that is consistent with a younger more functional population that are all likely to have a slower decline, even though the average age was slightly higher for the continuous treatment. In addition, I looked for other disease characteristics that would enable the assessment of functional capabilities at baseline. Greater number of subjects on continuous treatment could jump with both feet up at the same time, hop with clearing foot and heel from floor at the same time, rise from floor <4 seconds and had the ability to rise from floor without gower's maneuver. These are considered milestones that can predict loss of ambulation (McDonald). The percentage of subjects across the treatment groups are shown in Table 5, suggesting subjects in the 6mg/kg/week group have higher functional capabilities and likely to have a slower decline in the 6MWD. The randomization was conducted as per the master randomization schedule generated via an interactive voice response system. Hence, these differences in treatment groups occur by random chance.

Table 5 Percentage of subjects with Baseline Characteristics

Baseline Factors	Continuous 6mg/kg/week	Intermittent 6 mg/kg/week	Placebo
Age <7 years	50%	30%	39%
6MWD>400m	61%	41%	50%
Rise From Floor <4 secs	44%	18%	22%
On continuous regimen	67%	53%	61%
Other factors:	100%	88%	77%
Ability to jump with both feet up at the same time			
Ability to hop with clearing foot and heel from floor	50%	29%	27%
Ability to rise from floor without gower's maneuver	27%	6%	11%

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Interaction between treatment and baseline 6MWD, age and steroids in a statistical model did not lead to any statistically significant interaction, but the study size is small and not powered to show any differences due to covariates.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No imbalances in concomitant medications were noted. All subjects were 80% to 120% compliant with dosing. The median dose (in mg) was the lowest in the continuous drisapersen treatment arm. These exposure differences likely arise due the higher % of younger kids in the continuous treatment arm as dosing is based on mg/kg. The duration of exposure was similar across treatment arms.

Efficacy Results – Primary EndpointApplicant's Primary Analysis and conclusions:

Based on the primary efficacy MMRM analysis for change from baseline in 6MWD at Week 25, there was a statistically significant treatment benefit for the continuous regimen [35 m; $p=0.01$ ($p<0.025$)] over placebo, but not for the intermittent regimen (Table 6). A similar analysis was also done at week 49. A treatment differences between drisapersen and placebo of 36 m and 27 m were observed for the continuous and intermittent groups respectively at Week 49. The continuous group showed some decline towards baseline after the initial increase in 6MWD up to Week 25, whereas the intermittent group was relatively stable over the 48 week time-period (Table 6).

Note: After Week 25, the biostatistics and programming team was unblinded, but the subjects, investigators and monitors were blinded. There was also a blinded, independent Medical Monitor assigned to the study from the point of unblinding for the Week 25 analysis, to maintain the integrity of medical decisions.

Table 6 Summary of MMRM Analysis of Change from Baseline in 6MWD (m)

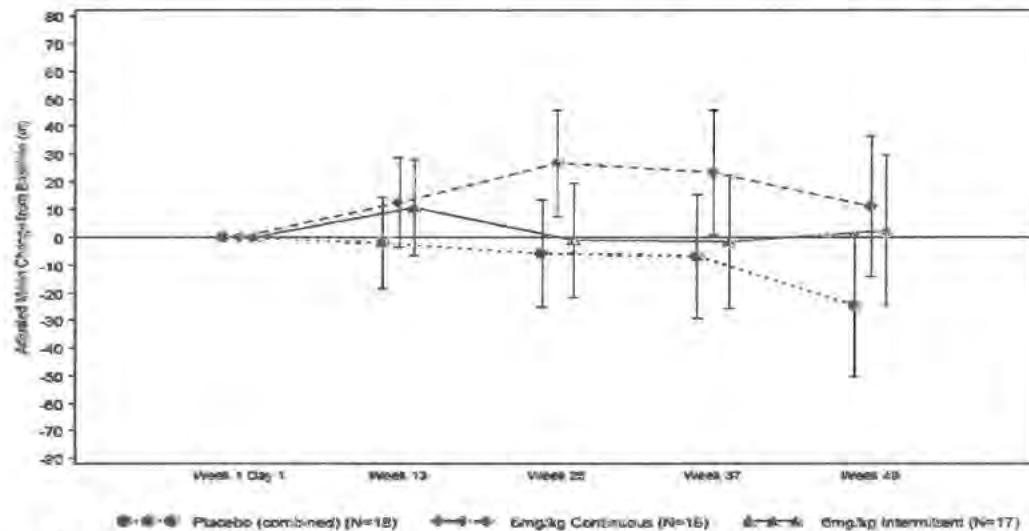
	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)
Baseline			
n	18	18	17
Mean (SD)	403 (45)	428 (70)	396 (70)
Week 25			
n	16	16	15
Adjusted mean change (SE)	-4 (10)	31 (10)	-0.1 (10)
Adjusted mean difference vs. placebo		35	4
95% CI		(8, 62)	(-24, 31)
p-value		0.01	0.80

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Week 49			
n	17	18	15
Adjusted mean change (SE)	-25 (13)	11 (13)	2 (14)
Adjusted mean difference vs. placebo		36	27
95% CI		(-0.11, 72)	(-10, 64)
p-value		0.05	0.15

Source: DMD114117 study report page 64

Figure 4 MMRM Analysis of Change from Baseline in 6MWD (m) at Week 49



Source: Study DMD114117 Study Report page 68

Interactions between treatment and age, baseline rise from floor, baseline lean body mass, baseline 6MWD, corticosteroid regimen and country grouping at week 25 showed only a statistically significant interaction ($p \leq 0.10$) for baseline rise from floor. The confidence interval was larger, so the applicant cautions the interpretation of this. In addition, the study size is small.

Reviewer's Comment: Note that not all subjects were included in the primary analysis at Week 25, since five subjects had their 6MWD assessment done at Week 24 and one subject at Week 27. A sensitivity analysis including these subjects gives a p value of 0.02 with a treatment difference of 31m for the continuous regimen compared to placebo (Table 7). The analysis at Week 49 was not a planned analysis and cannot be evaluated while controlling type 1 error.

Applicant's Sensitivity Analyses for the primary endpoint: The planned sensitivity analyses supported the primary analysis as shown in Table 7. Sensitivity analyses at week 49 support the MMRM analysis at week 49 (not shown in Table).

Table 7 Sensitivity analyses on change from baseline 6MWD at week 25 for drisapersen continuous regimen

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Analysis	Population	Dataset	Treatment Difference	95% CI	P-value
MMRM	PP	OC	38	(8, 68)	0.01
ANCOVA	ITT	OC	35	(7, 63)	0.01
ANCOVA	ITT	LOCF	31	(4, 57)	0.03
MMRM	ITT	OC (unslotted) ^a	31	(5, 58)	0.02
MMRM	ITT	OC (exc. outlier) ^b	31	(4, 58)	0.03
MMRM, Uncombined Placebo	ITT	OC	47	(12, 82)	0.01

Source: DMD114117 study report, page 66

- For reporting purposes, efficacy data were slotted to pre-defined visit windows, based on the time of the assessment since first dose. Where a visit was attending particularly early or late, the assessment would have fallen outside of the visit window and was thus excluded from analyses. This analysis of unslotted data, analyzed the data according to the investigator recorded visit, regardless of the time at which this occurred.
- Subject 3002, randomized to placebo intermittent was determined to be an outlier by the applicant (6MWD of 322 m, 432.2 m and 265 m at Baseline, Week 13 and Week 25 respectively): gained 110 m at Week 13.

Additional Analyses on 6MWD:

- MMRM analyses with placebo groups analyzed separately (continuous and intermittent placebo):
The treatment difference for the continuous regimen compared to continuous placebo was 47m. The placebo continuous and placebo intermittent performed differently (Table 8). The applicant is unclear of the difference in placebo response in the two regimens, but explains that this could be due to chance due to small group size combined with inherent inter-subject variability (including age).

Table 8: MMRM analyses with placebo groups analyzed separately

	Placebo Continuous (N=9)	Placebo Intermittent (N=9)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)
Baseline				
n	9	9	18	17
Mean (SD)	406 (49)	400 (43)	428 (70)	395 (70)
Week 25				
n	7	9	16	15
Adjusted mean change (SE)	-15 (14)	6 (13)	32 (10)	0.3 (10)
Adjusted mean difference vs. placebo			47	-6
p-value			0.01	0.72
Week 49				
n	9	8	18	15
Adjusted mean change (SE)	-36 (18)	-13 (18)	11 (13)	3 (13)
Adjusted mean difference vs. placebo			47	16
p-value			0.04	0.48

Source: NDA DMD114117 study report, page 69

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2. MMRM analysis in combined drisapersen regimens (continuous and intermittent combine):
No statistically significant difference ($p=0.12$) was observed at Week 25 when the two drisapersen treatment regimen groups were combined, but a nominal p -value of 0.05 was observed at Week 49 (Table 9).

Table 9 MMRM analyses of the combined drisapersen regimens

	Placebo (combined) (N=18)	6 mg/kg Drisapersen (combined) (N=35)
Week 25		
n	16	31
Adjusted mean change (SE)	-3 (10)	16 (7.4)
Adjusted mean difference vs. placebo		20
95% CI		(-5, 44)
p-value		0.12
Week 49		
n	17	33
Adjusted mean change (SE)	-25 (13)	7 (9)
Adjusted mean difference vs. placebo		31
95% CI		(0.5, 62)
p-value		0.05

Source: NDA DMD114117 study report, page 71

3. Change from baseline in 6MWD by response category:
Response was measured as the percentage of subjects that achieved a fixed change in 6MWD (≥ -30 m, ≥ 0 m, ≥ 30 m, ≥ 60 m or $\geq -10\%$, $\geq 0\%$, $\geq 10\%$, $\geq 20\%$ and $\geq 30\%$ change). Subjects could be included in more than 1 category. There were 19% subjects in the placebo and 38% drisapersen continuous arm and 20% in the intermittent arm that showed ≥ 30 m change in 6MWD at Week 25. A total of 31% subjects ($n=5$) in the drisapersen continuous arm and 13% ($n=2$) in the placebo group showed a $\geq 10\%$ change in 6MWD.
4. Change from baseline in percent-predicted 6MWD
As 6MWD distance is influenced by age and development, analysis of the percent-predicted 6MWD that takes these factors into account were conducted (Henricson 2012). The percent-predicted 6MWD in DMD provides an estimate of performance relative to a healthy control population. An increase in the percent-predicted 6MWD is consistent with functional improvement. A treatment benefit ($\sim 6\%$ difference) in favor of the continuous group over placebo was observed at both Week 25 ($p=0.01$) and Week 49 ($p=0.05$). The treatment difference over placebo with the intermittent regimen was 0.7% at Week 25 ($p=0.78$) and 5% at Week 49 ($p=0.14$).

Applicant's post-hoc analyses:

- MMRM analysis in subjects ≤ 7 years and > 7 years DMD:

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The 6MWD generally improves in boys until the age of 7 years (Henricson 2012). The sponsor's analysis showed a treatment benefit of 77 m in >7 years at Week 25 compared to 22 m for boys ≤7 years for the continuous regimen.

Reviewer's Comment: The sample size is too small for any interpretable subgroup analysis of age in this study.

A post-hoc analysis, when combining the patients on continuous and intermittent shows a treatment difference in favor of drisapersen at each time point and statistically significant p of 0.05 at Week 49. Combining the treatments appears reasonable as they have the same drug exposure at Week 49. This may suggest treatment benefit at Week 48, given a more heterogeneous population.

Data Quality and Integrity – Reviewers' Assessment

There are no issues with data integrity.

Durability of Response

The treatment difference of 35 m for the continuous drisapersen regimen is maintained for the 49 weeks. This is probably because the placebo declines more at Week 49, such that the effect size remains the same at Week 48. For the continuous arm, the change from baseline in 6MWD declines after Week 25. It is unclear if this is due to the variability in the measure or a true treatment effect (Figure 9).

Efficacy Results – Secondary and other relevant endpoints

Applicant's key conclusions:

- None of the secondary endpoints showed a statistically significant treatment difference from placebo at Week 25 or 49 (Table 11, Week 49 summary). The frequency of worsening was variable and greater at Week 49 for most endpoints.
 - **Timed Function Tests (rise from floor, 10 m walk/run, and 4-stair climb/descent):**
 - The primary efficacy was supported by directionally favorable trends (non-significant) for the continuous group compared with placebo at Week 25 and 49 (Table 11) for Timed Function Tests
 - The intermittent regimen showed inconsistent and variable results for different timed functions tests at Week 25, but a trend favoring treatment at Week 49.
 - **NSAA:** Both treatment groups showed a favorable treatment difference relative to placebo in NSAA total scores, which was more pronounced at Week 49. The applicant states that when assessed against natural history, the differences between drisapersen and placebo at 49 weeks (continuous, 2.50; intermittent, 2.29) appear to be clinically meaningful.

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Figure 5 MMRM Analysis of change from baseline for NSAA at each visit

- Muscle Strength and Pulmonary Function Tests:** Small decrease from baseline in mean total muscle strength was observed in the continuous and intermittent treatment groups, compared to an increase in the placebo group at Week 25. At Week 49, small improvements in mean total muscle strength was observed in the continuous group, but the intermittent group muscle strength remained similar to that at baseline and overall still worse than placebo. The variable small changes in pulmonary function tests were similar across treatment groups.
- PedsQL neuromuscular module questionnaire:** PedsQL showed a trend for improvement (higher scores indicating better quality of life) for the continuous group compared with placebo but not for the intermittent regimen (Table 10).

Table 10 Summary of Change from Baseline in PedsQL Total Score for both regimens

Assessor	Change from Baseline in PedsQL Total Score					
	Placebo (combined) (N=18)		6 mg/kg Drisapersen Continuous (N=18)		6 mg/kg Drisapersen Intermittent	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Child						
Baseline	18	80 (10)	18	78 (9)	16	82 (10)
Change from Baseline at Week 25	17	-4 (11)	17	4 (6)	15	-4 (10)
Change from Baseline at Week 49	17	0.4 (12)	18	7 (9)	13	-0.2 (8)
Parent						
Baseline	18	76 (11)	18	78 (11)	17	77 (14)
Change from Baseline at Week 25	18	-2 (5)	18	-0.9 (7)	16	-3 (6)
Change from Baseline at Week 49	18	-4 (12)	17	0.3 (7)	15	-2 (7)

Source: Adapted from Study DMD114117 Study Report

Note: The PedsQL total score ranges from 0 to 100, where higher scores indicate better health-related QoL

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Table 11: Secondary Endpoints at week 49

Treatment	n	Baseline Mean (SD)	Adj. Mean Δ from Baseline (SE) at Week 49	Treatment Difference	95% CI	p-value
NSAA Total Score						
Placebo	17	26 (4.4)	-2.7 (1.1)			
Drisapersen 6 mg/kg/wk	18	27 (4.5)	-0.2 (1.0)	2.5	(-0.4, 5)	0.09
4 Stair Climb Ascent Velocity (stairs/s)						
Placebo	17	3.5 (1.6)	1.0 (0.5)			
Drisapersen 6 mg/kg/wk	18	3.1 (1.2)	0.8 (0.5)	-0.2	(-1.7, 1.2)	0.72
10 m Walk/Run Velocity (m/s)						
Placebo	17	5 (0.8)	0.8 (0.3)			
Drisapersen 6 mg/kg/wk	18	5 (1.2)	0.1 (0.3)	-0.7	(-1.3, 0.05)	0.07
Rise from Floor (s)c						
Placebo	17	5 (1.0)	3.8 (1.2)			
Drisapersen 6 mg/kg/wk	18	5 (1.7)	0.9 (1.2)	-3	(-6.2, 0.4)	0.08
4 Stair Climb Descent Velocity (stairs/s)						
Placebo	17	3 (0.9)	0.3 (0.4)			
Drisapersen 6 mg/kg/wk	18	3 (0.7)	0.0 (0.4)	-0.3	(-1.5, 0.8)	0.57
Muscle Strength Total Score (lbs)						
Placebo	17 18	122 (28)	7.5 (5)			
Drisapersen 6 mg/kg/wk		124 (23)	5.9 (5)	-1.6	(-15, 12)	0.82

Source: Adapted from Study DMD114117 Study Report

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- **Serum Creatine Kinase:**

In early stages of DMD, increased muscle cell permeability (due to absence of dystrophin and increased membrane fragility) causes muscle specific enzymes such as creatine kinase to leak out of the cell. It is hypothesized that an improved membrane integrity induced by production of dystrophin can result in reduction of serum CK. At Week 25, there was a decline in CK for both drisapersen treatment arms compared with placebo, with a slightly greater treatment difference for the intermittent treatment group than the continuous treatment group. At Week 49, there was a trend of CK decline in both drisapersen arms compared with placebo, though the effect was smaller at Week 49 compared to Week 25 (Figure 6).

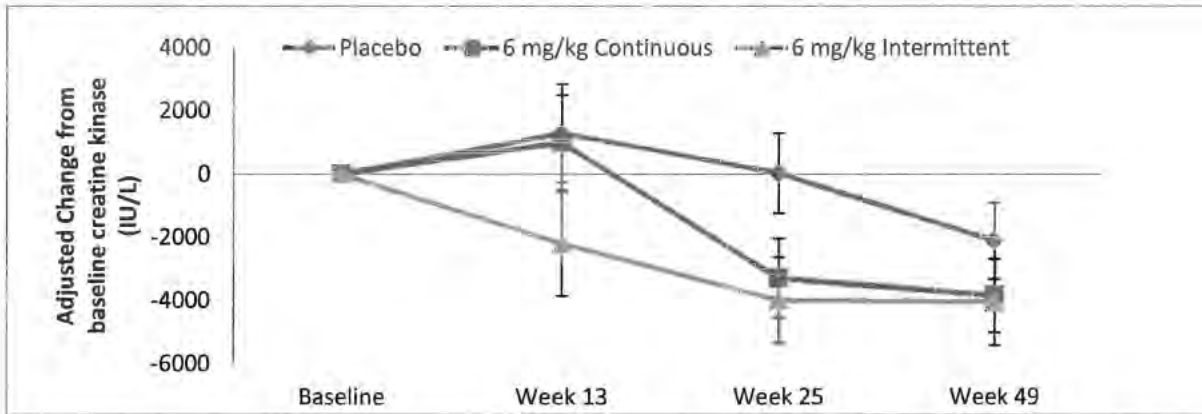
Table 12 Summary of MMRM Analysis of Change from Baseline in Creatine Kinase Serum Concentration (IU/L)

	Placebo (combined) (N=18)	6 mg/kg Drisapersen Continuous (N=18)	6 mg/kg Drisapersen Intermittent (N=17)
Baseline			
n	18	18	17
Mean (SD)	9525 (5415)	12267(6297)	14023 (7561)
Week 25			
n	18	17	16
Adjusted mean change (SE)	-62 (1290)	-3268 (1273)	-4093 (1390)
Adjusted mean difference vs. placebo		-3206	-4031
95% CI		(-6779, 366)	(-7844, -218)
p-value		0.08	0.04
Week 49			
n	18	18	14
Adjusted mean change (SE)	-2115 (1210)	-3851 (1169)	-4056 (1361)
Adjusted mean difference vs. placebo		-1736	-1941
95% CI		(-5090, 1618)	(-5601.86, 1720.15)
p-value		0.30	0.29

Source: page 88; check log transformed data

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Figure 6 MMRM Analysis of change from baseline of serum creatine kinsase (IU/L)

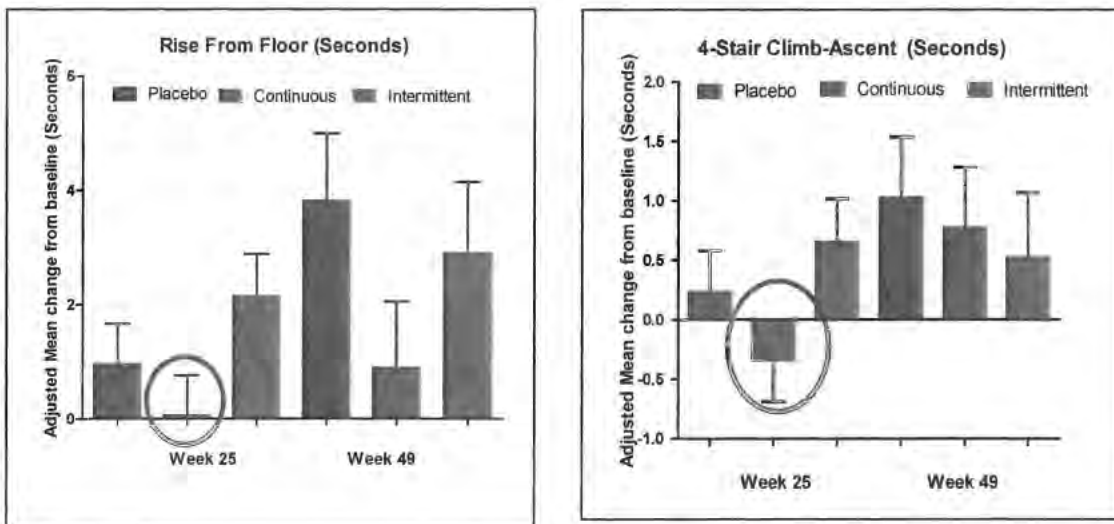


Reviewer’s Assessment of Secondary Endpoints:

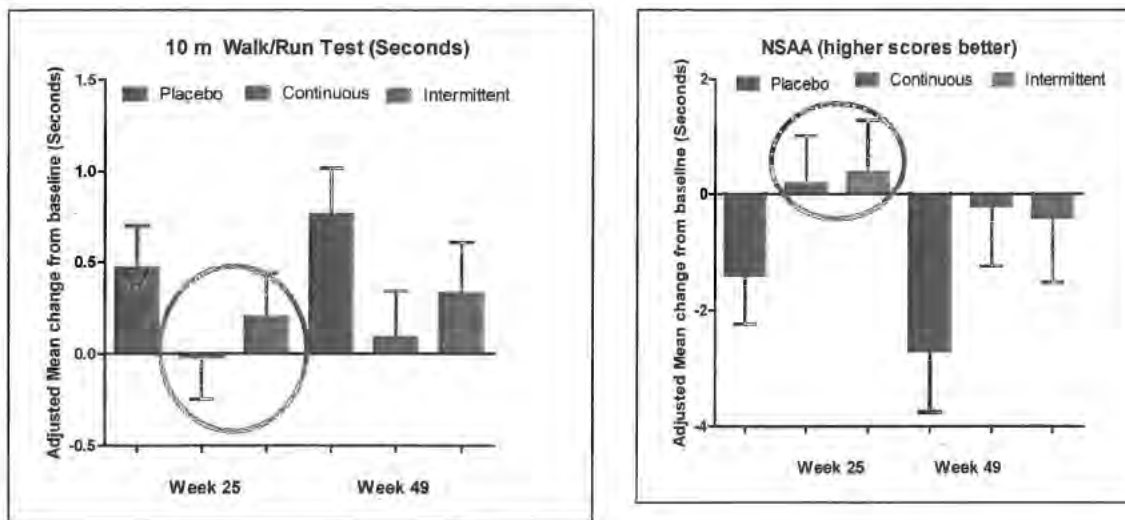
The secondary endpoints were not analyzed in a hierarchical manner and no endpoint was assigned as key endpoint, therefore the interpretation of these multiple endpoints is difficult.

Timed Function Tests: The adjusted mean changes from baseline for the Timed Function tests and NSAA are graphically presented in Figure 7. NSAA scores stay stable for the 48 weeks for the continuous arm, but NSAA is shown to be stable in patients below the age of 7 years in the first year [+0.15 (SD 4.8)] (Mazzone 2013) and the continuous arm had higher percentage of subjects <7 years. All endpoints show a trend of improvement with the continuous regimen at Week 25 as shown by the circled data, which worsens at week 49, but remains better than placebo.

Figure 7 MMRM analysis of secondary endpoints at Week 25 and 49



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All Timed Function scores had 6 gradings (with 1 being unable to do the task and 6 easily do the task with least maneuvers). Very few subjects showed improvement in the grading scores ($n \leq 3$) for Timed Function Tests, with the exception of 4-stair climb descent where 6 subjects showed improvement in the continuous group (e.g. holding one handrail vs. two handrails) compared to 2-3 subjects in the placebo and intermittent groups.

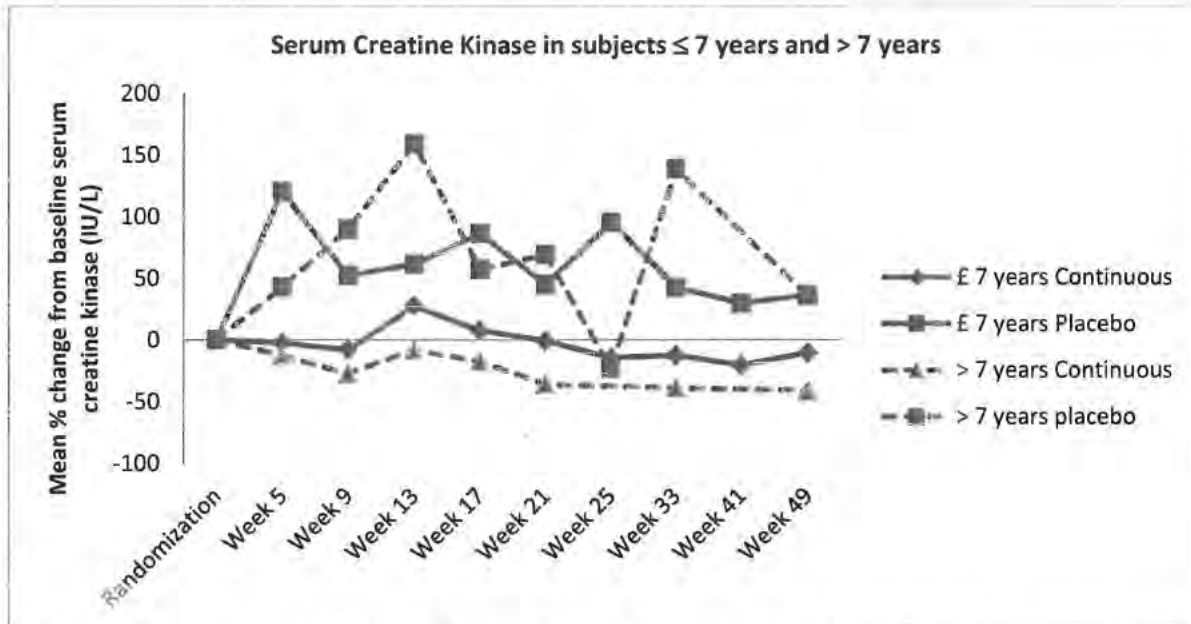
Peds QL: Parents perception of the problem was greater than that of the child's (e.g. More parent felt that their Child's leg hurts, child feels tired, child's back is stiff, wakes up tired etc.) at baseline. There was no systematic trend in the change from baseline at different visits. Many items on the PedQL neuromuscular module related to upper extremity weakness that are not likely to be impacted in an early ambulatory population (such as, My hands are weak, Hard to use my hands, long time to eat, hard to breath) and hence insensitive to overall meaningful change.

Creatine Kinase: Both drisapersen treatment arms showed a decline in CK compared to placebo, suggesting improvement in muscle cell integrity. However, this finding is associated with several confounders: CK levels are remarkably variable, with large within patient and between patient variability and are known to fluctuate day to day. It is affected by diurnal variation (increase during the day and decrease at night), exercise (reduced with inactivity), steroid use, and age (reduced with advancing age of the DMD boys as the muscle fibers are replaced with fat and fibrous tissue). There is no evidence of inactivity of the subjects from the Patient or Parent Reported Outcome measures, but the day to day activity level is unknown. The pain and discomfort from the injection site reactions could plausibly make the subjects less active.

Since CK peaks at ages 3-5 years and declines with age with levels reduced to 50% by age 7 years, I looked at the mean percent reduction of CK based on age. The following Figure shows the percent reduction in CK with treatment compared to placebo in subjects, ≤ 7 years and > 7 years. It is interesting to note that in this study Subjects >7 years had larger mean reduction in CK (-41%)

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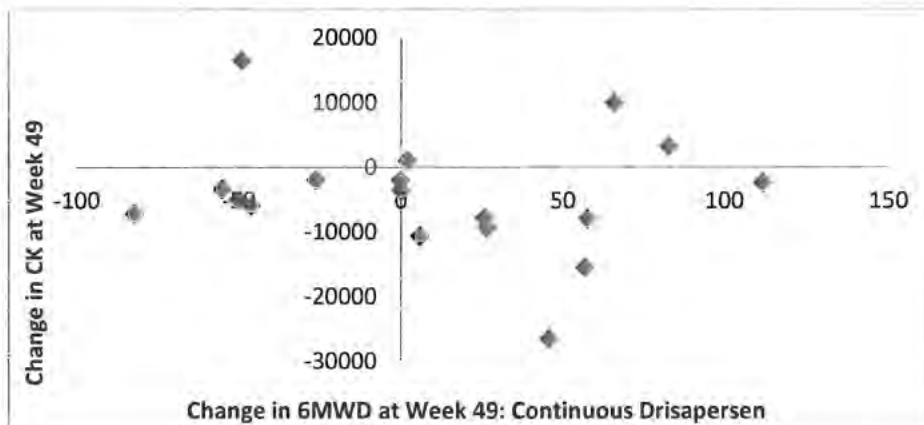
compared to subjects ≤ 7 years (-11%). This is consistent with a sub-group post-hoc analysis conducted by the applicant showing larger treatment benefit in older subjects. Given the small number of subjects and the large variability in the CK levels, this could be a chance finding and unreliable being post-hoc in nature. As a result of these confounding factors, a true treatment effect of a reduction in CK is difficult to discern.



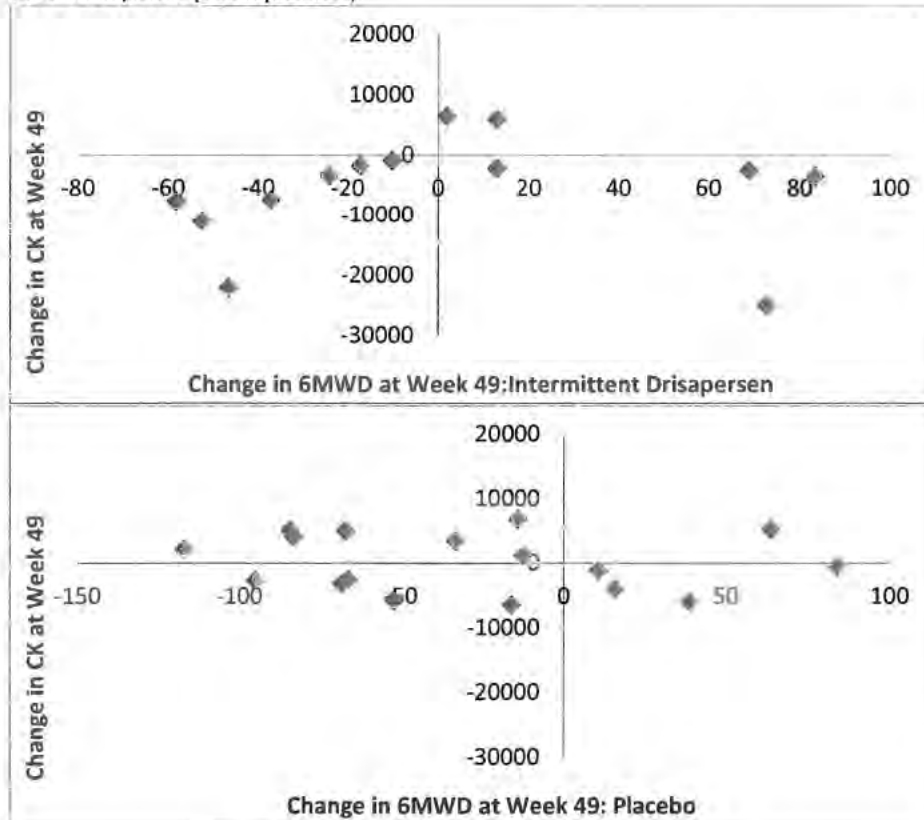
Note: Standard Deviations are not plotted as the variability is very high and overlaps between groups, including error bars constricts the graphs considerably

The following figures show the relationship of change in 6MWD and change in CK at Week 49.

- No clear relationship between change in 6MWD and CK was observed at Week 49. The sample size of this study and the variability in the endpoints may preclude the ability to see any relationship in this study.
- There were a higher number of subjects showing a decline in CK in the drisapersen arm compared to the placebo arm.



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Dystrophin Measurements

Muscle biopsies from the tibialis anterior (TA) were obtained from most subjects and from the quadriceps of 5 subjects at baseline and at Week 25 and were analyzed using the following methods:

- Detection of exon 51 skipped mRNA by Reverse Transcription-Polymerase Chain Reaction (RT-PCR)
- Detection of dystrophin protein expression by:
 - Qualitative Western blot analysis (WB).
 - Qualitative immunofluorescence assay (IFA), including percent change from baseline.

Dystrophin exon 51 skipped-mRNA measured by RT-PCR

Exon 51 skipped mRNA was detected in 2/18 (12%) of subjects in the continuous group and 5/17 (29%) of subjects in the intermittent group compared to 0/18 subjects in the placebo group at week 25, as shown by increased intensity. Increase in exon skip was detected more in quadriceps biopsy (3/4, 75%) compared to TA muscle biopsy (4/30, 13%). An increase in Exon 51 skip intensity was defined as: skip copies/ non skipped copies (Post treatment –pre-treatment/pre-treatment)*100>1%

OBP Reviewer Dr. Rao's Comment on methodology:

The gel-based PCR method used by the applicant was not quantitative because it involved a visual assessment of whether or not a band for the skipped mRNA product was observed. In addition to treated samples, baseline samples also showed exon 51 skipped band in 100% of

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patients. See Appendix B for additional comments on the impact of revertants on the PCR data and the limitations of measuring dystrophin mRNA.

With nested RT-PCR there was no apparent increase in median PCR fragment intensity at week 25 when comparing to pre-treatment biopsies for the drisapersen continuous group (Table 13). The applicant attributes this variable finding to the low number of subjects. There is also large variability in the samples in each group that obscures any conclusion of increase in dystrophin.

Table 13 Intensity of exon 51 skipped dystrophin mRNA product by nested RT-PCR

Study Treatment	Exon Skip (a.u) Mean (SD)	
	Week 0	Week 25
Placebo	1.30 (1.01)	0.73 (0.41)
Weekly 6mg/kg	1.29 (2.42)	1.30 (1.50)
Intermittent 6mg/kg	1.72 (2.38)	2.60 (1.29)

OBP Reviewer Dr. Rao's Comment on methodology:

The nested PCR approach used should provide the applicant greater specificity for detecting their exon skipped product because a second set of primers and PCR run were used to amplify a narrower region of the same target mRNA. However, this method does not provide absolute quantitation because no reference standard was used to provide a calibration curve. The quantitation provided with arbitrary units is derived from the relative band density of other samples and does not necessarily reflect copy numbers of the skipped product. See Appendix B for additional comments and supporting references.

Dystrophin Protein by IFA:

With IFA, an increase in the mean dystrophin of the entire fiber population was observed in 9/15 (60%) subjects in the continuous group and 4/15 (54%) subjects in the intermittent group compared with only 1/17 (6%) subject in the placebo group. An increase in dystrophin was defined as an increase in mean membrane intensity of more than 4% at week 25 compared to pre-treatment biopsy. The dystrophin intensity as measured by IFA is shown in Table 14. Mean percent change shows a 3% increase in dystrophin in the drisapersen continuous group compared to a 3% decrease in placebo. The Mean % change in the intermittent group was minimal.

Table 14 Dystrophin Intensity measurement by IFA (change from baseline at week 25)

	Muscle	Placebo (combined) (N=18)		6 mg/kg Drisapersen Continuous (N=18)		6 mg/kg Drisapersen Intermittent (N=17)	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Non-Qualified Mean	Quadriceps	0	0	2	4.0 (6)	1	30.0 (0)*

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Percentage Change (%)	Tibialis Anterior	17	-3 (5.3)	14	3.5 (6.9)	15	0.9 (8.6)
	All	17	-3.1 (5.3)	16	3.5 (6.7)	16	2.7 (11.0)
Non-Qualified Q90 Percentage Change (%)	Quadriceps	0	0	2	0.5 (6.4)	1	46.0 (0)
	Tibialis Anterior Muscle	17	-2.6 (7.1)	14	5.7 (10.0)	15	2.6 (10)
	All	17	-2.6 (7.1)	16	5.0 (9.6)	16	5.3 (14.3)

Q90 mean is the mean fiber membrane of the 10% brightest pixels in the membrane

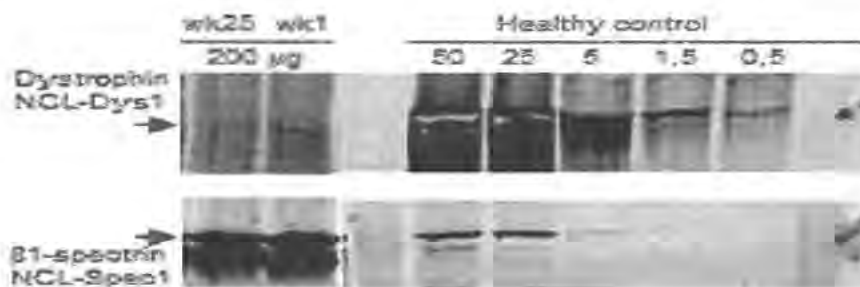
*Subject 2101 had the highest drisapersen concentration in the quadriceps (130 µg/g) and also the highest dystrophin

OBP Reviewer Dr. Rao's Comment on methodology:

No correlative human endpoint data (e.g. muscle function or dystrophin-associated protein complex (DAPC) protein co-localization) has been presented to support the biological/clinical significance of this scoring. See Appendix B for additional comments.

Dystrophin Protein by Western Blot:

With WB, an increase in the mean dystrophin intensity was observed in 5/17 (29%) subjects in the continuous group and 5/16 (31%) subjects in the intermittent group compared with 0/17 (0%) subject in the placebo group. An increase was defined as: $(\text{post treatment} - \text{pre-treatment}/\text{pre-treatment}) * 100 > 30\%$.



For western blotting, the applicant included serial dilution of a healthy control sample on each gel, although comparison between pre- and post-treatment samples from the same patient was used for scoring. No comparison was made to the values between the healthy controls dystrophin and the test samples.

Reviewer's Assessment:

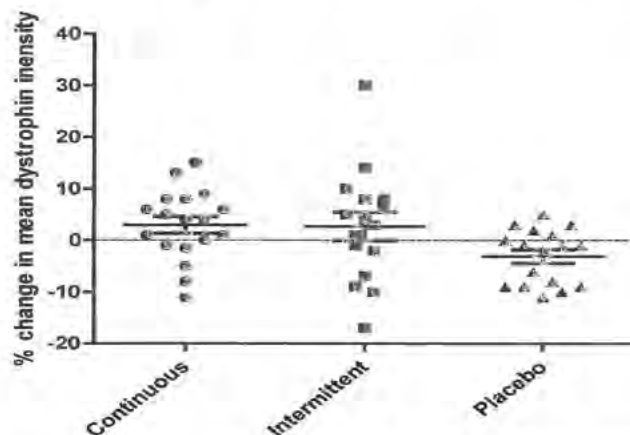
With WB, because baseline expression was at or below the lower limit of detection, the ratio of pre- to post-treatment expression in some cases was similar to "dividing by zero" leading to very high percent increases (up to 2500%) when the post-treatment expression level was only trace (about 1/3rd of 1% of normal levels). Some subjects similarly showed a large percent decrease in expression post-treatment likely due to small variations in measurements that were near zero.

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In response to an FDA request about relative dystrophin in healthy tissue, the applicant provided data from five donor samples that show a range of 58-115% of the mean dystrophin value in quadriceps and 87-118% in tibialis anterior. Immunofluorescence results also showed similar variability and have been published by Beekman et al (2014). The applicant also states that the mean dystrophin intensity in the pre-treatment DMD biopsies can be estimated to be 0.3% of a particular control. In all but one post-treatment sample, the applicant estimates that the percentage of dystrophin detected was less than 1%, which they claim is the lower limit of detection for their assay.

The individual subject change in mean dystrophin intensity by IFA in the three groups is shown in Figure 8. There is a trend towards greater mean dystrophin intensity (by IFA) in the drisapersen treatment groups compared to placebo. There is an increase in dystrophin expression in higher number of subjects in the continuous drisapersen regimen. However, the small mean *increase* of 3-5% *from baseline* is unlikely to be biologically relevant.

Figure 8 % change in mean dystrophin intensity in individual subjects (IFA)



There was no clear relationship between the changes in dystrophin expression (as measured by IFA at Week 25) in the biopsy of the TA and the primary endpoint, the 6MWD at Week 25 or Week 49 (not shown).

A pharmacodynamic response was not detected in 30-40% treated patients. The applicant speculates that this could be related in part to: differences in characteristics of individual subjects (including but not limited to: stage and rate of disease progression; age; total weight; and muscle exposure on an mg/kg basis); treatment regimen, continuous vs. intermittent treatment (continuous showed a more consistent pharmacodynamic effect); and muscle group analyzed. TA muscle is relatively well preserved in the disease and therefore possibly less permeable to drug delivery and histological improvement difficult to detect in TA muscle. It is noteworthy that only 2 subjects in the continuous group and 2 subjects in the intermittent group showed an increase by all three methods. Dr. Rao's assessment of this overall conclusion is given below.

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OBP Reviewer Dr. Rao's Comment:

A clear, consistent, and positive correlation between all three assays - IFA, WB, and Exon skip has not been established by the Applicant or published literature in the field using appropriate positive/negative controls (e.g. with BMD, DMD, healthy samples in the linear range). Taylor et al have reported a correlation between immunofluorescence-based intensity ratios of dystrophin/spectrin and dystrophin protein levels measured by Western blotting and normalized to actin. As presented by the applicant, the WB data is likely to be most reliable because a serial dilution with a healthy positive control was used for comparison and pre-treatment and post-treatment samples were run on the same gel in most instances. The IFA can suggest protein localization but is likely to be less meaningful for protein level quantitation. See Appendix B for additional comments on the caveats about each method.

Reviewer's overall assessment/discussion:

The strengths of Study DMD114117 are:

- Primary endpoint (change from baseline 6MWD at Week 25) was positive for the continuous drisapersen treatment regimen with a treatment difference from placebo of 35 m ($p=0.014$) based on Applicant's pre-specified analysis.
- At Week 49 a similar *treatment difference* from placebo of 36 m was observed for the continuous drisapersen treatment regimen.
- Secondary endpoints measuring functions similar to walking [timed function tests (rise from floor, 10 m walk/run, and 4-stair climb/descent), and NSAA] also had directionally favorable trends for continuous treatment group at both Week 25 and 49, although not statistically significant. The secondary endpoints were not analyzed in a hierarchical manner, therefore the interpretation of these endpoints are difficult. Muscle strength did not favor drisapersen. Small changes in pulmonary function were similar across treatment groups.
- The percent reduction in serum creatinine kinase concentrations was 30-40% in the drisapersen treatment groups ($p=0.08$ and 0.04 at Week 25 for the continuous and intermittent regimen, respectively) compared to placebo.

Some of the weaknesses of the study results are:

- The intermittent drisapersen treatment group did not show a statistically significant treatment difference.
 - Both the continuous and the intermittent regimen have comparable total doses administered for the duration of the study.
 - Both regimens have identical plasma-concentration time profiles and should perform similarly (15% higher plasma AUC₀₋₂₄ at Week 29 for the intermittent regimen).
 - The applicant states in the ISE that the difference between the intermittent and continuous treatment may have reflected the differences in age and advanced disease (time since diagnosis and duration of steroid treatment) in the intermittent group.
 - A post-hoc MMRM analysis with the two regimens combined showed a non-statistical difference from placebo of 20 m ($p=0.12$) at Week 25 and a treatment difference from placebo of 31 m ($p=0.05$) at Week 49. Given the

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heterogeneity in the DMD population and in the study arms (as discussed below), a combining the two regimens suggest a treatment benefit with drisapersen at Week 49 and may be viewed as a strength of this study, even though post-hoc in nature.

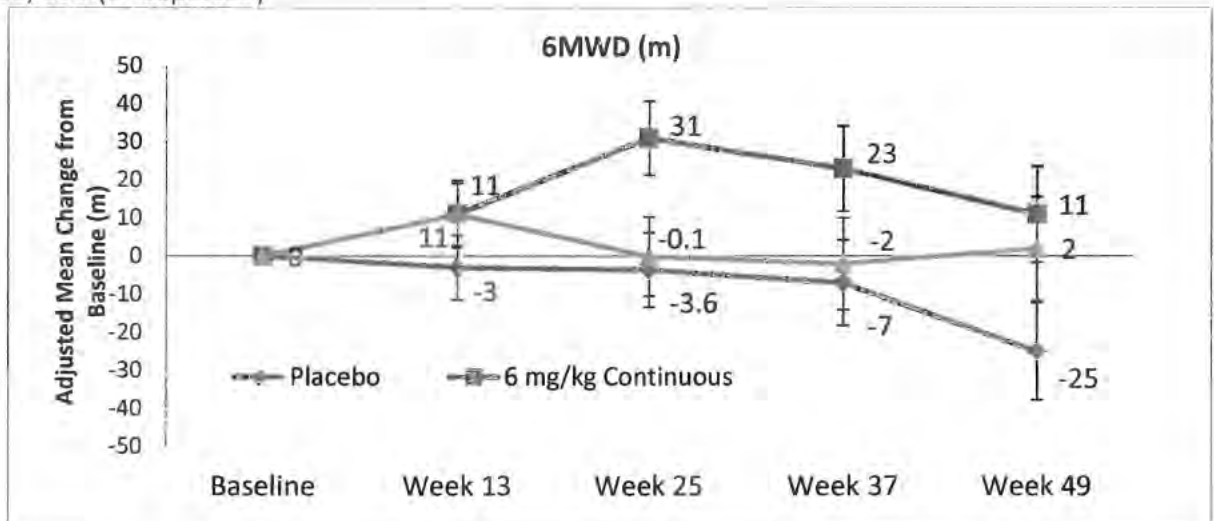
- Potential partial unblinding to the assigned treatment due to injection site reactions: Unblinding could affect the performance of 6MWD, which is considered an effort dependent endpoint. The incidence and the duration of injection site reactions was the largest for the 6 mg/kg continuous group and the least for placebo.
- Dystrophin expression increased *very slightly from baseline* in drisapersen treated subjects compared to placebo in some subjects

Discussion on primary endpoint 6MWD:

- The drisapersen continuous group appeared to consist of boys with less functional impairment compared to other treatment arms as discussed on page 37.
 - The continuous group shows an initial increase in *change from baseline* 6MWD at Week 13 and 25 and declined in subsequent weeks.
 - Figure 9 shows the magnitude of change from baseline at each time point. Improvement at Week 13 with both regimens could also be consistent with unblinding bias or the natural variation in the population. The change from baseline in the intermittent group on the other hand showed stability in the 48 weeks. The natural history studies also show that some subjects can remain stable in their ability to walk as assessed by 6MWD for 1-2 years before they begin to decline. It is uncertain if the improvement at Week 25 followed by decline is due to variability or a treatment effect.
- The applicant includes in their discussion of the study: "It is not known whether the apparent increase and decline in 6MWD in the continuous regimen versus the relative stability in the intermittent regimen is due to the drug effect or simply a result of natural variation in the population. Longer term treatment data and data from a larger number of subjects are needed to determine such an effect (page 134 of study report)."

Figure 9 MMRM Analysis of change from baseline in 6MWD

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- The natural history data as published in the literature also show variation on the reported decline in 6MWD (-22 to -58m per year based on literature). Given these concerns the benefit seen with the continuous drisapersen treatment group at week 25 may be a result of population variation (as shown in differences in disease characteristics at baseline), especially given that the intermittent regimen had a different treatment effect, as also speculated by the applicant. In DMD, fatigue and falls have been shown to be critical factors of six-minute walk distance variability. Motivation, concentration are other factors of variability for an effort dependent endpoint. The injection site reactions experienced by the subjects could add to the bias as well. Recent published data (Bello 2105) suggest that there are genetic modifiers that can either be associated with milder (LTBP4) or more progressive phenotypes (osteopontin gene-SPP1).

On secondary endpoints:

- The baseline imbalances in the continuous group would affect the secondary endpoints in a similar way.
- There was a greater decline in CK concentrations in the drisapersen intermittent treatment group compared to the continuous group, which is inconsistent with what was seen with 6MWD, NSAA, Rise From Floor, 10 m walk/run, nevertheless there was greater reduction in CK in drisapersen treated groups compared to placebo. There is a lot of variability in the assessment of CK that this may not be as concerning.

6.2. Study DMD 114876

6.2.1. Study Design

Overview and Objective

The primary objective of this study was to assess efficacy of 2 different doses of subcutaneous drisapersen versus placebo administered over 24 weeks in ambulant subjects with DMD. The

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secondary objectives were to assess safety, tolerability, PK, dystrophin half-life and persistence of efficacy at 48 weeks.

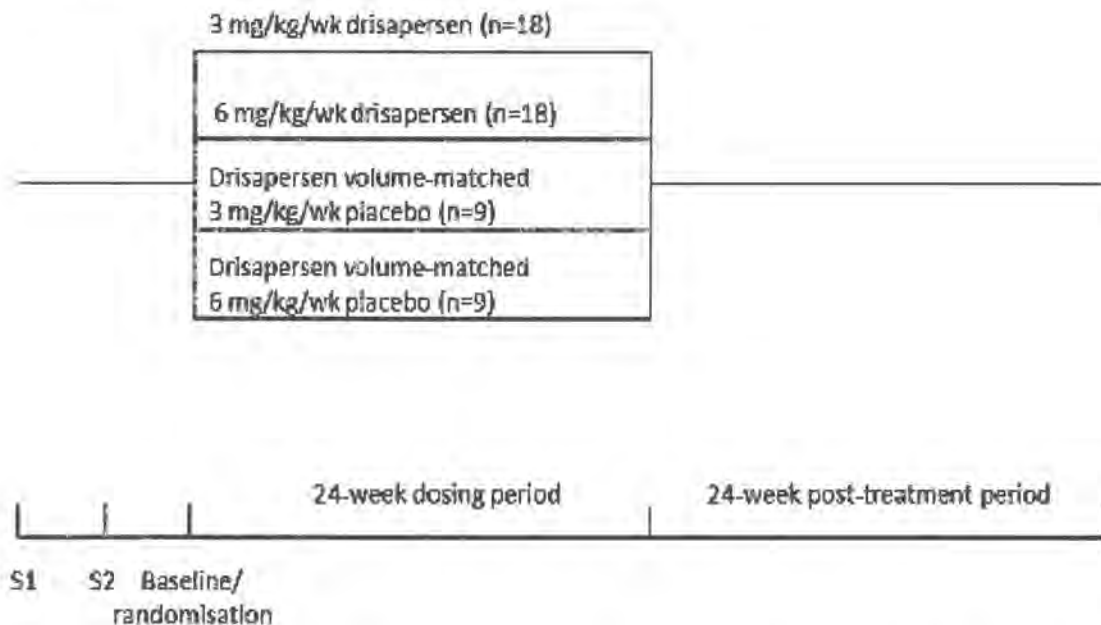
Studied period: 26 Oct 2011-4 Nov 2103

Study center(s): 13 centers in the United States

Trial Design

The study design was similar to study DMD114117, with the exception of a treatment period of only 24 weeks: and included 2 doses. The study design schematic is given in Figure 10. Screen 1 and 2 were 4 and 2 weeks prior to randomization, respectively. After the last dose of drisapersen /placebo, subjects continued into a 24 week post-treatment period off drug, after which subjects had the option to enter an open label extension study with drug treatment or have a 20 week follow up if the patient did not enter the open label extension. There were no life style restrictions during the study.

Figure 10 Study design schematic for Study DMD114876



Population: N=54 ambulant DMD boys with a mutation corrected by exon 51 skipping. The sample size is not based on statistical considerations.

Key Inclusion Criteria: Same as Study DMD114117.

Amendment 3 of the protocol changed the rise time from floor to ≤ 15 seconds from ≤ 7 seconds (without aids/orthoses)

Key Exclusion Criteria: Same as Study DMD114117 with the addition of:

- Baseline platelet count below the Lower Limit of Normal
- aPPT above the Upper Limit of Normal
- History of significant medical disorder which may confound the interpretation of either efficacy or safety data e.g. inflammatory disease

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Dosing Regimen:

Subjects were randomized to the following in 2:2:1:1 ratio using Interactive Voice Response System:

- 3 mg/kg/week SC drisapersen for 24 weeks (N=18)
- 6 mg/kg/week SC drisapersen for 24 weeks (N=18)
- 3 mg/kg/week SC placebo for 24 weeks (N=9)
- 6 mg/kg/week SC placebo for 24 weeks (N=9)

Injections were rotated on different sites in the abdomen, back, arm and thighs. Volume of placebo was matched to the dose to maintain the blind and limit bias. The different doses were not fully blinded, but administered by personnel not involved in efficacy assessments (Subjects on 3 mg received a lower volume of injection). Blinding of the study was maintained until completion of Week 24 assessment. After the 24 week analysis, the results were not communicated to the investigators or monitors.

The purpose of the post-treatment phase was to model the half-life of dystrophin, assess maintenance of response, and provided information about resolution of adverse event and laboratory abnormalities following cessation of treatment.

Study Endpoints

The following efficacy assessments were assessed at screening (1 and 2), randomization, week 24 or early withdrawal and week 48 or follow-up unless specified otherwise.

The primary efficacy endpoint were the same as Study DMD114117: 6MWD at week 24
6MWD

The secondary efficacy endpoints were also the same with the exception of the following additional secondary endpoints:

- The pulmonary function tests included (FEV₁, FVC, PCF, PF, sniff pressure test)
(Study DMD114117 had MIP and MEP instead of sniff pressure test)
- Clinical global Impression of Improvement
The CGI-I was measured on a 7-point Likert scale (1 = 'very much improved', 2 = 'much improved', 3 = 'minimally improved', 4 = 'no change', 5 = 'minimally worse', 6 = 'much worse', 7 = 'very much worse').
- Functional Outcome Assessments:
 - Physician Assessment of Daily Living [the ability of the subject to perform usual day-to-day activities (e.g., general health, mobility, general daily activities)]
 - Functional Outcomes Survey by Family/caregiver

Most secondary endpoints were not assessed at week 48, with the exception of CGI and Functional Outcomes Survey. Pediatric Quality of Life was not a secondary endpoint in this study.

Other:

- Dystrophin expression (muscle biopsies from tibialis anterior) was done at baseline, Week 24 in all subjects, and an randomly assigned third biopsy at Week 12 or Week 36 visit
- mRNA production in muscle tissue.
- Drisapersen in muscle tissue

Exploratory endpoints: at baseline, week 24 and 48

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- A set of T1-weighted (T1w) images to assess the level of fat infiltration and quantified according to the Mercuri scale and apparent fat fraction and set of T2-weighted (T2w) images to assess the combined effects of fat infiltration and edema and quantified according to the normalized T2-weighted signal intensity and T2 relaxation rate in skeletal muscle in the thigh as determined by structural MRI measures over time (optional for subjects). MRI scans of the mid-thigh were performed.
- 6MWD at week 48

Statistical Analysis Plan

Efficacy parameters were analyzed using the ITT population (same definition as Study DMD114117).

Primary Endpoint Analyses: Primary assessment of efficacy data was conducted using MMRM at week 24 on the Observed case (OC) data. The analysis was similar to Study DMD114117. Due to the two different doses, Type 1 error rate was preserved by utilizing a hierarchical approach, with 6 mg being assessed first. If no statistically significant difference was observed between the 6 mg/kg dose and placebo, then further analyses of the 3mg/kg dose were considered exploratory.

Sensitivity Analyses for primary endpoint: Same as Study DMD114117

Secondary endpoint analyses:

- For continuous endpoints ANCOVA analyses on OC data, with fixed terms of treatment center and baseline score (For Study DMD114117 MMRM analysis on OC data was used)
- Kaplan-Meier and Log rank test on time to event endpoints such as loss of ambulation

Protocol Amendments

Protocol amendments related to efficacy assessments are summarized below.

Amendment 1 (09 Sep 2011)	No significant change that would affect efficacy assessments
Amendment 2 (27 April 2012)	Muscle Biopsies to be conducted after functional efficacy assessments, no more than seven days after the scheduled visit.
Amendment 3 (09 Aug 2012)	Able to rise from floor in ≤ 15 seconds (without aids/orthoses) at Screening Visit 1 and Screening Visit 2 instead of in ≤ 7 seconds (without aids/orthoses) in the original protocol. Sponsor's rationale: A review of blinded data from other ongoing Drisapersen studies suggests an increase to the RFF inclusion criteria to include subjects with RFF up to 15 seconds at screening should not increase the likelihood of subjects losing ambulation during the study or increase variability in the 6MWD significantly. It will enable more potential subjects in this rare disease to be eligible.

Reviewer's Comment: The impact of including subjects with rise from floor in ≤ 15 seconds will be discussed in the results section.

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Data Quality/ Integrity and Good Clinical Practices: Sponsor's Assurance

Management of clinical data was performed in accordance with GSK standards. The study was conducted in accordance with ICH GCP (ICH E3 and E6) and applicable country-specific requirements. Written commitments were obtained from investigators to comply with GCP. Study was conducted with written informed consent from subjects and their parents.

6.2.2. Study Results

Patient Disposition

All 51 subjects completed the study. The distribution of subjects in each group is given in Table 15.

Protocol Violations/Deviations

A total of 4 subjects had major protocol violations. (Table 15)

Table 15 Protocol Violations

	Number (%) of Subjects			
	Placebo (combined) (N=16)	Drisapersen 3 mg/kg/week (N=17)	Drisapersen 6 mg/kg/week (N=18)	Total (N=51)
Intent-to-Treat Population	16 (100)	17 (100)	18 (100)	51 (100)
Per Protocol Population	15 (94)	14 (82)	18 (100)	47 (92)
Total Number of Subjects with Major	1 (6)	3 (18)	0	4 (8)
Subject 000226 had history of aortic root dilatation	0	2 (12)	0	2 (4)
Subject 000176 had idebenone until Day 3	0	1 (6)	0	1 (2)
Subject 000176 missed 5 doses (<80% compliant)**	0	1 (6)	0	1 (2)
Subject 000201 with history of cardiomyopathy being managed with lisinopril	0	1 (6)	0	1 (2)
Subject 000158 Treatment blind broken*	1 (6)	0	0	1 (2)

*due to ER visit for flu-like symptoms (a member of the investigators staff was unblinded). The family stated the ER staff did not unblind them to the treatment assignment; however this could not be positively confirmed.

**protocol required follow-up for lab values falling outside the study reference ranges (proteinuria)

Reviewer's Comment: The Protocol deviations were all in the 3 mg/kg group, except one in the placebo group. The impact of this subject is shown in the Sensitivity analysis.

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NDA 206, 031 (Drisapersen)

Table of Demographic Characteristics

Baseline demographic characteristics were similar across treatment groups with the drisapersen 6 mg/kg group having slightly lower median age (Table 16).

Table 16 Summary of demographic characteristics

	Number (%) of Subjects			
	Placebo (combined) (N=16)	Drisapersen 3 mg/kg/week (N=17)	Drisapersen 6 mg/kg/week (N=18)	Total (N=51)
Age (yrs)				
Mean	8.0	7.8	7.6	7.8
SD	1.79	1.91	2.70	2.15
Median	8.0	8.0	6.5	8.0
Min., Max.	5, 11	5, 11	5, 13	5, 13
Ethnicity				
Hispanic/Latino	4 (25)	1 (6)	1 (6)	6 (12)
Not Hispanic/Latino	12 (75)	16 (94)	17 (94)	45 (88)
Race				
African American/African Heritage	1 (6)	1(6)	1(6)	3 (6)
Asian – East Asian Heritage	0	0	1 (6)	1 (2)
Asian – South East Asian Heritage	0	0	1 (6)	1 (2)
White – White/Caucasian/European Heritage	14 (88)	16 (94)	15 (83)	45 (88)
Mixed Race	1 (6)	0	0	1 (2)
Height (cm)				
Mean (SD)	123 (6)	120(8)	120 (14)	NA
Median	122	120	117	NA
Min., Max.	109, 133	102, 130	101, 146	NA
Weight (kg)				
Mean (SD)	30 (9)	29 (6)	30 (13)	NA
Median	28	31	25	NA
Min., Max.	19, 51	18, 42	17, 64	NA

Source: Study report DMD114876, page 69

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

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Other baseline characteristics are summarized in Table 17. There were some differences in corticosteroid use and duration across treatment groups. The subjects in the 6 mg/kg group had the shortest time since first symptoms.

Table 17 Summary of disease characteristics

	Number (%) of Subjects			
	Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)	Total (N=51)
Time Since First Symptoms (months)^a				
Mean (SD)	57 (30)	67 (27)	59 (30)	61 (29)
Median	60	60	60	60
Min., Max	13, 112	25, 124	8, 112	8, 124
Time Since Diagnosis (months)^a				
Mean (SD)	46 (30)	47 (26)	46 (27)	46.4 (27)
Median	45	38	46	43
Min., Max.	9, 111	13, 108	7, 96	7, 111
Time Since First Corticosteroid Taken (months)^a				
Mean (SD)	37 (24)	33 (16)	27 (22.51)	32 (21)
Median	39	28	19	27
Min., Max.	7, 85	8, 58	6, 81	6, 85
Corticosteroid Regimen^b				
Continuous	15 (94)	15 (88)	18 (100)	48 (94)
Intermittent	1 (6)	2 (12)	0	3 (6)
6MWD (m)				
Mean	416	415	396	NA
(SD)	(57)	(58)	(61)	NA
EXON Mutation, n (%)				
DMD 43-50 deletion	0	0	1 (6)	1 (2)
DMD 45-50 deletion	9 (56)	4 (24)	4 (22)	17 (33)
DMD 47-50 deletion	1 (6)	0	0	1 (2)
DMD 48-50 deletion	4 (25)	5 (29)	3 (17)	12 (24)
DMD 49-50 deletion	1 (6)	5 (29)	6 (33)	12 (24)
DMD 50 deletion	1 (6)	2 (12)	1 (6)	4 (8)
DMD 52 deletion	0	1 (6)	3 (17)	4 (8)

Source: Study report DMD11487, page 70

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Concomitant medication usage was similar across groups. Fifty subjects (98%) were >80% compliant. Duration of exposure was similar across groups.

Reviewer's Assessment of Baseline characteristics:

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The baseline assessment of functional capabilities in each treatment group is summarized below:

Baseline Factors	Continuous 6mg/kg/week	Continuous 3 mg/kg/week	Placebo
Age <7 years	50%	24%	25%
6MWD>400m	44%	52%	75%
Rise From Floor <4 secs	28%	35%	50%
On continuous regimen	100%	88%	94%
Other factors:	61%	82%	81%
Ability to jump with both feet up at the same time			
Ability to hop with clearing foot and heel from floor	38%	58%	56%
Ability to rise from floor without gower's maneuver	0%	0%	13%

A higher percentage of subjects were of age <7 years in the 6 mg/kg/week group that tend to improve in function. The 3 mg/kg/week group has some factors that could suggest lower functional capability compared to the placebo group, such as percent of subjects with Rise from Floor<4s and 6MWD>400m.

Efficacy Results - Primary Endpoint

Applicant's analysis:

In the primary efficacy MMRM analysis of change from baseline in 6MWD (m) at Week 24, a non-statistically significant ($p=0.07$) difference of 27 m was observed for the 6mg/kg group compared to placebo. The difference observed at 24 weeks was maintained at 48 weeks (28 m) during the drug free period and so was the change from baseline 6MWD. A decrease of baseline of 11-13 m was observed at week 24 and 48 in the placebo group. The applicant considers this modest decrease consistent with the range expected in an early ambulant population (Table 18).

Table 18 Summary of Repeated Measures Analysis of Change from Baseline in 6MWD (m) by Visit

	Placebo (combined) (N=16)	Drisapersen 3 mg/kg/week (N=17)	Drisapersen 6 mg/kg/week (N=18)
Baseline			
n	16	17	18
Mean (SD)	416 (57)	415 (58)	396 (61)
Week 24 primary analysis			
n	16	17	18
Adjusted mean change (SE)	-11(11)	-20 (10)	16 (10)
Adjusted mean difference vs. placebo		-9	27
95% CI		(-39, 21)	(-2, 56)
p-value		0.55	0.07

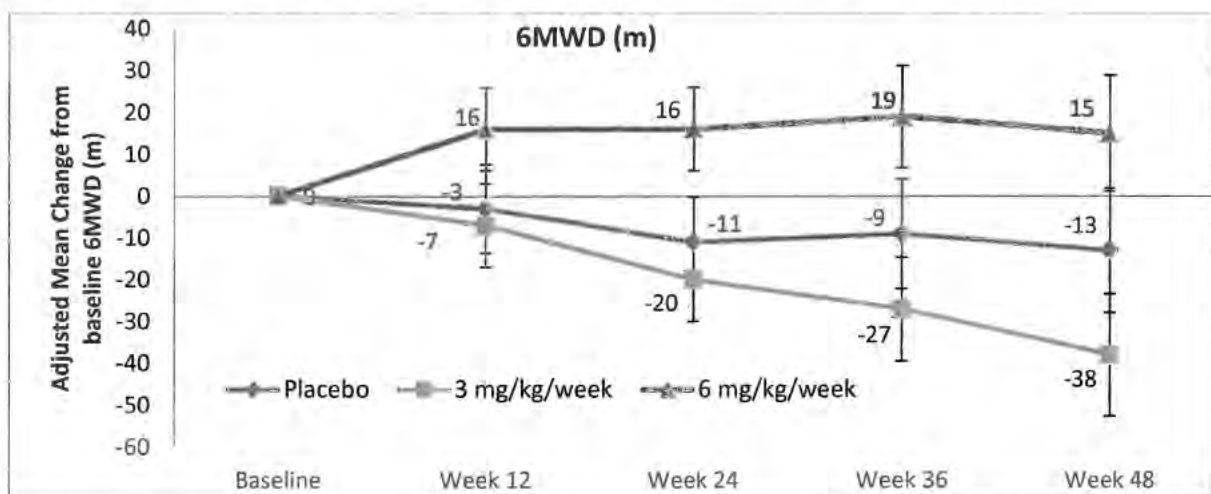
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Week 48 (end of post treatment period)			
n	15	17	18
Adjusted mean change (SE)	-13 (15)	-38 (14)	15 (14)
Adjusted mean difference vs. placebo		-25	28
95% CI		(-66, 17)	(-13, 69)
p-value		0.24	0.18

Source: DMD114876 study report, Page 74

None of covariates (visit, treatment, center grouping, baseline 6MWD, age, and age group) tested were significant at the 5% or 10% level.

Figure 11 MMRM analysis of change from baseline at week 24 and 48



Applicant's Sensitivity Analysis:

Sensitivity analyses with the ITT population show similar magnitude of treatment difference. A lower magnitude of treatment difference was observed with the PP population after removing the protocol violators.

Drisapersen 6 mg/kg/week Sensitivity Analyses: Change from Baseline in 6MWD (m) at Week 24

Analysis	Population	Dataset	Treatment Difference	95% CI	P-value
Drisapersen 6 mg/kg/wk					
MMRM	ITT	OC	27	(-2, 56)	0.07
MMRM	PP	OC	19	(-11, 50)	0.21
ANCOVA	ITT	OC	27	(-3, 57)	0.07
ANCOVA	ITT	LOCF	27	(-3, 57)	0.07

Source: DMD114876 study report, page 76

Reviewer's Comment: One subject in the placebo group made this difference. The subject # 158 in the placebo group had a 6MWD decline of 70 m and had the second largest decline in the placebo group (-127m was the largest decline at Week 24). This subject had his treatment unblinded due to an ER visit.

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Additional Analyses on 6MWD:

- Change from baseline in 6MWD by response category
Response was measured as the percentage of subjects that achieved a fixed change in 6MWD ($\geq -10\%$, $\geq 0\%$, $\geq 10\%$, $\geq 20\%$ and $\geq 30\%$ change). Subjects could be included in more than 1 category. At week 24, 3 subjects showed $\geq 10\%$ change in the 6 mg/kg/week group and none in the placebo. At 48 weeks 8 subjects showed $\geq 10\%$ change in the 6 mg/kg/week group and one in the placebo group. 8 subjects in the 6 mg/kg/week group and 2 subjects in the placebo group had $\geq 30\%$ change in 6MWD.
- Change from baseline in percent-predicted 6MWD
As 6MWD distance is influenced by age and development, analysis of the percent-predicted 6MWD that takes these factors into account were conducted (Henricson 2012). A treatment benefit ($\sim 5\%$ difference) in favor of the 6 mg/kg group over placebo was observed at Week 24 ($p=0.05$). A treatment difference of -1.5% was observed with the 3mg/kg group at Week 24.
- Number of Falls: Number of falls were similar across treatment groups
- Loss of ambulation: No subject in any group lost ambulation during the study.

Post-hoc analyses on 6MWD:

By age group (≤ 7 and > 7 years): No statistically significant treatment differences were noted for either drisapersen treatment group compared to placebo, but the mean treatment difference from placebo was 31m in subjects ≤ 7 years.

Table 19 Summary of Repeated Measures Analysis of Change from Baseline in 6MWD by Visit Split by Age Group

	Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
≤ 7 years at baseline			
Baseline			
n	6	8	10
Mean (SD)	445 (63)	439 (50)	385 (60)
Week 24			
n	6	8	10
Adjusted mean change (SE)	-14 (21)	-22(18)	17 (17)
Adjusted mean difference vs. placebo		-8	31
95% CI		(-66, 49)	(-29, 90)
p-value		0.77	0.29
>7 years at baseline			
Baseline			
n	10	9	8
Mean (SD)	399 (48)	394 (59)	410 (62)
Week 24			
n	10	9	8
Adjusted mean change (SE)	-16 (12)	-16 (12)	12 (14)
Adjusted mean difference vs. placebo	NA	-0.14	28
95% CI	NA	(-39, 39)	(-9, 65)
p-value	NA	0.99	0.13

Source: DMD114876 study report, page 82

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Reviewer's Comment:

- This post-hoc analysis is un-interpretable due to small number of subjects. It is noteworthy, that Study DMD114117 showed larger treatment difference in subjects >7 years.
- In this study the impact of including subjects with Rise from Floor of ≤15 seconds was not significant as only two subjects were enrolled with RT of >7 seconds (one in the 3 mg/kg group with RT of 10 seconds and one in the 6 mg/kg group with RT of 12 seconds).

Data Quality and Integrity - Reviewers' Assessment

There are no data integrity issues.

Dose/Dose Response

There was no clear dose-response established. It is unclear why the 3 mg/kg performed worse than placebo and may suggest random noise.

Efficacy Results - Secondary and other relevant endpoints

Applicant's Analysis:

Timed Function tests, NSAA, Muscle Strength, and Pulmonary Function:

At Week 24, changes on timed function tests (rise from floor, 10 m walk/run, 4-stair climb) were small (generally less than one second). Rise from floor, 4-stair climb, muscle strength and NSAA favored the 3mg/kg group more (Table 20). The number of subjects improving or worsening was similar for each test or showed greater number of subjects worsening from baseline in the Rise from floor and 10 m walk/run in the 6 mg/kg group. Changes in pulmonary function measures were small and variable across both treatment groups. The secondary endpoints were not measured in the post treatment period at Week 48.

Table 20 Secondary Endpoints, unadjusted mean baseline (SD), adjusted treatment difference (95% CI), p-value at Week 24

	Placebo (n=16)	3mg/kg/week (n=17)		6 mg/kg/week (n=18)	
Rise from Floor (s)					
Baseline (SD)	4.49 (1.61)	4.96 (2.21)		5.19(2.46)	
Adj. treatment difference		0.39	p=0.69	0.83	p=0.38
10 m walk/run (s)					
Baseline (SD)	5.12 (1.35)	4.97 (1.17)		5.38 (1.35)	
Adj. treatment difference		0.56	p=0.05	0.04	p=0.89
4 step ascent (s)					
Baseline (SD)	3.53 (1.80)	3.14 (1.29)		4.60 (3.17)	
Adj. treatment difference		0.002	p=0.99	-0.80	p=0.06
4 step descent (s)					

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Baseline (SD)	2.94 (1.2)	3.34 (2.2)		4.05 (2.3)	
Adj. treatment difference		-0.68	p=0.31	-0.41	p=0.52
NSAA (total score)					
Baseline (SD)	26.5 (5.0)	26.5 (5.2)		24.6 (5.7)	
Adj. treatment difference		-0.49	p=0.68	-0.18	p=0.87
Muscle Strength					
Baseline (SD)	128.4	129.2 (22)		125.2 (43)	
Adj. treatment difference		2.36	p=0.72	0.82	p=0.89

Source: Adapted from applicant's analysis.

Creatine Kinase:

A decline in CK was observed from baseline at Week 24 for both active treatment arms compared to placebo, with a greater treatment difference for the drisapersen 6 mg/kg/week group than for the drisapersen 3 mg/kg/week group. However at the end of the post-treatment period at week 48, a continued decrease in CK compared with placebo was observed for the drisapersen 3 mg/kg/week arm, but not for the drisapersen 6 mg/kg/week arm (Table 21).

Table 21 Summary of Repeated Measures Analysis of Change from Baseline in Creatine Kinase Serum Concentration (IU/L) by Visit

	Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
Baseline			
n	16	15	18
Mean (SD)	12715 (5606)	14553 (7810)	13059 (8288)
Week 24			
n	16	17	17
Adjusted mean change (SE)	-3479 (1230)	-4079 (1173)	-4537 (1189)
Adjusted mean difference vs. placebo	NA	-600	-1058
95% CI	NA	(-4121, 2920)	(-4456, 2340)
p-value	NA	0.73	0.53
Week 48			
n	15	17	18
Adjusted mean change (SE)	-2783 (1249)	-4838 (1171)	-2616 (1149)
Adjusted mean difference vs. placebo	NA	-2055	167
95% CI	NA	(-5587, 1478)	(-3209, 3544)
p-value	NA	0.25	0.92

Source: DMD114876 Study Report, page 96

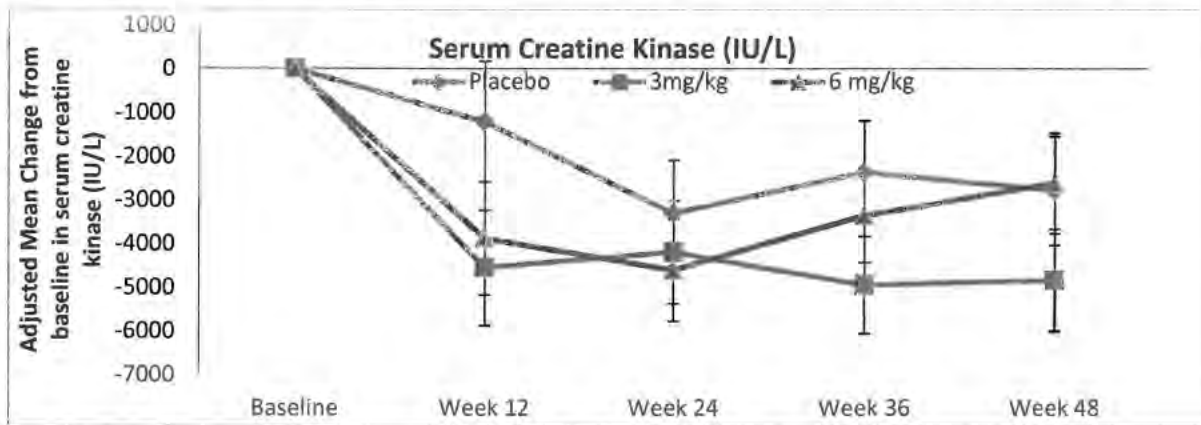
Reviewer's Comment:

The 3 mg/kg dose group continues decline during the drug free period up to Week 48, but the 6 mg/kg dose group shows an increase in CK. The reliability of this finding is unclear. Exercise induced changes in CK are difficult to ascertain, nevertheless CK declined in drisapersen treated groups.

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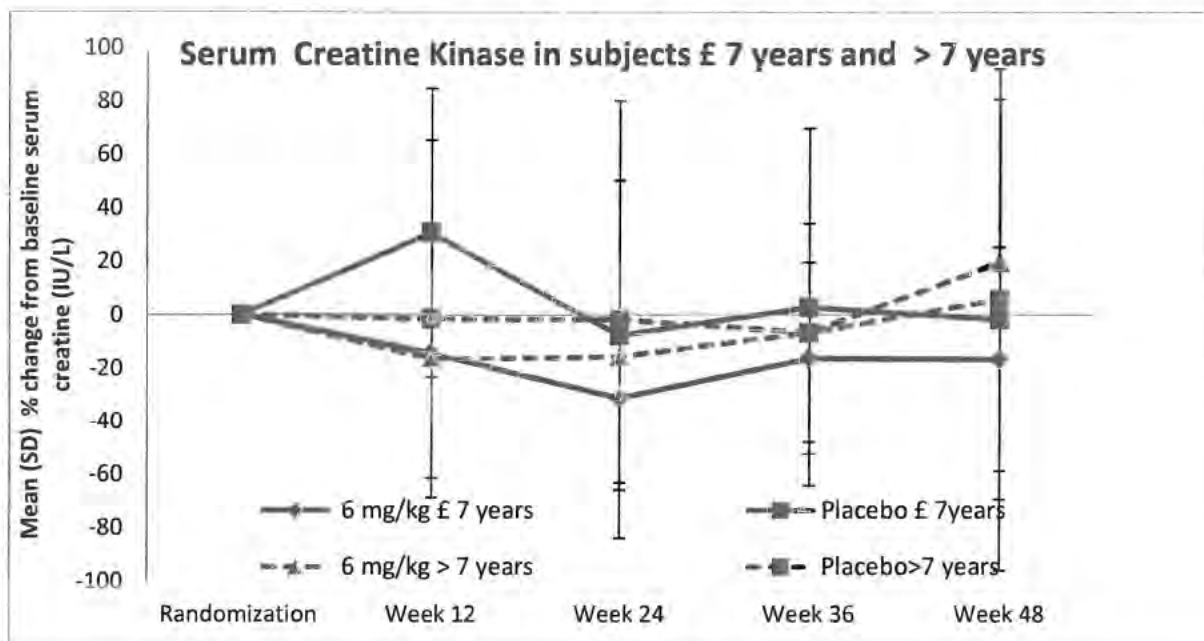
Figure 12 shows the time course of adjusted mean change in CK.

Figure 12: MMRM analysis of change from baseline in serum creatine kinase concentrations



In a post-hoc subgroup analysis, subjects ≤ 7 years showed greater treatment difference on 6MWD compared to subjects > 7 years, therefore I looked at percent reduction of CK in these subgroups. Consistent with the finding with 6MWD, the reduction in CK was greater in subjects ≤ 7 years compared to subjects > 7 years (Figure 13). The sample size is small and variability is large, therefore these findings should be interpreted with caution.

Figure 13 Change from baseline serum creatine kinase in subjects ages ≤ 7 years and > 7 years



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CGI, Functional Outcome Survey, Physician assessment of daily living:

No differences among treatment groups were observed on CGI-I and Functional Outcome Survey (29 assessed by parents (including general health, mobility, physical activities, hand dexterity and use of assistive devices domains). For CGI-I, there were 11% (2/18) with “much improved” or “very much improved” response in the 6 mg/kg group and 14% (2/14) responders in the placebo group. For the Functional outcome survey, some trends in favor of the 6 mg/kg group were observed for “general health” and “hand dexterity” compared to placebo and 3 mg/kg group. On some questions in the functional outcome survey, placebo and 3 mg/kg were rated as “improvement”.

MRI:

The applicant cites MRI data showing trends for reduction in edema (swelling) and adipose (fatty tissue) replacement signals at Week 24 and Week 48, based on T2 mapping and fat fraction methodology, in the small number of subjects. The applicant concludes:

- T2-weighted signal decreased (-0.07 to -0.23; N = 14) compared to controls (0.07 – 0.14; N = 10)
- Apparent fat fraction increased (2.7 – 5.2%; N = 5) in placebo group compared to 6 mg/kg/week treatment (0.9 – 3.8%; N = 6), suggesting a reduced rate of fat infiltration in subjects in 6 mg/kg.
- Effects persisted up to 24 weeks post-treatment

Consult review of the MRI data conducted by Dr. Daniel Krainak (CDRH Imaging Division) concludes that the data presented in the application are unconvincing for several reasons: the small number of subjects with fat fraction data at baseline, 24 weeks and 48 weeks, variability in the MR systems used, and lack of data concerning the actual quality control measurements from phantoms. The limited data show substantial overlap between treatment groups, large variability by muscle and a wide range of fat fraction observed at baseline. The magnitude of the changes observed in the study population is on the order of the uncertainty in the measurement technique (approximately 3%). Dr. Krainak concludes greater uncertainty about quantitative T2 measures in the context of edema as T2 may be influenced by many physiologic factors (including inflammation/edema, local bleeding/hematocrit, fat, [fat effects T1 more than T2] and more). Most of the commonly seen pathologies (infection/inflammation, tumor [benign or malignant], etc.) lead to an increase in T2 values. Therefore, an altered T2 is sensitive but not specific unless correctly interpreted in the context of the underlying pathophysiology.

Dystrophin Measurements

Muscle biopsies were obtained from the tibialis anterior (TA) muscle from each subject at baseline, Week 24 and either week 12 or 36. The following analyses were done:

- Detection of exon 51 skipped mRNA by RT-PCR
- Detection of dystrophin protein expression at baseline and Week 24 (N=36) and at Week 12 by IFA (N=4)
- Detection of dystrophin protein expression at baseline and Week 24 (N=9) by WB analysis, when IFA was not possible because of poor sample quality for IFA. For 2 subjects WB analysis was performed to confirm IFA results.

Exon 51 skipped mRNA by RT-PCR

A total of 10/17 (59%) subjects in each of the drisapersen 3 mg/kg/week group and 6 mg/kg/week group compared to 2/15 (13%) subjects in the placebo group had an increase in exon 51 skipping

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compared to baseline (Table 22). For about 24-60% of the subjects, the relative intensity was below the reporting level across treatment groups. The applicant notes that the increase was more pronounced at week 36, where 43% of the 3 mg/kg and 100% of the 6 mg/kg subjects and 14% in the placebo group showed an increase in exon skipping (Note: sample size, N=7 at week 36). Note that doses were administered only up to 24 weeks.

Table 22 Summary of DMD Exon 51 Skip Muscle Biopsy Data at Weeks 12, 24, and 36

Parameter/ Visit	Result	Number (%) of Subjects		
		Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
Relative Intensity				
Week 12	n	7	6	8
	Increase	1 (14)	3(50)	4 (50)
Week 24	n	15	17	17
	Increase	2 (13)	10 (59)	10 (59)
Week 36	n	7	7	7
	Increase	1 (14)	3 (43)	7 (100)

Source: adapted from Page 98

The mean PCR fragment intensity (a.u) for exon 51 skipped product was increased for both 3 and 6 mg/kg at Week 24 (Table 23).

Table 23 Intensity of exon 51 skipped dystrophin mRNA product by nested RT-PCR and capillary electrophoreses

Study Treatment	Exon Skip (a.u) Mean (SD)	
	Week 0	Week 25
Placebo	2.0 (1.5)	1.5 (1.2)
Weekly 3mg/kg	2.7 (4.1)	4.4 (3.6)
Weekly 6mg/kg	2.4 (4.4)	4.4 (6.6)

The applicant also provided Digital Doppler PCR (ddPCR) data with supporting information that the assay precision was >25% and the limit of reporting for DMD biopsies carrying exon 50 deletion was >140 for skipped copy numbers in total 1500 ng RNA. The RNA integrity number (RIN) value for many samples was lower than 5, suggesting moderate to low RNA quality (the highest possible value being 10). The applicant has provided ddPCR data for all RIN value samples and those with RIN >5. No appreciable increase in skip numbers relative to placebo group was observed in majority of the samples of the treated groups.

OBP Reviewer Dr. Rao's Comment on Methodology:

Given that the applicant identified a high inter-assay variation of 25%, it is unlikely that this method, as performed, could provide the Applicant with any meaningful quantitative data regarding dystrophin mRNA because the relative increases in mRNA are small and in most instances within the applicant's proposed variability. Additionally, the very small sample

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number, low RIN values for many samples, and different skip numbers across various exon deletion subgroups, do not allow a clear interpretation of a trend in dystrophin skip product increase between groups.

Dystrophin expression by IFA:

The results of dystrophin analysis by IFA were not supportive for the treatment group. The relative intensity was increased in maximum number of subjects in the placebo group and only 1 subject in the 6 mg/kg group (Table 24).

Table 24 Summary of Immunofluorescence Assay and Western Blot Qualitative Muscle Biopsy Data

Parameter/ Testing Method	Result	Number (%) of Subjects		
		Placebo (combined) (N=16)	Drisapersen 3 mg/kg (N=17)	Drisapersen 6 mg/kg (N=18)
Relative Intensity (All muscles)				
Week 24 Immunofluorescence assay (IFA)	n	12	11	13
	Increase	7 (58)	5 (45)	1 (8)
Western blot (WB) Week 24	n	5	5	1
	Increase	0	1 (20)	0

Source: Adapted from page 99

Predefined criteria for increase: (>4% increase compared to baseline)

Based on an initial analysis at Week 24, the mean percent increase from baseline in dystrophin were observed in both the drisapersen 3 mg/kg/week group (2%) and placebo group (6%) compared with a decrease in the drisapersen 6 mg/kg/week group (-3%) as shown in Table 25.

Table 25 Summary of Dystrophin Intensity Measurement by IFA (change from Baseline to Week 24)

Parameter		Placebo (combined) (N=16)		Drisapersen 3 mg/kg (N=17)		Drisapersen 6 mg/kg (N=18)	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Non-Qualified Mean Percentage Change (%)	Week 12	0	NA	2	-2 (6)	2	-0.5 (5)
	Week 24	12	6 (10)	11	2 (11)	13	-3 (6)
	Week 36	0	NA	0	NA	0	NA
Non-Qualified Q90 Percentage Change (%)	Week 12	0	NA	2	-6 (4)	2	-2 (3)
	Week 24	12	8 (13)	11	-0.2 (11)	13	-4 (8)
	Week 36	0	NA	0	NA	0	NA

Source: Study DMD114876 report, page 100

After this initial analysis, due to the large variability, no difference between the treated and placebo group and large changes in spectrin between 2 biopsies, the applicant further investigated the variability and presented the results in a separate report. A repeat analysis of these biopsies was conducted in 2-3 experiments. An average of the 2-3 repeat experiments was reported for each subject. These were used to calculate the non-qualified mean percentage change as shown in Table 26 and Figure 14. The highest increase at Week 24 was observed in the 3 mg/kg group.

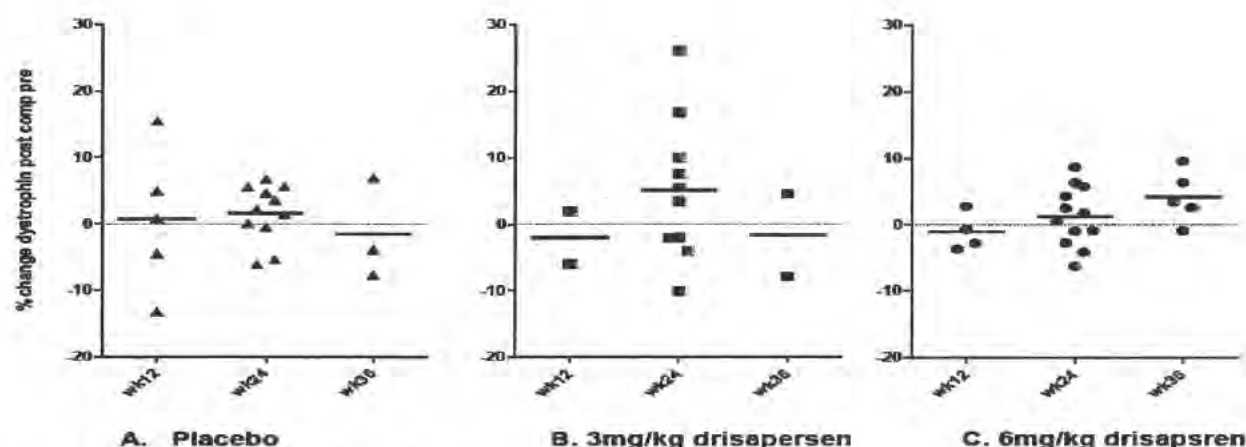
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Table 26 Summary of dystrophin intensity measurement (by average by 2-3 experiments for each subject)

Parameter	Visit	Placebo (N=16)		Drisapersen 3 mg/kg (N=17)		Drisapersen 6 mg/kg (N=18)	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Non-Qualified Mean Percentage Change (%)	wk12	5	1% (11%)	2	-2% (6%)	4	-1% (3%)
	wk24	11	2% (4%)	10	5% (11%)	12	1% (4%)
	wk36	3	-2% (8%)	2	-2% (9%)	5	4% (4%)
Non-Qualified Q90 Percentage Change (%)	wk12	5	1% (17%)	2	-6% (5%)	4	-2% (1%)
	wk24	11	1% (6%)	10	5% (11%)	12	0% (6%)
	wk36	3	0% (14%)	2	-6% (3%)	5	-13% (12%)

Source: DMD114876-LAB-01 report, page

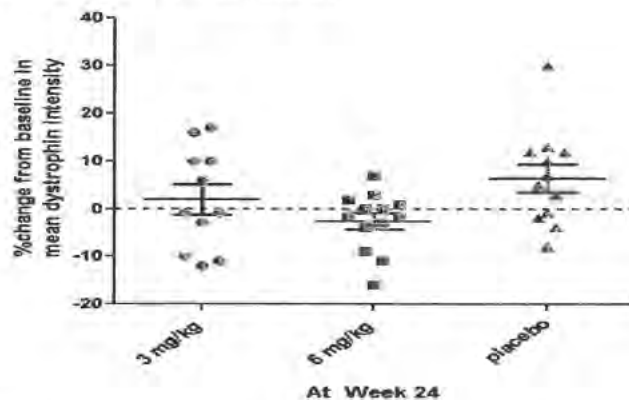
Figure 14 % change in mean dystrophin intensity in individual subjects from an average of 2-3 experiments (IFA)



Reviewer's Comment: The applicant's scatter plot in Figure 14 shows larger variability in the % change in mean dystrophin intensity in the 3 mg/kg group (-10% to 26%) compared to the 6 mg/kg group (-4% to 9%), driving a higher mean % change for the 3 mg/kg group at Week 24. There is also no appreciable differences in dystrophin expression between placebo (-6 to 7%) and 6 mg/kg group (-4% to 9%). While there appears to be an upward trend in the mean values, the values are within the known assay variability and not apparently or statistically significant. In addition, no dose was given beyond 24 weeks, hence the reason for the upward trend observed is unclear. The scatter plot based on their original analysis is shown in Figure 15

Figure 15: % change in mean dystrophin intensity in individual subjects from original experiment (IFA)

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OBP Reviewer Dr. Rao's Comment on IFA:

The applicant states that the inter-assay reproducibility of their IFA assay between experiments for placebo and drisapersen-treated subjects combined was 5% and ranged between 0-16% for the study. It is not clear if the mean values reported in Table 26 that are below 5% represent biologically-relevant responses or expected assay variability. There also appear to be several critical deficiencies in the applicant's design of experiments that preclude an interpretable assessment of dystrophin increase: (1) the Applicant states that the IFA analyses were repeated up to 3 times to "investigate further the inter-biopsy and inter-assay precision from one subject 027; however repeated analyses were carried out for several other subjects without any accompanying justification regarding why 2 or, in some cases, 3 replicates were obtained, (2) the Applicant states that the operators and managers were blinded to the treatment groups at the time of the 2013 analysis, after which the treatment regime was unblinded. The IFA repeat analyses were carried out in 2014 and after the study was unblinded, (3) in the case of each of the 2nd or 3rd replicate values, it was noted that the placebo samples showed lower dystrophin intensity values and the treatment samples showed higher values in the re-analysis. In the absence of a systematic, consistent, and prospective design of experiment, it may not possible to conclude that the repeated analyses generated unbiased and robust mean dystrophin values. See Appendix B for additional deficiencies.

Dystrophin expression by WB:

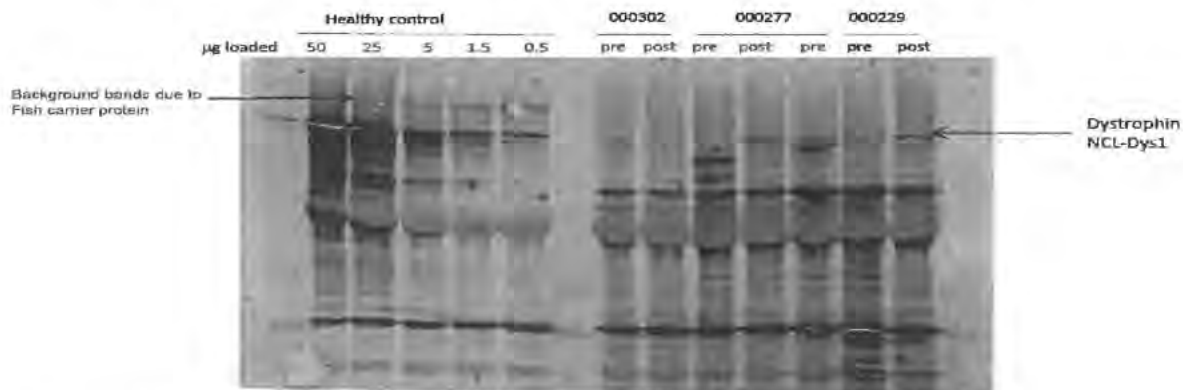
The applicant has provided limited western blot analysis data for this study. They claim that in most instances the biopsies were of too poor quality to generate data. In the 3 mg/kg/wk group, 5 subjects were analyzed and one showed an increase in dystrophin protein. The one subject in the 6 mg/kg/wk group that was analyzed did not show an increase.

OBP Reviewer Dr. Rao's Comment on WB:

In addition to the poor quality of biopsies and very low sample number, the Applicant chose to examine the 11 subjects for western blotting whose samples were originally deemed unsuitable for IFA analysis.

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The applicant did include a loading control healthy sample in their western blots and used beta3-spectrin as a loading control. However, there is no clear trend showing an increased band in post-treatment samples. The dystrophin band appears to diminish in some post-treatment samples (e.g. subject 277). Image below was provided by the Applicant upon request for raw data from this study. While the applicant has not compared their dystrophin values to the healthy control samples on the same gel, in most cases the dystrophin band appears to be at or lower than the lowest dilution of healthy control sample tested. The applicant was asked to clarify how the dystrophin values compared to the healthy controls on the same gels. They stated that while it is not possible to accurately calculate the relative dystrophin signal due to a lack of linearity at the low levels of signal from the DMD samples, they estimate that the dystrophin expression they observed is generally around 0.3% or below of the highest control dilution. They further state that only 4/18 samples tested showed dystrophin levels above their lower limit of detection of 1% of normal, and that those 4 samples with 2.1-4.1% of normal dystrophin levels did not show an appreciable treatment effect when compared to their corresponding pre-treatment sample.



Persistence of Effect

Reviewer's Comment: One of the objectives of this study was to determine the persistence of effect during the drug free observation period from week 25- Week 48. The treatment difference was maintained at Week 48 for the 6mg/kg group.

Also interesting to note that the change from baseline was not maintained for the 6 mg/kg group in Study DMD114117, which in treatment was given for 48 weeks. So it is unclear if the persistence of effect observed in this study is a true treatment effect or the natural variation in the DMD population.

Reviewer's Analysis and Discussion:

The study results in general appear weak, some weak trends in favor of treatment observed were:

- * The primary endpoint (change from baseline in 6MWD at Week 24) had a numerical advantage on 6MWD with a treatment difference of placebo of 27 m for the 6mg/kg dose, but the study was negative ($p=0.07$).

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- The reduction in creatinine kinase was in favor of the drisapersen treated groups. There was a dose related response in the reduction of CK at week 24, with a greater decline in the 6 mg/kg group compared to the 3 mg/kg group, but only the 3 mg/kg group continued to decline during the drug free period at Week 28.

The weaknesses of the observed results from Study DMD114876 are:

- Based on the pre-specified primary efficacy analysis for the change from baseline 6MWD, the study was negative with a p-value of 0.07
- Removing one subject in the placebo group who was unblinded due to a hospital visit, the treatment difference was 19 m, p=0.21
- There was no dose response:
 - 6 mg/kg/week was superior than placebo (27m)
 - 3 mg/kg/week was worse than placebo (-9 m)

This could be suggestive of noise in the data or difference in disease characteristics of the two dose groups as discussed earlier.

- The secondary endpoints in this study were not supportive of the primary endpoint. There was no dose related trends in the secondary endpoints, with 3 mg/kg trending better compared to 6mg/kg in some endpoints (10m walk/run, 4 stair climb, muscle strength, NSAA).
- Potential partial unblinding to the assigned treatment due to injection site reactions: Unblinding could affect the performance of 6MWD, which is an effort dependent endpoint. The incidence and the duration of injection site reactions was the largest for the 6 mg/kg group and the least for placebo.
- The dystrophin expression (IFA and WB) did not favor treatment benefit. The dystrophin expression as evaluated by IFA showed the similar response in the placebo group and 6 mg/kg group. The RT-PCR exon skipping data showed higher percent of exon skip subjects in favor of the 6mg/kg group, but this was not supported by IFA analysis. The WB analysis did not show any treatment response.

6.3. Study DMD114044

6.3.1. Study Design

Overview and Objective

This study was designed to assess the efficacy of drisapersen 6 mg/kg once weekly for 48 weeks in ambulant subjects with DMD compared to placebo. The secondary objectives were to assess safety, tolerability, PK and impact on quality of life.

Studied period: 02 December 2010 to 28 June 2013

Study center(s): 44 centers in 19 countries: Argentina, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Italy, Japan, Korea, Netherlands, Norway, Poland, Russia Federation, Spain, Taiwan, and Turkey.

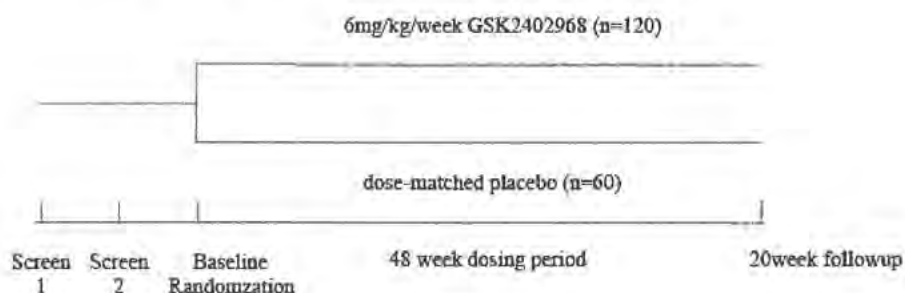
Trial Design

Clinical Review (Efficacy)

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This phase III, randomized, double-blind, parallel-group clinical study similar in design to Studies DMD114117 and DMD114876, with the exception of primary endpoint assessments at Week 48. Any differences will be outlined in this section. Subject completing this study entered an open label extension (Study DMD114349). The study design schematic is shown in Figure 16.

Figure 16 Study design schematic for Study DMD114044



Population: N= 186 DMD boys with a mutation corrected by exon 51 skipping. The study was designed to have 90% power to detect a difference in 6MWD between drisapersen and placebo of 30 meters, assuming a common standard deviation of 55 meters.

Key Inclusion/Exclusion Criteria: Same as Study DMD114117 and DMD114876, with the exception of:

- There was no restriction on ability to rise from floor (in ≤ 7 seconds for Study DMD114117, and ≤ 15 seconds for Study DMD114876). Subjects with any rise time could be enrolled in this study.

Dosing Regimen:

Subjects were randomized to the following in 2:1 ratio using Interactive Voice Response System. Similar blinding approaches were adopted as the Phase 2 studies.

- 6 mg/kg/week SC drisapersen for 48 weeks (N=125)
- SC placebo for 48 weeks (N=61)

To minimize injection site reactions, rotation of site on a weekly basis was recommended. Abdomen, arms, thighs, back and buttocks were all used as injection site.

Applicant's Dose Rationale: Prior to randomization in this study, 12 subjects from open label study DMD114673 had received 6 mg/kg/week for 48 weeks. A mean change from baseline in the 6MWD at Week 24 was 37 m (range -58 m to +115 m). The applicant considered this supportive of the choice of the dose. In addition, due to early signs of potential subclinical renal effects (mild proteinuria) in the open label study and the preclinical pro-inflammatory findings (including data from the 39 week monkey study), 6 mg/kg was considered to be the maximum tolerated dose (MTD) and selected for this study.

Reviewer's Comment: This study was initiated 3 months after the initiation of the 48 week Study DMD114117.

Study Endpoints

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The primary efficacy endpoint was 6MWD at week 48. 6MWD was assessed at screening (1 and 2), randomization, at weeks 24, 36 48 or follow-up.

The secondary efficacy endpoints were same as Study DMD114117 and DMD114876. Some of the differences between the endpoints were:

- For pulmonary function tests, MIP, MEP (Study DMD114117 only) and sniff nasal pressure (Study DMD114876 only) were not measured in this study.
- The quality of life assessments in this study were:
 - Pediatric Quality of Life Neuromuscular module (also on Study DMD114117)
 - Clinician Global Impression of Improvement (CGI-I) (also in study DMD114876)
 - Health Utilities Index
 - Activities of Daily Living

Key Secondary Endpoints:

1. Change from baseline in the NSAA linearized score
2. Change from baseline in the 4-stair climb (ascent) velocity
3. Change from baseline in the 10-meter walk/run velocity

Other exploratory endpoints:

- MRI and DEXA

Statistical Analysis Plan

Primary Analysis: Change from baseline in the 6MWD at week 48 was analyzed for the OC dataset on ITT population using MMRM with fixed effects of treatment, visit, treatment by visit interaction, country grouping, and continuous fixed covariates of baseline 6MWD and baseline 6MWD by visit. Other supportive information was derived from Week 12, 24, and 36. The covariates assessed were: country group, baseline 6MWD, age, age group (≤ 7 and > 7 years), corticosteroid regimen (Continuous or Intermittent), Baseline rise from floor group (Less than or equal to 7 seconds or greater than 7 seconds), 117 Data dissemination group (Week 48 visit before or after 117 dissemination), country, and race. Statistical significance tests were 2 sided.

Sensitivity analyses were also similar to Study DMD114117 and DMD114876.

Secondary Analysis: If a statistically significant treatment difference at the 5% level was observed for the primary efficacy endpoint, then the key secondary endpoints were tested in a hierarchical manner. For all other endpoints no adjustment for multiplicity was made and all were performed at α of 5% and considered supportive.

Protocol Amendments

Amendment 1 (Sep 2010)	• If subjects become non ambulatory and are unable to perform the 6MWD assessment for this reason, their distance will be imputed to be 0m for the purposes of analysis • Clarified that the primary analysis will be on OC data. • Sensitivity analyses will be on LOCF data • Efficacy analysis using PP population will be a sensitivity analysis • MMRM analysis for PP population will be a sensitivity analysis.

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	ANCOVA with the LOCF and OC dataset will be carried out for the 6MWD at week 48
Amendment 2 (21 Jun 2011)	- Allow subjects who withdrew for safety reasons to enter the extension study - MRI sub-study as requested by EMA. This would be performed only in Argentina and Brazil due to logistical and timing issues

Reviewer's Comment: Amendments related to study analysis were made prior to initiation of enrollment

Data Quality and Integrity: Sponsor's Assurance

Management of clinical data was performed in accordance with GSK standards. The study was conducted in accordance with ICH GCP (ICH E3 and E6) and applicable country-specific requirements. Written commitments were obtained from investigators to comply with GCP. Study was conducted with written informed consent from subjects and their parents.

6.3.2. Study Results

Patient Disposition

A total of 181 subjects completed the study (Table 27).

Table 27 Summary of subject disposition

Subject Status	Number (%) of Subjects		
	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
Completed	60 (98)	121 (97)	181 (97)
Withdrawn	1 (2)	4 (3)	5 (3)
Primary reason for study withdrawal			
Adverse event ^a	0	2 (2)	2 (1)
Withdrew consent	0	2 (2)	2 (1)
Protocol deviation ^b	1 (2)	0	1 (<1)

Source: Study DMD114044 report, page 64

a. An AE of glomerulonephritis leading to discontinuation was reported in 1 subject (Subject 527). Intracranial venous sinus thrombosis and spinal pain AEs leading to discontinuation were reported for 1 subject (Subject 1270).

b. Subject 1266 in the placebo group had mutation not correctable by exon 51 skipping

Protocol Violations/Deviations

A total of 7 (11%) subjects in the placebo group and 22 (18%) subjects in the drisapersen group had a major protocol deviation. Summary of major protocol violations leading to exclusion from the PP population is shown in Table 28.

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 NDA 206, 031 (Drisapersen)
Table 28 Protocol Deviations

	Number (%) of Subjects		
	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
ITT Population	61 (100)	125 (100)	186 (100)
PP Population	54 (89)	103 (82)	157 (84)
Total Number of Subjects with Major Protocol Deviations	7 (11)	22 (18)	29 (16)
Mutation not correctable by exon 51 skipping.	1 (2)	0	1 (<1)
Not able to complete 6MWD test with minimal distance of at least 75 m at each pre-drug visit. In addition, results must be within 20% of each other at each pre-drug visit.)	1 (2)	6 (5)	7 (4)
Symptomatic cardiomyopathy.	0	2 (2)	2 (1)
Use of prohibited concomitant medication.	2 (3)	9 (7)	11 (6)
Significant change in corticosteroid regimen	2 (3)	2 (2)	4 (2)
Subjects not adequately complying with dosing specifications of the study	1 (2)	6 (5)	7 (4)

Source: Study DMD114044 report, page 65

Reviewer's Comment: A sensitivity analysis removing protocol violators did not change the overall conclusions, but treatment difference was reduced (Table 32).

Table of Demographic Characteristics

Most demographic characteristics were similar across treatment group, with numerically higher weight in drisapersen group (Table 29).

Table 29 Summary of demographic characteristics

	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
Age (yrs)			
Mean (SD)	8.0 (2.4)	8.3 (2.4)	8.2 (2.4)
Median	8.0	8.0	8.0
Min., Max.	5, 16	5, 16	5, 16
Ethnicity, n (%)			
Hispanic/Latino	10 (16)	23 (18)	33 (18)
Not Hispanic/Latino	51 (84)	102 (82)	153 (82)

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Race, n (%)			
African American/African Heritage	1 (2)	0	1 (<1)
Asian - Central/South Asian Heritage	1 (2)	3 (2)	4 (2)
Asian - East Asian Heritage	3 (5)	6 (5)	9 (5)
Asian - Japanese Heritage	5 (8)	9 (7)	14 (8)
Asian - South East Asian Heritage	0	2 (2)	2 (1)
White - Arabic/North African Heritage	4 (7)	5 (4)	9 (5)
White - White/Caucasian/European Heritage	46 (75)	95 (76)	141 (76)
White - Mixed Race	0	1 (<1)	1 (<1)
Mixed Race	1 (2)	4 (3)	5 (3)
Height (cm)			
Mean (SD)	122 (10)	124 (11)	NA
Median	122	123	NA
Min., Max.	102, 145	101, 148	NA
Weight (kg)			
Mean (SD)	27(7)	30 (10)	NA
Median	24	27	NA
Min., Max.	17, 46	17, 68	NA

Source: Study DMD114044 report, page 67

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Mean baseline values for the 6MWD was lower, time since first corticosteroid taken, time since first symptoms and time since diagnosis were all was numerically longer in the drisapersen group than in the placebo group.

Table 30 Summary of Muscular Dystrophy Disease Baseline Characteristics

	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)	Total (N=186)
Time Since First Symptoms (months)^a			
n	58	122	180
Mean (SD)	66.7 (31)	71.8 (31.5)	70.2 (31.5)
Median	60.8	70.2	66.8
Min., Max.	11, 168	12, 176	11, 176
Time Since Diagnosis (months)^a			
n	61	125	186
Mean (SD)	54.2 (32.8)	58.0 (35.2)	56.7 (34.4)
Median	49.8	54.5	53.1
Min., Max.	6, 148	6, 163	6, 163
Time Since First Corticosteroid Taken (months)^a			
n	61	125	186
Mean (SD)	29.1 (25.8)	35.6 (28.9)	33.5 (28.1)
Median	7, 135	6, 146	6, 146
Min., Max.			

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Corticosteroid Regimen, n (%)^b			
n	61	125	186
Continuous	52 (85)	108 (86)	160 (86)
Intermittent	9 (15)	17 (14)	26 (14)
6MWD (m)			
Mean (SD)	61 348 (92)	125 337 (95)	NA NA
Method of Diagnosis, n (%)^c			
n	61	125	186
Clinical symptoms	56 (92)	110 (88)	166 (89)
Muscle biopsy	21 (34)	47 (38)	68 (37)
Genetic testing	61 (100)	125 (100)	186 (100)
Multiplex Ligation-dependent Probe Amplification	59 (97)	117 (94)	176 (95)
Comparative Genomic Hybridisation	0	7 (6)	7 (4)
Single Condition Amplification/Internal Primer	1 (2)	1 (<1)	2 (1)
Other	1 (2)	0	1 (<1)
EXON Mutation, n (%)			
n	61	125	186
DMD 45-50 deletion	16 (26)	40 (32)	56 (30)
DMD 47-50 deletion	1 (2)	0	1 (<1)
DMD 48-50 deletion	7 (11)	26 (21)	33 (18)
DMD 49-50 deletion	20 (33)	31 (25)	51 (27)
DMD 50 deletion	5 (8)	11 (9)	16 (9)
DMD 52 deletion	10 (16)	16 (13)	26 (14)
Other	2 (3)	1 (<1)	3 (2)

Source: Study DMD114044 report, page 68

Reviewer's Assessment of baseline characteristics:

The baseline characteristics were generally balanced across treatment groups, with a small number of subjects with greater functional impairment in the drisapersen group based on age and 6MWD. The mean time since first diagnosis and time since first symptoms was greater in the drisapersen group. For a large study these differences are not likely to adversely affect the study results.

- **Impact of age distribution:** The subjects <7 years are balanced between the two groups. Subjects ≥ 7 years are also balanced between the two groups, but there were 17% subjects >11 years in the drisapersen group compared to 11% in the placebo group.
- **Impact of 6MWD:** Mean baseline 6MWD was lower in the drisapersen group. I looked at the distribution of 6MWD in the treatment groups. There were higher number of subjects with baseline 6MWD <150m and in between 250-300m in the drisapersen group (18%) compared to placebo (12%), and a higher % of subjects with 6MWD greater than 350 m in the placebo group (54%) compared to drisapersen group (49%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

About 60 (98%) subjects in the placebo group and 119 (95%) subjects in the drisapersen group were >80% compliant. The total dose and duration of exposure were similar.

Efficacy Results - Primary Endpoint

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

Applicant's Analysis: A statistically non-significant ($p=0.415$) treatment difference of 10.3m for drisapersen over placebo at week 48 was observed for the primary endpoint change from baseline in 6MWD.

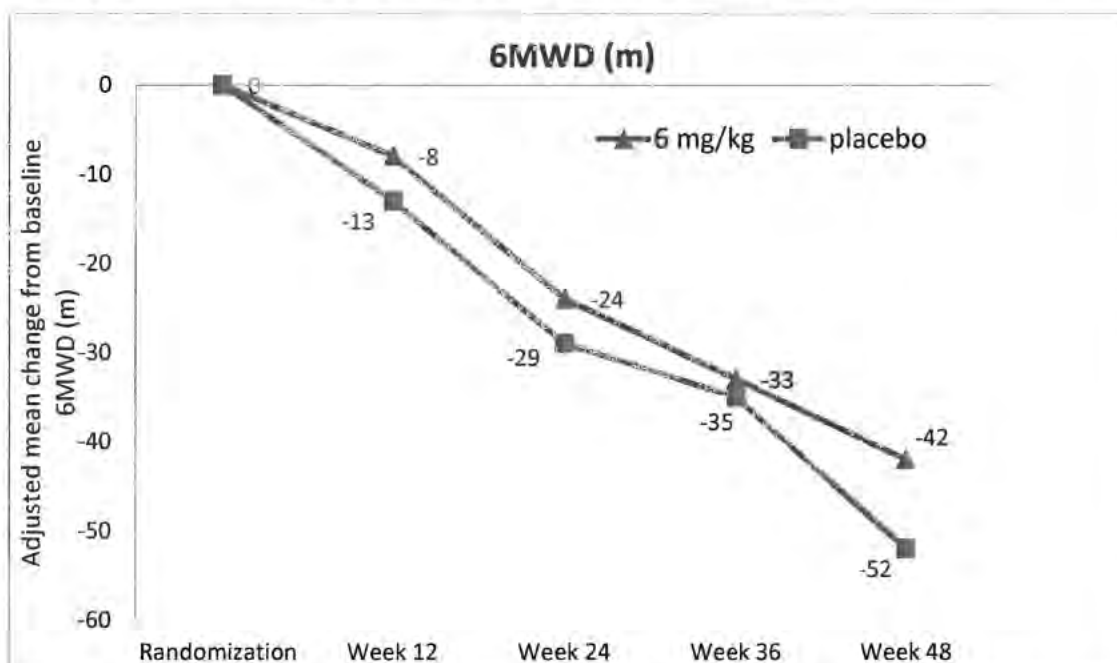
Table 31 MMRM Analysis of change from baseline in 6MWD (m)

	Placebo (N=61)	Drisapersen 6 mg/kg/week (N=125)
Baseline		
n	61	125
Mean (SD)	348 (92)	337(95)
Week 48		
n	59	117
Adjusted mean change (SE)	-52 (10)	-42 (7)
Adjusted mean difference vs. placebo		10
95% CI		(-15, 35)
p-value		0.42

Source: Study DMD114044 report, page 77

I generated the following Figure that shows the time course of the change from baseline for drisapersen 6 mg/kg/week and placebo at each visit.

Figure 17 MMRM Analysis of change from baseline in 6MWD (m)



None of the covariates evaluated showed a significant treatment interaction. Exon mutation and baseline CK were fitted as covariates retrospectively and did not show any significant interaction as well.

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

Sensitivity Analyses:

Most sensitivity analyses were consistent with the primary analyses and gave similar treatment differences, with the exception of MMRM analysis with the PP population (removing protocol violators), where the treatment difference was reduced to 4.9 m ($p=0.703$) (Table 32)

Table 32 Sensitivity Analyses for Change from Baseline in 6MWD (m) at Week 48 (ITT Population)

Analysis/Treatment	n	Adjusted Mean Change from Baseline (SE)	Treatment Difference ^a	95% CI	p-value
MMRM OC (ITT)^a					
Placebo	59	-52 (10)			
Drisapersen 6 mg/kg/wk	117	-42 (7)	10	(-15, 35)	0.42
MMRM OC (PP)^b					
Placebo	53	-45 (10)			
Drisapersen 6 mg/kg/wk	99	-40 (7)	5	(-20, 30)	0.70
ANCOVA OC (ITT)^c					
Placebo	59	-50 (11)			
Drisapersen 6 mg/kg/wk	117	-38 (8)	12	(-14, 37)	0.36
ANCOVA LOCF (ITT)^c					
Placebo	60	-50 (10)			
Drisapersen 6 mg/kg/wk	125	-38 (7)	11	(-13, 36)	0.36
ANCOVA Multiple Imputed (MAR approach) (ITT)^d					
Placebo	59	-50 (10)			
Drisapersen 6 mg/kg/wk	117	-40 (8)	10	(-15, 35)	0.43
ANCOVA Multiple Imputed (CIR approach) (ITT)^d					
Placebo	59	-50 (10)			
Drisapersen 6 mg/kg/wk	117	-40 (8)	10	(-15, 35)	0.44

Additional analyses on 6MWD:

1. Percent-predicted 6MWD: The percent predicted 6MWD in DMD provides an estimate of performance relative to a healthy control population to account for age and development differences. An increase in the percent-predicted 6MWD is consistent with functional improvement. The results of this analysis showed a 2 % difference between the placebo and drisapersen group at Week 48 (95% CI: -2, 6) which was not statistically significant ($p=0.32$)
2. Change from baseline in 6MWD by response category
At week 48, the percent of subjects with ≥ 30 m change in 6MWD was 18% in the drisapersen group and 12% in the placebo group. The percent of subjects with ≥ 60 m change in 6MWD were similar in the two groups.
3. Time to persistent 10% decrease in 6MWD: 43% subjects show persistent 10% decrease in placebo compared to 36% subjects in drisapersen group.
4. Sub-group Analyses: Post-hoc analyses on various subgroups were conducted. Only sub-groups that showed a greater treatment difference at week 48 in the change from baseline in 6MWD over placebo are summarized in Table 33. These large numbers of post-hoc analyses in smaller number subjects are uninterpretable. Sub-group analysis (as summary statistics) in subjects ≤ 7 years and > 7 years was pre-specified, other sub-group analyses were post hoc. Subjects

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

>7 years showed a treatment difference of 7 m, whereas subjects less than 7 years showed a treatment benefit of 21 m (Table 33). Other sub-group analyses showing treatment difference in favor of 6 mg/kg is summarized in the following Table.

Table 33 Sub-group Analyses

Treatment	N	Baseline Mean (SD)	n	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI
Age ≤7 years at Baseline (pre-specified)						
Placebo	29	383 (66)	29	-25 (11)	21	(-6, 48)
Drisapersen 6 mg/kg/wk	51	368 (65)	50	-4 (8)		
Rise from Floor >7s at Baseline						
Placebo	26	318 (77)	25	-88 (16)	21	(-20, 61)
Drisapersen 6 mg/kg/wk	47	307 (75)	43	-67 (12)		
Able to Stand from Supine at Baseline (Rise from Floor Grade >1)						
Placebo	55	363 (82)	53	-43 (10)	15	(-10, 40)
Drisapersen 6 mg/kg/wk	106	360 (80)	102	-28 (7)		
≤330 m at baseline						
Placebo	22	256 (67)	21	-93 (22)	18	(-32, 69)
Drisapersen 6 mg/kg/wk	57	253 (66)	50	-75 (14)		
Centers previously enrolled in other studies						
Placebo	9		9	-109(25)	62	(-2, 126)
Drisapersen 6 mg/kg/wk	17		17	-47(18)		

Change from baseline by country grouping showed largest treatment difference in Northern Europe and Russia-Eastern Europe grouping, but the number of subjects was small.

5. Time to a 25, 50% and 75 % decrease in 6MWD: These similar across treatment groups.
6. 6MWD in subjects with Rise from Floor ≤7 seconds: In this study there were no restrictions on rise from floor time. As a post-hoc analysis in this subgroup, the treatment difference (5m) was smaller than in the DMD114044 population as a whole (10m). In fact the treatment difference was larger in subjects with rise from floor >7 seconds (21m). The applicant indicates that the greater range of rise from floor values at baseline was not the primary reason for the differing results (Table 34).

Table 34: MMRM Analysis of Change from baseline in 6MWD at week 48 by baseline Rise from Floor

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

Treatment	N	Baseline Mean (SD)	n	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI
Rise from Floor $\leq$7s at Baseline						
Placebo	29	404 (62.520)	28	-4 (10)	5	(-18, 28)
Drisapersen 6 mg/kg/wk	59	402 (55.540)	59	1 (7)		
Rise from Floor $>$7s at Baseline						
Placebo	26	318 (77)	25	-88 (16)	21	(-20, 61)
Drisapersen 6 mg/kg/wk	47	307 (75)	43	-67 (12)		

Source: Study DMD114044 Study Report, page 83

Data Quality and Integrity - Reviewers' Assessment

There were no issues with data quality or integrity.

Efficacy Results - Secondary and other relevant endpoints

No significant treatment differences or consistent trends in favor of drisapersen were observed for any key or other secondary endpoints (Table 35)

Table 35 Secondary endpoints

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

Treatment	n	Baseline Mean (SD)	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI	p-value
Key Secondary Efficacy Endpoints						
Linearized NSAA Total Score						
Placebo	58	58.4 (17.71)	-6.7 (1.43)			
Drisapersen 6 mg/kg/wk	117	56.6 (18.85)	-7.2 (1.01)	-0.53 ^a	(-3.95, 2.88)	0.757
4 Stair Climb Ascent Velocity (stairs/s)						
Placebo	55	0.88 (0.573)	-0.12 (0.049)			
Drisapersen 6 mg/kg/wk	111	0.86 (0.658)	-0.14 (0.035)	-0.021 ^a	(-0.137, 0.095)	0.718
10 m Walk/Run Velocity (m/s)						
Placebo	58	1.57 (0.542)	-0.20 (0.050)			
Drisapersen 6 mg/kg/wk	117	1.54 (0.575)	-0.21 (0.035)	-0.009 ^a	(-0.129, 0.111)	0.881
Other Secondary Efficacy Endpoints						
Rise from Floor (s)^c						
Placebo	44	13.41 (15.882)	7.48 (2.080)			
Drisapersen 6 mg/kg/wk	91	12.34 (14.984)	6.36 (1.463)	-1.115 ^b	(-6.097, 3.866)	0.658
4 Stair Climb Descent Velocity (stairs/s)						
Placebo	55	0.98 (0.601)	-0.15 (0.052)			
Drisapersen 6 mg/kg/wk	109	1.02 (0.634)	-0.11 (0.037)	0.041 ^a	(-0.082, 0.164)	0.513
Muscle Strength Total Score (lbs)						
Placebo	58	98.55 (30.527)	-1.21 (2.729)			
Drisapersen 6 mg/kg/wk	118	102.49 (34.941)	-2.18 (1.926)	-0.965 ^a	(-7.446, 5.516)	0.769
Creatine Kinase (IU/L)						
Placebo	60	11901.1 (7133.32)	-1228.5 (500.59)			
Drisapersen 6 mg/kg/wk	118	10956.5 (7316.07)	-5273.5 (359.05)	-4044.99 ^b	(-5232.21, -2857.77)	<0.001

Source: Adapted from Study DMD114044 report

There were no meaningful changes in pulmonary functions tests (not shown in the Table).

Creatine Kinase:

A statistically significant treatment difference in favor of drisapersen in change from baseline in creatinine kinase serum concentration was observed at week 48 with a 48% decrease in absolute mean CK in the drisapersen group compared to 10% in the placebo group.

Table 36 Summary of MMRM analyses of Serum creatine kinase (IU/L)

Treatment	N	Baseline Mean (SD)	n	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI P-value
Placebo	61	11901 (7133)	60	-1228 (500)		
Drisapersen 6 mg/kg/wk	125	10956 (7316)	118	-5273 (359)	-4044	(-5232, -2858) <0.001

Source: page 91

Clinical Review (Efficacy)

NDA 206, 031 (Drisapersen)

Post-hoc analyses on CK: Post-hoc analyses showed a greater decline in CK compared to placebo in subjects ≤ 7 years vs. > 7 years, consistent with a larger treatment difference with 6MWD observed in ≤ 7 years (Table 37).

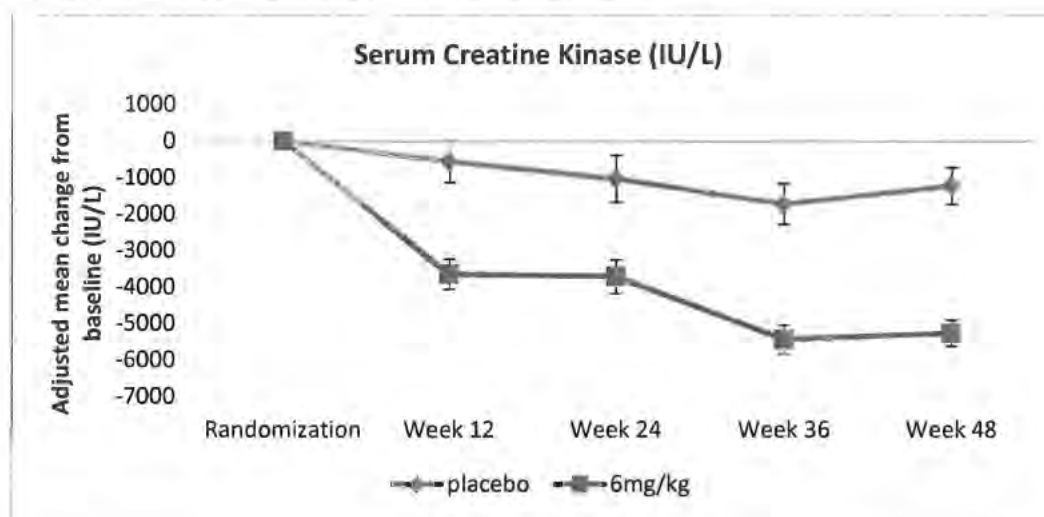
Table 37 MMRM analysis of CK based on age group

Treatment	N	Baseline Mean (SD)	n	Adjusted Mean Change from Baseline (SE) at Week 48	Treatment Difference	95% CI
≤ 7 years at baseline						
Placebo	29	15471 (6834)	29	-1314 (831)		
Drisapersen 6 mg/kg/wk	51	15626 (8422)	49	-7230 (613)	-5916	(-7890, -3942)
> 7 years at baseline						
Placebo	32	8666 (5794)	31	-1439 (570)		
Drisapersen 6 mg/kg/wk	74	7738 (4075)	69	-3589 (407)	-2149.	(-3455, -845)

Source: Study DMD114044 report, page

I generated the following Figure 18 that shows the time course of reduction in CK.

Figure 18 MMRM analysis of change from baseline in CK



CGI-I, PedsQL, Health Utility Index Scores, and Activities of Daily Living: A total of 1 (2%) subject in the placebo group and 12 (10%) subjects in the drisapersen group were considered responders (much improved or very much improved) on the CGI-I at Week 48. Two (4%) subjects in the placebo group and 23 (20%) subjects in the drisapersen group minimally improved on the CGI-I at Week 48. There were no clinically meaningful treatment differences between drisapersen and placebo for the PedsQL Neuromuscular Module, HUI health outcomes assessments and Activities of Daily Living.

Time to loss of ambulation: A total of 6 (10%) subjects in the placebo group and 15 (12%) subjects in the drisapersen group lost ambulation during the study. A Kaplan-Meier analysis of Time to loss of ambulation did not show any difference (Figure not shown). There was a complete overlap of the 95%

Clinical Review (Efficacy)

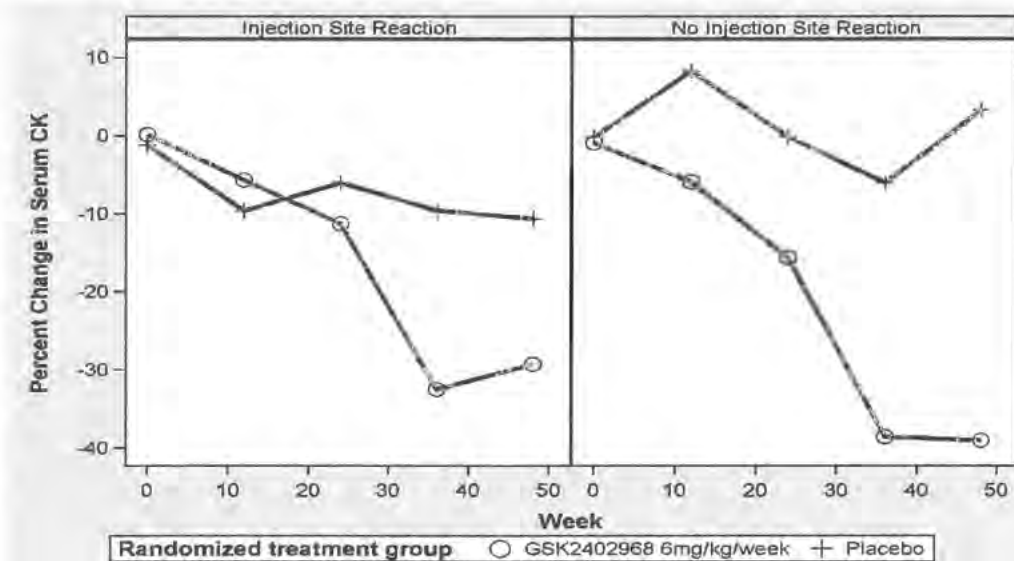
NDA 206, 031 (Drisapersen)

confidence interval between treatment groups. Subjects who lost ambulation had a higher mean age in both treatment groups (placebo: 9 years; drisapersen: 10 years) compared with subjects who remained ambulant during the study (placebo: 8 years; drisapersen: 8 years).

Reviewer's Analysis and Comment:

Since the difference in CK between the treatment and placebo groups were statistically significant ($p < 0.001$), I wanted to explore if this difference was due to inactivity resulting from injection site reactions. The reduction of CK was greater in the treatment group compared to placebo whether subjects had an injection site reaction or not, as depicted in Figure 19. The level of activity/inactivity could not be assessed by patient reported outcomes or other means. Overall CK was reduced by 32% in the drisapersen group.

Figure 19 Change from baseline serum CK in subjects with or without injection site reactions



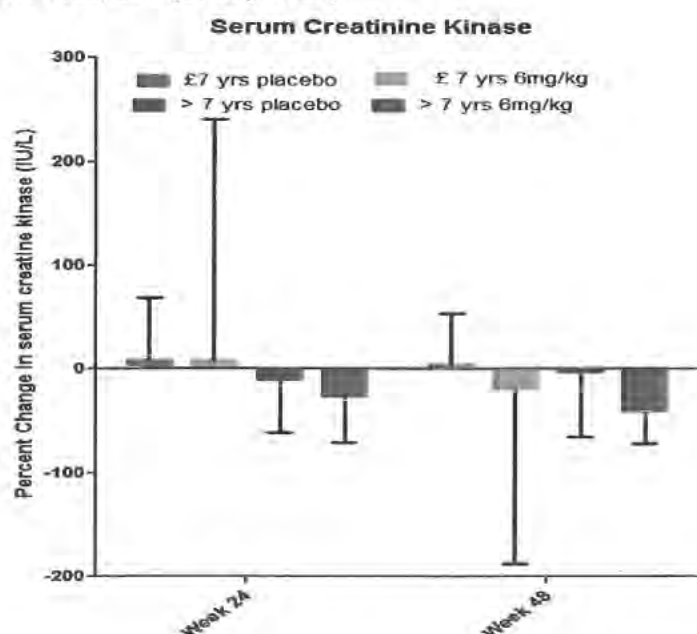
Source: Dr. Bhattaram

The MMRM analysis of serum CK based on age groups (≤ 7 years and > 7 years), showed greater reduction in CK in subjects ≤ 7 years, consistent with the age based analysis on 6MWD.

Since, the baseline CK is higher in the younger age group, I looked at percent reduction in these groups. At Week 48, the subjects > 7 years showed greater mean reduction in serum CK (-41%) compared to the subjects ≤ 7 years (-18%), opposite to what was observed when looking at adjusted mean change from baseline. There was much larger variability in the CK in subjects ≤ 7 years.

Figure 20 Percent change in serum creatine kinase in subjects ≤ 7 years and > 7 years

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)



Dystrophin Measurements

Two muscle biopsies were obtained from each subject, one at Week 48, the other biopsy at either Week 8, 12, 24 or 36 from the tibialis anterior in most subjects with the exception of quadriceps in 3 subjects. No muscle biopsies were performed at baseline. Therefore the applicant analyzed the muscle biopsies for drisapersen concentration, detection on exon 51 skipping by non-quantitative RT-PCR only and the number of revertant fibers (as it could influence the amount of exon skip observed in total RNA).

Exon 51 Skipped mRNA:

With a non-quantitative RT-PCR, skipping of exon 51 was detected in 48 (81%) subjects in the placebo group and 106 (89%) subjects in the drisapersen group at Week 48. There was a weak trend to higher intensities in the drisapersen treated group beyond 24 weeks of treatment. (Table 38).

Table 38 Exon 51 skip with non-quantitative RT-PCR

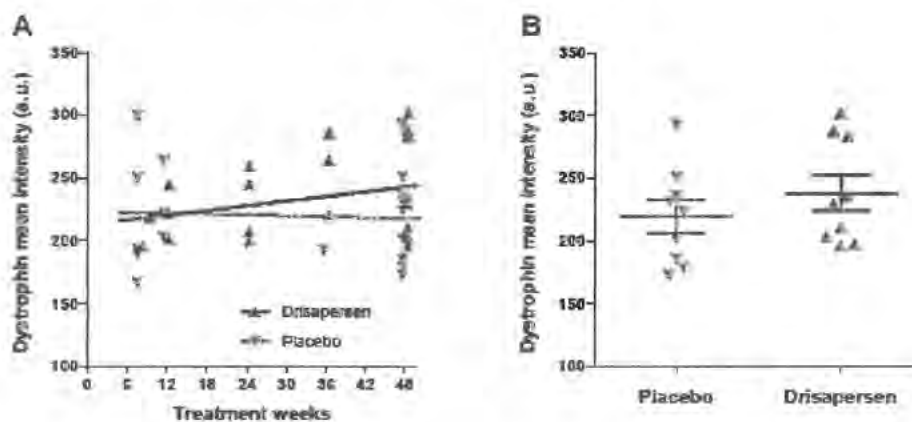
Test/ Visit	Placebo (N=61)		Drisapersen 6 mg/kg/week (N=125)	
	n	Mean (SD)	n	Mean (SD)
DMD Exon 51 skip - Integrated intensity (units)				
Week 8	20	1.75 (1.25)	26	1.25 (1.55)
Week 12	16	2.02 (1.78)	30	1.64 (1.79)
Week 24	9	1.52 (1.03)	34	2.32 (2.90)
Week 36	13	0.91 (0.56)	26	2.86 (5.18)
Week 48	56	1.43 (1.69)	114	2.49 (3.46)

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

Dystrophin expression by IFA:

According to the Applicant, many biopsies were not acceptable for dystrophin analysis: due to freeze damage, small size and/or relative large areas of adipose and connective tissue (indicative of advanced disease state), an insufficient number of fibers with intact membranes can be identified for a representative and reproducible result. A summary of dystrophin analysis on selected biopsies were performed by the operators that were blinded to study treatment during analysis is presented in Figure 21. The results in placebo patients show the presence of dystrophin both with IFA and WB, which is considered a result of trace dystrophin expression in many fibers and/or dystrophin expression in revertant fibers. Therefore, the applicant concluded that in the absence of pre-treatment biopsies, the IFA results would not provide relevant information in this study.

Figure 21 Dystrophin mean intensities on selected biopsies



Reviewer's Comment: The numbers of subjects were few at each time point. There was a trend of increased dystrophin intensity with a large inter-subject variability in the drisapersen group.

OBP Reviewer Dr. Rao's comments:

The applicant reports several problems with the quality of the biopsy samples. They state that repeated freeze-thaws of the tissue samples being shipped from multiple international sites in an aluminum tube container to a central re-distributing laboratory for analysis led to rejection of a large number of samples with freezing-related artifacts that were deemed unsuitable for IFA or WB. The absence of pre-treatment samples from the same patients probably renders any treatment-related conclusions questionable.

MRI:

According to the Applicant, MRI data were only acquired in a small number of subjects and data were not analyzed due to technology issues at acquisition.

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

Applicant's discussion on lack of response in this study:

The applicant attributes the following factors to have led to a less favorable outcome in this Phase 3 study:

- **Demographic and baseline population makeup** – Subjects in DMD114044 had, on average, more functional impairment than subjects in the Phase II studies (as measured by baseline 6MWD). Also, unlike the Phase II trials, DMD114044 did not include a baseline requirement for performance on the rise from floor assessment. This change led to further enrolment of older, more severely progressed subjects in DMD114044, most of whom would not have met the criteria for enrolment in the Phase II studies. According to the applicant, these patients would have had fewer intact muscle cells where increased dystrophin levels due to exon skipping would have an impact. Pre-specified subgroup analyses of the DMD114044 data show that subjects ≤ 7 years performed similarly at Week 48 to subjects in the Phase II studies, with a 21 meter treatment effect in favor of 6 mg/kg/week drisapersen (not statistically significant). Subjects > 7 years in DMD114044 showed a small numerically favorable treatment effect (7 meters) and a large decline from baseline 6MWD performance (-76 meters), possibly indicating subjects in the decline phase of their ambulatory capacity.
- **Treatment duration**- 48 weeks not adequate to demonstrate treatment benefit in a heterogeneous population
- **Lack of a loading dose** – unlike Study DMD114117, there was no loading dose in DMD114044. As a result, subjects likely took longer to achieve steady state for drug effect. This could be important in an already more progressed population.
- **Multiple centers** – because of the size of the study, DMD114044 required more study sites in more countries (44 sites in 19 countries) than were employed in the Phase II studies, including some sites that were not specialized in DMD management. This global reach is likely to have led to increased variability in standard of care in areas such as steroid usage and frequency of formal physiotherapy. A post hoc analysis of DMD114044 sites previously participating in study DMD114117 showed a difference of 62 m ($p=0.06$) in change from baseline 6MWD at Week 48 between drisapersen 6 mg/kg/week (-47m; $n=17$) and placebo (-109m; $n=9$) suggesting that experience in management of DMD patients and in conducting assessments in the context of a clinical trial, may help to decrease variability and enable detection of a treatment effect.

Reviewer's analysis/discussion:

The only strength of this study was:

- A favorable effect of serum creatine kinase at Week 48 ($p<0.001$). No apparent relationship was observed between reduction in CK from baseline and 6MWD response. There is a 30-40% reduction in CK across studies.
- There were some differences observed in the patient population that could have an unfavorable prognosis in the drisapersen group in this study, although it is unlikely that these differences could account for some modest differences in the outcome in a large study. In a large study these differences in baseline characteristics are difficult to interpret.
 - There were 17% subjects >11 years in the drisapersen group compared to 11% in the placebo group.

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

- There were 18% of subjects with baseline 6MWD <150m and in between 250-300m in the drisapersen group compared to 12% in the placebo group.
- There were 49% subjects with baseline 6MWD >350 m in the drisapersen group compared to 54% in the placebo group.
- The study design was identical to the phase 2 studies, with the exception of no restriction on the ability to rise from floor. Hence, subjects >7 seconds were also enrolled in this study. In a post-hoc analysis in subjects with Rise from Floor <7seconds, the treatment difference of 5 m was observed, which was smaller than in the DMD114044 population as a whole (10 m). The applicant indicates that the greater range of rise from floor values at baseline was not the primary reason for the differing results.
- In a post-hoc analysis, the applicant states there was a treatment difference of 62m in favor of drisapersen in study sites that participated in prior drisapersen studies, and might have been more experienced at collecting data. However, I assessed the quality of data for the primary and key secondary endpoints across studies and centers and there did not appear to be any meaningful or systematic differences in the values or trajectories between centers that would suggest differences in the way the data was collected (See Appendix C). The sponsor's analysis therefore does not appear reasonable. Furthermore, the remaining sample size of this entirely post-hoc analysis is so small, 9 subjects in the placebo group and 17 in the drisapersen group, that it could have readily arisen by chance alone.

The weaknesses of this study are:

- The primary endpoint (change from baseline in 6MWD at Week 48) did not show a statistically significant treatment difference from placebo, although the study was a well-designed and executed study with good statistical power to detect a small effect.
- Percent change from baseline in CK based on age group is not consistent with age group effect on treatment response on 6MWD, but so was reduction in CK not consistent with treatment effect in the primary analysis. (i.e. treatment difference with 6MWD negative, treatment difference with CK positive)
- No consistent trends in favor of drisapersen were observed for any key or other secondary endpoints.
- There could have been partial unblinding due to differences in injection site reactions between the drisapersen (78%) and placebo groups (16%) leading to lean in 6MWD in favor of drisapersen. Although, the impact of potential unblinding is not as apparent in this study as though directionally favorable, the effect size was small. Nevertheless, a small numerical difference between treatments could be due to unblinding.
- There was a weak trend of higher intensity of exon 51 skipping.

6.4. Study DMD114349 (Open label extension study)

6.4.1. Study Design

Overview and Objective

Clinical Review (Efficacy)

NDA 206, 031 (Drisapersen)

This study was designed to assess the long-term safety, efficacy, and tolerability of drisapersen for at least 104 weeks in subjects with DMD who previously participated in either feeder study (DMD114117 or DMD114044). The study was terminated early because results of Study DMD114044 showed that the primary efficacy endpoint was not achieved.

Study Dates: 19 September 2011 to 17 March 2014 (termination) (no dosing occurred after 20 September 2013)

Study Centers: 58 centers in 24 countries: Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, The Netherlands, Norway, Poland, Russian Federation, Spain, Taiwan, Turkey, and United Kingdom.

Trial Design

This was a Phase III, multicenter, open-label, uncontrolled extension study in subjects with DMD who had completed the double-blind treatment phase in DMD114117 or DMD114044. Eligible subjects entered into a 4-week Run-in period of the study. No assessments were conducted and no drug was administered during this Run-in period.

Study Population: 6- to 17-year-old (median of 9 years) males were enrolled. Subjects entering this study had mean times since first symptoms, diagnosis, and first corticosteroid use of 80.4, 66.1, and 43.9 months, respectively. The corticosteroid regimen given during the feeder studies (DMD114117 or DMD114044) was continuous for 80% of the subjects and intermittent for 20%.

Dosing Regimen: The primary dosing arm for all subjects was 6 mg/kg/week continuous dosing for at least 104 weeks, but subjects had the option of intermittent dosing (6 mg/kg/week for 8 weeks and 4 weeks off drug) based on safety and tolerability issues. At any point during the study, subjects could discontinue active treatment and move to the natural history observation arm for the duration of the study or until Early Withdrawal.

Primary endpoint: Change from baseline in muscle function using the 6MWD test assessed at Week 104. (Note: Baseline efficacy assessments were only required for those subjects who had withdrawn early from the feeder studies and who did not have these assessments performed within the previous 3 calendar months, for other last assessment from feeder studies were used as baseline).

Secondary endpoints: same as feeder studies.

Muscle Biopsy for dystrophin expression: Only subjects who showed an unexpected decrease in efficacy required a muscle biopsy, defined as two consecutive 20% decreases in 6MWD after Week 24 in those subjects previously demonstrating improvement or maintenance of 6MWD (unless an alternative explanation (e.g., fall))

MRI: MRI was to be conducted in those subjects where it was obtained in Study DMD114044

Statistical Analysis Plan

No formal interim analysis, but the first data-cut was planned for 05 June 2013.

The primary population for evaluation of efficacy parameters was the Modified ITT population, defined as all subjects enrolled in the study that received at least 1 dose of investigational product, or entered the natural history arm at the start of the study and as such did not take any investigational product, and had at least one post-baseline efficacy assessment. A Modified Ambulant ITT population, defined

Clinical Review (Efficacy)

NDA 206, 031 (Drisapersen)

as above, but only in the ambulant population was used for analysis using pre-specified MMRM model with a 5% significance level was used for 6MWD, NSAA and timed function tests. An analysis pooling all the subjects from the two studies was uninterpretable; hence the applicant conducted post-hoc analyses based on parent studies.

Data Quality and Integrity: Sponsor's Assurance

This study was conducted in accordance with ICH GCP and all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008. Management of clinical data was performed in accordance with applicable GSK standards. The study was monitored in accordance with ICH E6.

6.4.2. Study Results**Patient Disposition**

A total of 233 subjects were enrolled. 228 subjects were assigned to continuous treatment with drisapersen 6 mg/kg/week, 4 subjects were assigned to intermittent treatment with drisapersen 6 mg/kg (12 week cycles of drisapersen 6 mg/kg/week for 8 weeks followed by 4 weeks of no dosing), and 1 subject was assigned to the natural history arm (no treatment). Of the 228 subjects assigned to continuous treatment with drisapersen 6 mg/kg/week at the start of the long-term extension study, 8 switched to intermittent treatment, 15 subjects switched to the natural history arm, and 1 of the subjects who initially switched to intermittent treatment switched to the natural history arm due to an AE. The final numbers in each arm after switching regimens during study were: Continuous N=205, Continuous to Intermittent N=7, Continuous to Intermittent to natural History N=1, Continuous to Natural History N=15, Intermittent N=4, Natural History N=1. The number of subjects that withdrew during the study and the reason is shown in Table 39. The rest of the subject's attrition was due to termination of the study.

Table 39 Subjects withdrawn

	Number of subjects
Subjects Withdrawn	17
Reason	
AE	3
Lack of efficacy	2
Protocol Deviation	1
Withdrew Consent	11

Note: only 1 subject who withdrew was from Study DMD114117

Subjects were treated with 6 mg/kg drisapersen continuously over a mean total duration of 353 days; 74%, 57%, and 24% of the subjects received investigational product for ≥ 24 weeks, ≥ 48 weeks, and ≤ 72 weeks, respectively. Due to the small numbers of subjects in the drisapersen intermittent treatment group or the natural history arm at the time of early study termination, applicant's discussion focuses

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on the drisapersen continuous treatment group through 72 weeks (N=55). The cumulative exposure of each regimen is given in Table 40.

Table 40 Summary of cumulative exposure

	6 mg/kg Drisapersen Continuous	6 mg/kg Drisapersen Intermittent	6 mg/kg Drisapersen (Combined)	Natural History
Cumulative Duration of Exposure (weeks), n (%)				
n	228	12	232	17
0 weeks	0	2 (17)	0	0
>0 weeks	228 (100)	10 (83)	232 (100)	17 (100)
≥6 weeks	226 (>99)	9 (75)	229 (99)	15 (88)
≥12 weeks	201 (88)	8 (67)	205 (88)	13 (76)
≥18 weeks	178 (78)	7 (58)	181 (78)	11 (65)
≥24 weeks	168 (74)	5 (42)	171 (74)	9 (53)
≥48 weeks	131 (57)	3 (25)	136 (59)	3 (18)
≥72 weeks	55 (24)	0	60 (26)	0
≥104 weeks	0	0	0	0

Source: NDA 206, 031 Study Report DMD114379

Protocol Violations/Deviations

Protocol deviations were reported by the site for 230 (99%) subjects overall, mostly related to study procedures/assessments not performed on the exact day, but reviewing the data they were mostly within 1 week of the scheduled visit. A total of 23% of the subjects either had an extra dose, did not get a dose, got a wrong dose or dose was given at an incorrect time.

Table of Demographic Characteristics

The study population consisted of 6- to 17-year-old (median of 9 years), predominantly White (78%), non-Hispanic (86%) males. Baseline age characteristics are shown in Table 41.

Table 41 Baseline Age

Demographic Characteristic	6 mg/kg Drisapersen Continuous (N=205)	6 mg/kg Drisapersen Intermittent (N=11)	Natural History (N=17)	Total (N=233)
Age (years)				
Mean (SD)	8.9 (2.12)	9.9 (1.73)	8.7 (1.69)	9.0 (2.14)
Median	9.0	9.5	9.0	9.0
Min, Max	6, 17	8, 14	6, 12	6, 17

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

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 81% of the subjects were more than 80% compliant.

Efficacy Results - Primary Endpoint

Applicant's Analysis:

The applicant considered the results pooling subjects from the two parent studies uninterpretable, because the parent studies showed different results and the population was more progressed in Study DMD114044, an analysis based on each parent study was considered appropriate by the applicant. The applicant considers subjects from study DMD114117 more functional population and subjects in Study DMD114044 as a more progressed population. The change from original baseline in 6MWD from parent studies is shown in Table 42 and Table 43.

Table 42 Change from original baseline in 6MWD (m) by parent study (Study DMD 114117)

Treatment in parent study (DMD114117)	Placebo	Drisapersen 6 mg/kg/week	
Treatment in DMD114349	Drisapersen 6 mg/kg weekly or intermittent	Drisapersen 6 mg/kg/week	Drisapersen 6 mg/kg weekly or intermittent
Original baseline, n Mean (SD)	18 403 (45)	18 428(70)	18 428 (70)
Change to Study 349 Week 48, n Mean (SD)	14 -55 (78)	16 1.24 (69)	17 -5 (68)
Change to Study 349 Week 72, n Mean (SD)	11 -89 (126)	12 -33 (71)	13 -39 (71)

Source ISE Table 10.1.3

Table 43 Change from original baseline in 6MWD (m) by parent study (Study DMD 114044)

Treatment in parent study	Placebo	Drisapersen 6 mg/kg/week	
Treatment in DMD114349	Drisapersen 6 mg/kg weekly or intermittent	Drisapersen 6 mg/kg/week	Drisapersen 6 mg/kg weekly or intermittent

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Original baseline, n Mean (SD)	60 348 (93)	116 346 (92)	119 343 (94)
Change to Study 349 Week 48, n Mean (SD)	37 -123 (135)	61 -92 (130)	61 -92 (130)
Change to Study 349 Week 72, n Mean (SD)	25 -173 (132)	35 -108 (134)	37 -106 (132)

Source ISE Table 10.1.3

According to the applicant, subjects who received drisapersen in both the parent study were combined, the subjects on drisapersen continuous regimen in both parent and the extension study had a smaller decline in 6MWD (-89 m) than those who received placebo in the parent study followed by drisapersen in the extension study (-142 m) at Week 72 (overall Week 120). The treatment difference in the two groups (continuous and delayed start was, 31m at Week 96 (from study baseline) and 59m at Week 120.

Based on these results, the applicant believes that this reinforces the notion that subjects who are treated younger (and presumably prior to the onset of more serious functional impairment) will get a greater benefit of treatment with drisapersen in the long-term. At the time of study termination, 21 (10 %) subjects in the continuous treatment arm lost ambulation. Four subjects required respiratory support during sleep.

Efficacy Results - Secondary and other relevant endpoints:

Timed Tests, Muscle strength and NSAA: Small changes from baseline were observed on secondary endpoints (e.g., muscle strength, timed muscle function tests [rise from floor, 10-meter walk/run, 4-stair climb (ascent/descent)], NSAA total score) in both the delayed placebo and drisapersen arms in both studies at different visits. The applicant only discusses the results in terms of the continuous regimen. Subject on the intermittent regimen when switched to continuous regimen continued to show larger decline, consistent with the greater impairment in this group at baseline.

Pulmonary Function tests: No clinically meaningful change was seen in any pulmonary function test.

PedsQL, Health Utilities Index, CGI-I, Functional Outcome Assessment: No meaningful differences in the continuous drisapersen arm and the delayed drisapersen arm

Serum CK: CK showed a decline over 72 weeks, but was very variable.

Dystrophin and MRI: No subjects demonstrated an unexpected decrease in efficacy that required a muscle biopsy to quantitate dystrophin expression. No MRI or dystrophin expression data has been provided from this study.

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Durability of Response

Reviewer's Comment: The durability of response is uninterpretable from this study as not all subjects completed the study.

Reviewer's Comments/Discussion:

The dropout of subjects during the study and the lack of control make this study uninterpretable, even if the analyses are on parent studies. A total of 26%, 43% and 76% of the subjects dropped out from the study at 24 weeks, 48 weeks and 72 weeks due to AE or termination of the study.

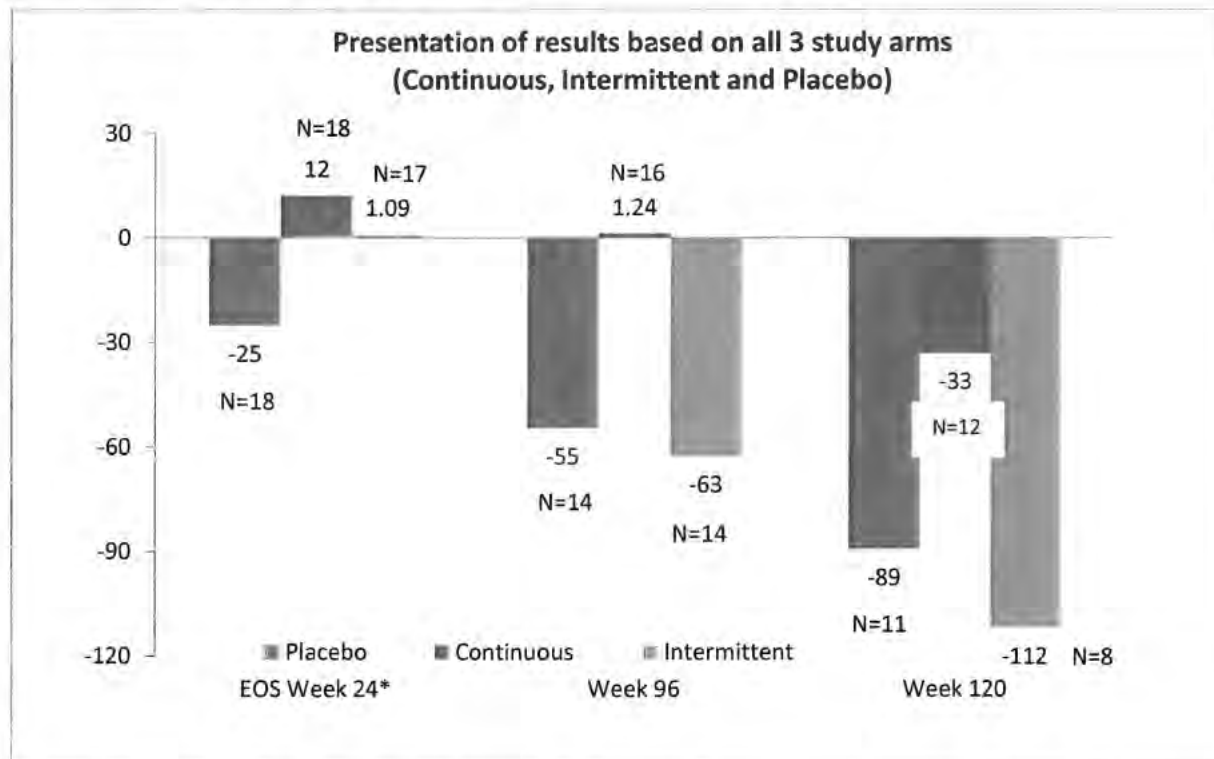
The Applicant has discussed the open label extension results based on the parent studies. For Study DMD114117, the results have been discussed only for the continuous 6 mg/kg/week drisapersen arm and the placebo arm switched to the 6mg/kg/week regimen. The parent study DMD114117 was a three arm study with 18 subjects each on intermittent and continuous drisapersen 6mg/kg regimen. The subjects that were in intermittent regimen in the parent study, when switched to continuous 6mg/kg/week regimen under Study DMD114349, continued to decline (Figure 22). These subjects appeared to have more functional impairment compared to the continuous treatment arm at baseline of the parent study as also stated by the applicant in the ISE and their probable reason that the intermittent group did not show treatment difference from placebo. The applicant has not explained the evidence supporting efficacy in context of the deterioration seen in these subjects when switched to continuous regimen from the intermittent regimen in the parent study. While these data are not completely interpretable because not all subjects completed their assigned treatments during the study, but do suggest the subjects appear to follow their course of progression. The disease trajectories appeared to be different in the three treatment arms at the start of the study.

Based on these results of extension of Study DMD114117, the applicant believes that this reinforces the notion that subjects who are treated younger (and presumably prior to the onset of more serious functional impairment) will get a greater benefit in the long-term of treatment with drisapersen. While it may seem logical that it may be pharmacologically easier to restore dystrophin before much muscle damage occurs, and hence benefit may be discernable when treated young, there is no clear evidence supporting this hypothesis. Published natural history data suggest that some subject can have better prognosis than other based on baseline 6MWD, age and genetic disposition (LTBP4 genotype predicts age of ambulatory loss in DMD). In addition, experts in the area have also shown that higher baseline function is almost always associated with slower long-term decline in DMD. (McDonald:

http://www.treatnmd.eu/downloads/file/meetings/2013/workshop/Session1/McDonald_NH.pdf

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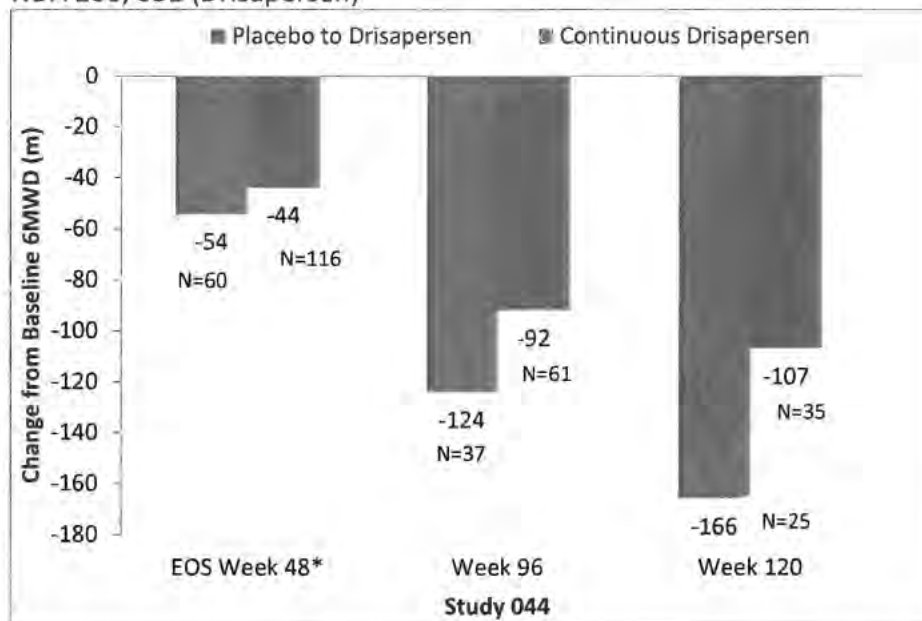
Figure 22: Adjusted mean change from baseline 6MWD in the open label extension of Study DMD114117 (all three arms presented)



At weeks 96 and 120, treated subjects from parent Study DMD114044 had larger decline in the extension phase (Figure 23). This is consistent with a more impaired population. The applicant also asserts that that treatment benefit is slower to emerge in subjects with advanced age. While this could be true, the drop out of subjects during the study (N's shown in the figure), preclude reliable conclusions from this study. Therefore, there is no convincing evidence suggesting longer treatment would be needed to show treatment benefit in subjects with advanced age and more functionally impaired subjects.

Figure 23 Adjusted mean change from baseline 6MWD in the open label extension of Study DMD114044

Clinical Review (Efficacy)
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6.5. Study DMD114673 (Open Label Extension Study)

6.5.1. Study Design

Overview and Objective

This was an open label long-term extension of Study PRO051-02 (a 5 week dose escalation study with 0.5, 2, 4 and 6 mg/kg doses) in patients with Duchenne muscular dystrophy. The Applicant has used this as a historically controlled Study.

Study Date: 30 July 2009 (start of Continued Treatment Phase) to 26 Mar 2013 (completion of 188 week), 25-Jun 2013 (completion of IV sub-study)

Study Centers: 2 centers (Belgium and Sweden)

Trial Design

All subjects from Study DMDPRO51-02 were moved to a Continued Treatment Phase with 6 mg/kg/week dose. The applicant's intention is to continue treatment for 216 week. Data up to 188 week has been included in this NDA. Baseline assessments were conducted again prior to the first dose in the Continued Treatment Phase at Visit 13. Safety, efficacy and pharmacokinetic assessments were conducted at regular intervals throughout the Continued Treatment phase. Glucocorticoid use was to be kept constant during the study unless medical reasons dictated otherwise.

Inclusion Criteria:

- Boys aged between 5 and 16 years
- Not ventilator dependent
- Life expectancy of at least six months

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Exclusion Criteria:

- Any subject who did not complete the initial Study Period of PRO051-CLIN-02
- Aberrant RNA splicing and/or aberrant response to drisapersen, detected by in vitro drisapersen assay during screening.
- Known presence of dystrophin in $\geq 5\%$ of fibers in a pre-study diagnostic muscle biopsy
- Severe muscle abnormalities defined as increased signal intensity in $>50\%$ of the tibialis anterior muscle at MRI
- FEV1 and/or FVC $<60\%$ of predicted, history of liver or renal disease, severe cardiac myopathy

Dosing Regimen:

- Between PRO051-02 and DMD114673 subjects received no drisapersen treatment for 6-15 months.
- From Visit 13 to Visit 85 (Study Week 72), all subjects received a weekly s.c. dose of 6 mg/kg.
- Starting Visits 86 to 93 (Study week 73-80), all subjects had a 8 week wash-out period due to the emerging safety data from other studies. It was anticipated that the washout would not compromise efficacy due to the predicted retention of drug in muscle and the known long half-life of dystrophin.
- At Visit 94 (Week 81) subjects restarted drisapersen on a 12 week cycle intermittent regimen (8 weeks treatment of 6 mg/kg followed by 4 weeks off-treatment). Based on PK/PD, the intermittent regimen, the dystrophin levels were predicted to be 70% of the level prior to wash-out and 80% at the end of the 8 week treatment period. This measure was taken to minimize the hepatotoxicity and nephrotoxicity.

If a perceived continuous decline in efficacy was observed and where safety and tolerability was acceptable, subjects was given the option to return to continuous regimen. Treatment is currently ongoing in all subjects according to the intermittent dosing schedule and no subjects have reverted to continuous weekly dosing up to Visit 201 (Week 188).

A weight cap on dosing was implemented:

- subjects with body weight <50 kg continued to be dosed with 6 mg/kg drisapersen;
- subjects with body weight ≥ 50 kg received a fixed maximal dose of 300 mg drisapersen.

Injection was preferred in the abdominal subcutis but alternate sites were allowed. Injections had to be separated by at least 4 inches, if two or more injections were required at a given time.

Study Endpoints

- 6MWD
- Timed Function Tests (10m walk/run, Rise from Floor, Stair Climb)
- Muscle Strength by handheld myometry
- Pulmonary Function (FVC, FEV1, MEP, MIP, PC and PCF)
- Muscle Biopsy at Visit 37 (week 24) and Visit 65 (Week 52, optional), Visit 81, optional
 - mRNA production
 - Dystrophin Expression
- Parent Questionnaire to capture:
 - loss of any skills or daily activities,
 - improvements in daily activities,

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 ▪ development of new skills

Statistical Analysis Plan

Study was analyzed by only descriptive statistics.

Data Quality and Integrity: Sponsor's Assurance

The study was conducted according to ICH GCP guidelines for assuring proper study conduct with regard to protocol adherence and validity of the data recorded on the CRFs. The study was monitored in accordance with ICH E6.

6.5.2. Study Results

Patient Disposition

All 12 subjects who participated in the initial 5 week Study DMD PRO051-02 were subsequently enrolled into the Continued Treatment phase and the study is ongoing.

Protocol Violations/Deviations

There were no major protocol deviations; hence ITT and PP population are the same. All subjects had missed one or more doses up to Visit 202. 8 subjects had ≤ 10 missed doses. The number of missed doses in the 4 other subjects were 11, 15, 25 and 32.

Table of Demographic Characteristics

At the end of Visit 190, subjects are between the ages 9-18 years

	N	Mean	Min	Max
Age at Screening	12	9	5	13
Age at Visit 190	12	13	9	18

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The time interval between the two baseline visits was approximately 6 to 15 months. At entry, subjects were classified as either "Stable" or "Declining" based on the investigators' clinical examinations combined with judgments from the subjects' parents, home physiotherapists or other relevant individuals (e.g. teachers). Subjects in the 'decline' group were on average older, taller and heavier than subjects in the 'stable' group. The subjects' baseline classification is presented in Table 44. The applicant notes that the median walking distance (N=11) had reduced by ~20 m in the time between their inclusion in the initial Study Period and Baseline (Visit 13) in the Continued Treatment Phase.

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Table 44 Baseline Status of Subjects

Demographics at Visit 13 by baseline status	N	Mean	SD	Median	Min	Max
Stable						
Age (years)	7	9	2	9	6	11
Body height (cm)	7	116	9	118	97	124
Body weight (kg)	7	24	4	25	15	28
Body Mass Index (kg/m ²)	7	18	2	18	15	21
Decline						
Age (years)	5	12	2	12	10	14
Body height (cm)	5	135	6	136	125	141
Body weight (kg)	5	39	13	37	28	61
Body Mass Index (kg/m ²)	5	21	5	18	18	31

*Stable subjects included Subjects 101, 102, 104, 105, 202, 206 and 207.

*Declining subjects included Subjects 103, 106, 107, 201 and 205 (Subject 103 had the maximum number (N=32) of missed dose, subject 201 was non ambulant).

Reviewer's Comment: The "Stable" and "Decline" groups differed in their baseline 6MWD and Rise from Floor Time as shown below. The "Stable" subjects were atypical in the entire development program, with very Rise From Floor Time.

Baseline	Mean (SD) 6MWD (m)	Mean (SD) Rise From Floor (s)
Stable	435 (108)	2.4 (0.36)
Decline	217 (96)	8.5 (1.85)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects received corticosteroids during the Continued Treatment phase and no changes in dosing regimen, other than for routine weight adjustment, except Subject 207 who had his steroid treatment changed to an intermittent dosing regimen.

All subjects missed at least one dose. None of the subjects were dosed at Visits 86 to 93 (washout) and Visits 102 to 105, 114 to 117, 126 to 129, 138 to 141, 150 to 153, 162 to 165, 174 to 177, 186 to 189 and 198 to 201 (off-drug periods). These were not counted as missing dose. Overall compliance was considered to be 92%

Efficacy Results - Primary Endpoint

Applicant's results and Conclusions:

6MWD:

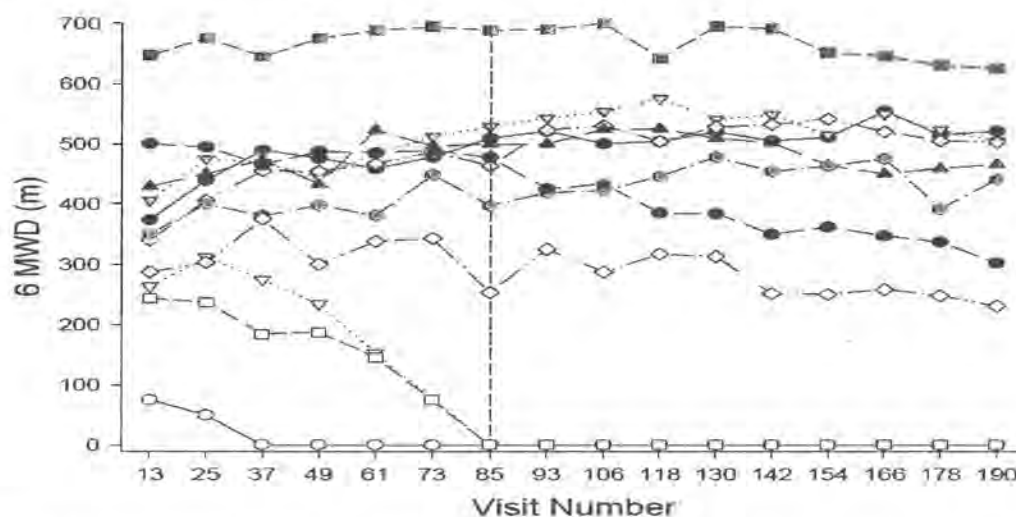
- 10 subjects completed the 6MWD, two subjects (103 and 201) lost ambulation at Visit 37 and 85 respectively.

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- 7 subjects were classified as “stable” and 5 as “decliners” at entry to the study, based on baseline 6MWD and medical judgment.
 - Amongst the “stable” subjects, one subject (#207), continued to decline (500 m to 302 m). The mean change from baseline for the 6MWD at Week 177 in the stable group showed an improvement of 45m (range -198 to +163m). In general improvement appears to be maintained until Visit 142 (Week 129) (Table 45)
 - Amongst the 5 “decliners”,
 - 2 subject became non ambulant.
 - The remaining 3 subjects had continued to decline to the extent that they could not attempt the 6MWD at later visits.
 - A reduction in those in the decline group (excluding Subject #103 who couldn’t complete the assessment at entry) of -187m (range -263 to -56m) (Table 45).
- In the 10 subjects who were able to complete the 6MWD at Visit 13 (study baseline), the median change in 6MWD from Visit 13 to Visit 190 (Week 177) was 8 m (mean change: -25m).
- Five of the 10 subjects who could complete the 6MWD at baseline (Visit 13), could still walk further (range 37 to 163 m) at Week 177 with 2 subjects still being able to walk over 140 meters further at Visit 190 (Week 177) than they could at baseline (Visit 13).
- Introduction of an intermittent dosing regimen following Week 72 (Visit 85) did not appear to adversely affect efficacy parameters.

The absolute change from baseline in 6MWD is shown in Figure 24

Figure 24 Absolute 6MWD over 190 Weeks



Source: Study DMD114673 report, page 65, Note: Stable subjects have filled symbols; 'Decline' subjects have open symbols. Vertical line denotes start of intermittent dosing regimen at Visit 85

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Table 45 6MWD – Only Subjects Who Completed Test at Visit 13 (Split by Baseline Status)

Visit	Stable Subjects					Declining Subjects				
	N	Change from Baseline in Continued Treatment Phase (Visit 13) (m)		Change from Baseline in Main Study (m)		N	Change from Baseline in Continued Treatment Phase (m) (Visit 13) (m)		Change from Baseline in Main Study	
		Mean (SD)	Median	Mean (SD)	Median		Mean (SD)	Median	Mean (SD)	Median
13	7	-	-	5.7 (53.97)	-5.0	3	-	-	-73.0 (15.52)	-74.0
25	7	41.9 (28.40)	50.0	47.6 (42.48)	39.0	3	19.7 (27.68)	16.0	-53.3 (24.95)	-63.0
37	7	46.9 (56.27)	44.0	52.6 (40.76)	42.0	3	13.3 (73.53)	11.0	-59.7 (58.07)	-63.0
49	7	46.0 (47.23)	39.0	51.7 (47.14)	28.0	3	-24.0 (34.77)	-29.0	-97.0 (19.70)	-103.0
61	7	63.1 (47.24)	79.0	68.9 (55.58)	59.0	3	-52.0 (89.44)	-97.0	-125.0 (77.67)	-154.0
73	7	79.9 (51.06)	99.0	85.6 (49.12)	86.0	3	-99.0 (134.50)	-168.0	-172.0 (122.43)	-225.0
85	7	73.9 (57.39)	71.0	79.6 (47.13)	87.0	3	-180.0 (126.84)	-243.0	-253.0 (114.95)	-300.0
93	7	82.1 (85.55)	71.0	87.9 (71.27)	87.0	3	-156.0 (168.31)	-243.0	-229.0 (156.12)	-300.0
106	7	88.1 (82.67)	95.0	93.9 (74.10)	111.0	3	-168.7 (146.41)	-243.0	-241.7 (134.36)	-300.0
118	7	76.4 (102.59)	96.0	82.1 (81.09)	97.0	3	-158.7 (163.70)	-243.0	-231.7 (151.53)	-300.0
130	7	87.0 (100.37)	128.0	92.7 (85.82)	115.0	3	-160.0 (161.39)	-243.0	-233.0 (149.24)	-300.0
142	7	76.6 (110.85)	104.0	82.3 (97.91)	93.0	3	-180.7 (125.68)	-243.0	-253.7 (113.81)	-300.0
154	7	65.9 (110.86)	109.0	71.6 (91.22)	89.0	3	-181.0 (125.11)	-243.0	-254.0 (113.24)	-300.0
166	7	70.6 (122.38)	125.0	76.3 (95.97)	106.0	3	-178.3 (129.71)	-243.0	-251.3 (117.80)	-300.0
178	7	45.0 (112.65)	42.0	50.7 (90.33)	67.0	3	-181.7 (123.96)	-243.0	-254.7 (112.10)	-300.0
190	7	45.3 (124.47)	91.0	51.0 (101.24)	79.0	3	-187.3 (114.18)	-243.0	-260.3 (102.43)	-300.0

Source: Study DMD114673 report, page 68

Note: Treatment was halted from Visit 86-93, after which subjects were on intermittent regimen (shown as grey shaded area)

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Reviewer's Comment: There is a wide range of change in 6MWD for all subjects (-263 to 163m)

Efficacy Results - Secondary and other relevant endpoints

Timed Tests:

Subjects in the stable group were all able to complete the tests rapidly (<5 secs), compared to the subjects in the declining group in which the ability to complete the tests continued to diminish. The ability to rise from the floor was the first of these functions to deteriorate. The changes in timed tests were small Table 46.

Table 46 Timed Tests – Change from continued treatment phase baseline

Visit	N	10m Walk/run (sec)		Rising from floor (sec)		Stair Climb (sec)	
		Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
21	11 ^a	0.08 (1.184)	0.14	0.50 (1.723)	0.43	-0.85 (1.791)	-0.14
25	11 ^a	0.27 (0.515)	0.30	-0.20 (0.577)	-0.08	-1.07 (2.110)	-0.34
29	11 ^a	0.61 (0.621)	0.53	0.06 (0.655)	0.07	-0.40 (1.603)	-0.14
33	10 ^a	0.56 (0.761)	0.33	1.000 (2.632)	0.22	-0.45 (1.064)	-0.34
37	10 ^{a,b}	0.40 (0.388)	0.30	-0.08 (0.923)	-0.06	-0.18 (1.554)	-0.04
41	10 ^a	0.79 (1.133)	0.58	0.55 (0.789)	0.31	-0.61 (1.690)	-0.15
49	10 ^{a,b}	0.51 (1.010)	0.31	0.82 (1.620)	0.24	-0.37 (1.248)	-0.21
61	10 ^{b,c}	0.82 (1.181)	0.38	0.30 (0.656)	0.14	-0.50 (0.996)	-0.30
73	10 ^c	0.94 (1.696)	0.12	1.04 (2.620)	0.20	-0.15 (0.677)	-0.21
85	9 ^c	1.32 (2.446)	0.38	1.75 (4.031)	0.48	0.04 (1.201)	-0.04
93	9 ^c	2.21 (5.229)	0.35	1.27 (2.472)	0.58	0.32 (0.859)	0.00
106	8 ^b	0.49 (1.080)	0.12	1.75 (4.588)	0.12	0.76 (1.422)	0.24
118	8	0.72 (1.360)	0.24	3.09 (6.439)	0.35	1.34 (3.041)	-0.03
130	8 ^d	0.99 (1.695)	0.28	1.06(1.976)	0.32	0.85 (2.063)	-0.12
142	8 ^e	1.00 (1.360)	0.40	0.67 (0.904)	0.24	1.62 (3.469)	0.26
154	8 ^e	1.29 (1.925)	0.66	0.44 (0.497)	0.44	1.73 (3.446)	0.59
166	8 ^{e,f}	1.52 (1.789)	0.65	0.79 (0.625)	0.73	1.78 (4.061)	0.43
178	8 ^e	1.91 (2.059)	0.78	1.12 (1.097)	0.78	3.48 (5.654)	1.01
190	8 ^{e,f}	1.61 (2.039)	0.86	1.05 (0.914)	0.94	4.23 (10.382)	0.74

Source: DMD114673 Study Report

^a N=9 for rising from floor

^b N=9 for stair climb

^c N=8 for rising from floor

^d N=7 for rising from floor

^e N=6 for rising from floor

^f N=7 for stair climb

In order to interpret the results from all subjects, missing values were replaced by an arbitrary number of 30 seconds (timed considered to be maximum likely).

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Reviewer's Comment: In the Table presented, the applicant excluded the worst performing subjects from the summary statistics at later visits, potentially biasing the results.

Muscle Strength: The data were highly variable both between and within subjects.

Pulmonary Function tests: The data were highly variable both between and within subjects. FVC (% predicted) and FEV1 (% predicted) tended to be lower in the declining subjects than the stable subjects. There was a trend in increase in absolute values over time, which the applicant presumes is related to growth over Visit 190. The applicant acknowledges that both the absolute and '% predicted' values have their limitations. The absolute values do not take into account subject growth, however the '% predicted' values use algorithms based on healthy subjects with a 'normal' correlation between age and height. There are no data on how well these correlations apply to DMD subjects whose growth may be stunted. In addition, accurate measurement of DMD subjects' height becomes more difficult if they have contractures and/or lose ambulation. When not measured directly, height may be over-estimated by measuring arm span, which in turn may lead to an apparent reduction in '% predicted' values compared to when their standing height could be measured.

Parent Questionnaire: In general, the majority of parents felt that their child's general condition, walking ability, and endurance was either the same or better than at the beginning of the Continued Treatment phase, with the exception of Visits 154-157 where the majority felt their child's general condition was worse than at the beginning of the Continued Treatment phase. The majority of parents considered their child's ability to climb stairs was the same or better than at the beginning of the Continued Treatment phase up to Visit 123, although subsequently the perception of this ability appeared to worsen through to Visit 178.

Table 47 Summary of Responses to Parent Questionnaire

Visits	N	Response	Questions: change in condition over the Continued Treatment phase			
			General condition	Walking	Taking stairs	Endurance
81-89	11	Better	4 (36%)	4 (36%)	3 (27%)	4 (36%)
		Same	5 (45%)	5 (45%)	3 (27%)	7 (64%)
		Worse	2 (18%)	2 (18%)	5 (45%)	0
109-123	12	Better	3 (25%)	3 (25%)	1 (8%)	0
		Same	5 (42%)	5 (42%)	6 (50%)	10 (83%)
		Worse	4 (33%)	4 (33%)	5 (42%)	2 (17%)
154-157	12	Better	1 (9%)	2 (17%)	1 (8%)	2 (17%)
		Same	4 (36%)	6 (50%)	4 (33%)	7 (58%)
		Worse	6 (55%)	4 (33%)	7 (58%)	3 (25%)
178	12	Better	1 (8%)	1 (8%)	1 (8%)	2 (17%)
		Same	8 (67%)	6 (50%)	3 (25%)	8 (67%)
		Worse	3 (25%)	5 (42%)	8 (67%)	2 (17%)

OBP Reviewer Dr. Rao's assessment of dystrophin expression:

Dystrophin expression by IFA:

- No reliable estimate of dystrophin expression was obtained at Week 24 of the open label

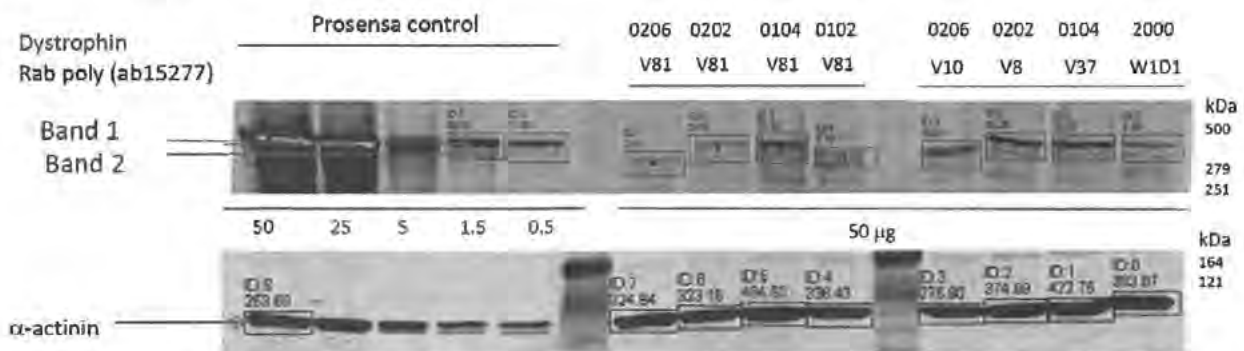
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phase due to poor muscle biopsy quality in the 12 subjects.

- 8/12 subjects had additional biopsy at Week 72. For IFA analysis, 6/8 subjects had baseline biopsies. Compared to baseline, 3/6 subjects showed slight increase (2 to 8%) in mean membrane intensity, 3/6 subjects showed a decrease (1 to 9%) at Week 72.

Dystrophin expression by WB:

- WB analysis was conducted on 8 patients. An increase of 21-46% at week 24 over previous time point was observed; however, at week 72 the same patients did not consistently show an increase.
- Each western blot image included a serial dilution of a healthy positive control. One representative image shown below shows the serial dilution between 0.5-50 μ g of healthy control and 50 μ g of DMD patient samples. Based on reviewer estimation, the observed dystrophin levels approximately ranged between 0.24 to 0.28 % (for subject 0206/V81 sample) and 1.27 to 1.47% (for subject 0104/V81 sample) of healthy control in the gels (looking at the lightest and the darkest bands on the gel). However, importantly, the α -actinin loading for these two samples do not appear to be comparable to each other, so the dystrophin expression in these two subjects cannot be reliably compared to each other.



It appeared that most DMD samples showed a reasonable dystrophin band that was within the tested range of the positive control serial dilution shown on each gel; although, densitometric numbers are only provided for the 0.5 and 1.5 μ g loaded bands for all gels suggesting saturation beyond these samples. The α -actinin bands appeared to be reasonably resolved, consistent between samples and adequately clear to allow a quantitative estimation of protein loading. Overall, for all the gel images provided, it is not possible to get an exact quantitation of the relative dystrophin due to the saturation in the dystrophin bands at higher concentrations of the healthy controls and no quantitation provided for α -actinin at the lower concentrations. The densitometric quantitations for all samples suggest a slight increase in normalized dystrophin compared to the prior time-point for some samples but a decrease for others. The modest increase appear to be below the applicant's stated threshold of >30% above baseline for a positive response.

Reviewer's Comment: This suggests that there is no evidence of increased dystrophin intensity over time, i.e. 72 week after the start of the open label study. The Applicant suggests that problems with the quality of the sample preclude conclusive interpretation. However, it appears that the quality of

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the samples and Western blots was adequate to exclude that there was anything other than a very small increase in dystrophin expression due to treatment.

OBP Reviewer Dr. Rao's comment:

Upon request, the applicant clarified that, with the exception of one sample at 1.1% the dystrophin levels observed in this study were all below 1%, which is their lower limit of detection by WB.

Persistence of Effect

No dose was given between Visits 86-93, after which subjects were switched to intermittent regimen. Change from baseline appeared to be the same in the "Stable" subjects. However, it is unclear if this is persistence of effect (see Reviewer discussion below)

Additional Analyses Conducted on the Individual Trial

Comparison to Natural History (NH):

Applicant's conclusion on natural history comparison:

- Most NH subjects had worse functional trajectory compared to matching drisapersen subjects. Three subjects were excluded from the matching analysis:
 - Subject 104 was considered atypical, had baseline 6MWD of >600m and functional capacity was maintained for 3.4 years
 - Subject 201 was non ambulant at baseline
 - Subject 103 had a single match and only one assessment from the point of matching
- Substantial gains up to 192 m from baseline were reported. Increases of this magnitude were not seen in NH controls.
- The difference in subjects that declined and NH was less easy to discern.

FDA Analysis based on natural history

This analysis was conducted by Dr. Bhattaram (Pharmacometrics). FDA analysis suggested that there were insufficient number of patient matches (based on age, 6MWD, rise from floor and exon 51) from the natural history dataset provided to obtain reliable comparisons. Please refer to Dr. Bhattaram's review for details on the analysis.

Reviewer's Analysis and Discussion:

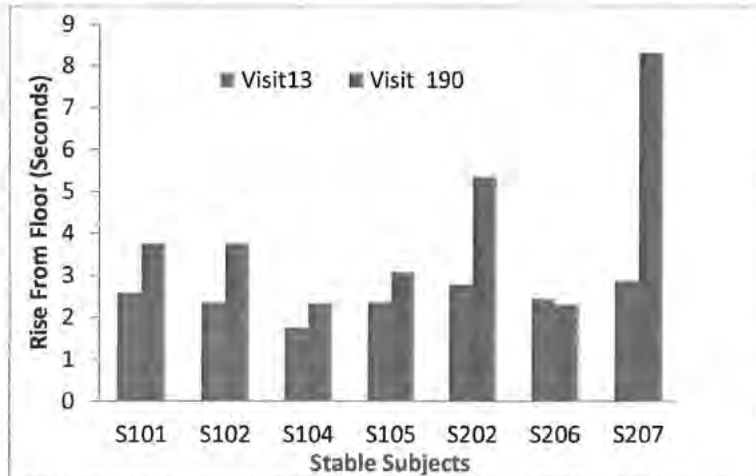
The "Stable" subjects (N=7) were between 5 and 10 years of age. The "Stable" subjects had Rise Time From Floor between 1.7 -2.8 seconds at study baseline (Week 13) and between 2.3-5.3 seconds at end of study at Week 190. Only one subject had a Rise from Floor Time of 8.3 seconds at Week 190. Five of these subjects had baseline 6MWD between 374-647 m and two subjects had baseline 6MWD of 340 and 350 m. (Figure 25). These subjects appear to have a milder prognosis. The mean (SD) change from baseline in the "Stable" subjects was 45 (124)m at Week 190.

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The "Decline" subjects (N=3) had baseline Rise from Floor of 7.2-9.4 seconds and a maximum of 28.5 seconds at Week 118. No subject could perform the test beyond Week 118 (See Figure and Table below for the Rise from Floor Time and the baseline 6MWD in the "Stable" Subjects).

Figure 25 Rise from Floor and 6MWD in "Stable" subjects



Subject	Baseline Rise Time	Baseline 6MWD
101	2.58	374
102	2.35	406
104	1.75	647
105	2.35	340
202	2.78	429
206	2.44	350
207	2.86	500

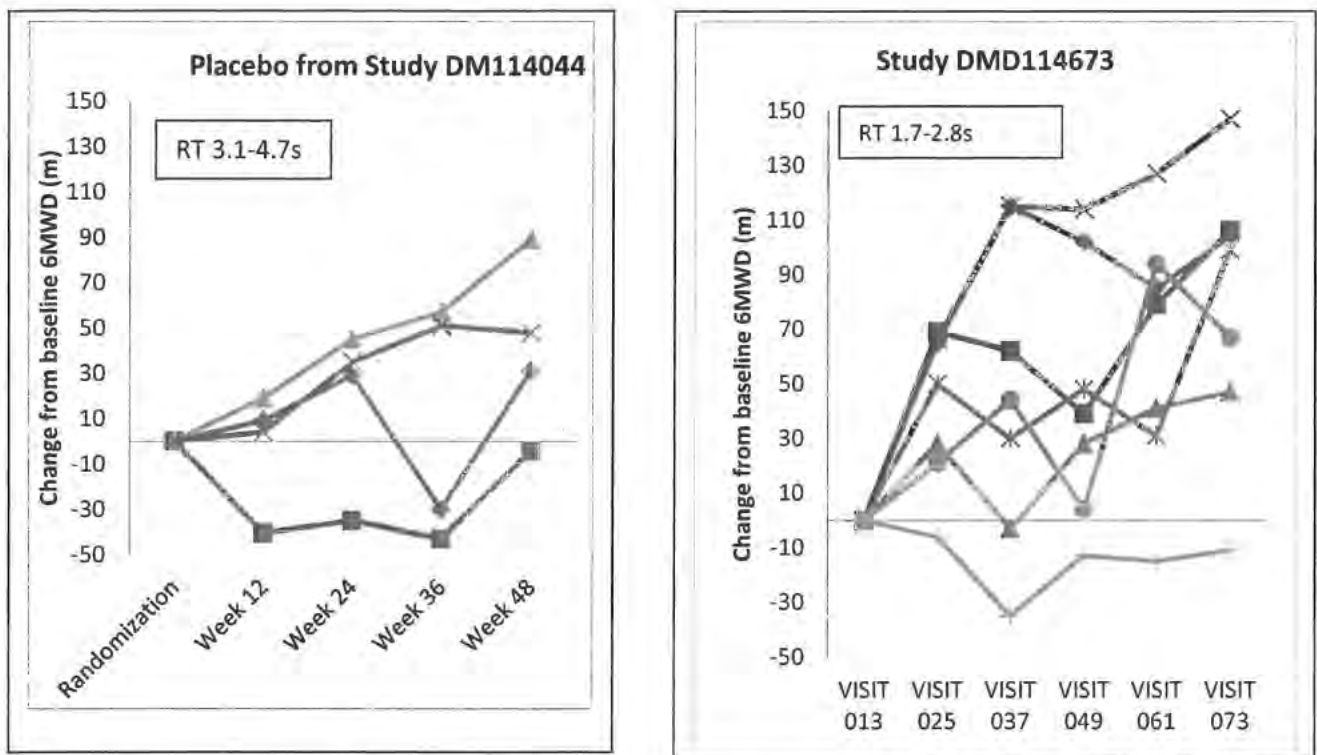
I looked at placebo subjects from Study DMD114044 that would be between the ages 8 and 14 years (for the 3+ years of study duration) and would have a rise time of < 5 seconds to match the baseline characteristics of the stable population in this study to explore the disease trajectory in such subjects. There were no matching subjects >10 years with similar characteristics. The "Stable" subjects in the open label study were atypical, that had extraordinarily low rise time from floor time, at an age when many patients with this genotype lose ambulation. As can be seen the Figure 26, placebo subjects in the similar baseline (age, 6MWD and Rise time) characteristics also show a gain in the 6MWD *over a year* of similar magnitude (up to 90 m). Subjects with low Rise from Floor Time appear to have a milder prognosis and can remain more functional for couple years before they begin to decline. For comparisons, I plotted the disease trajectory for the patients in this study up to 1 year.

The disease trajectory in this one year duration appear similar, even though the placebo subjects from Study DMD114044 have baseline Rise from Floor *higher* (worse prognosis) than those in Study DMD114673. No other study in the application has a mean rise from floor time of 2.4s (Stable group). The mean rises from floor time in other studies range from 4.8-12.3s.

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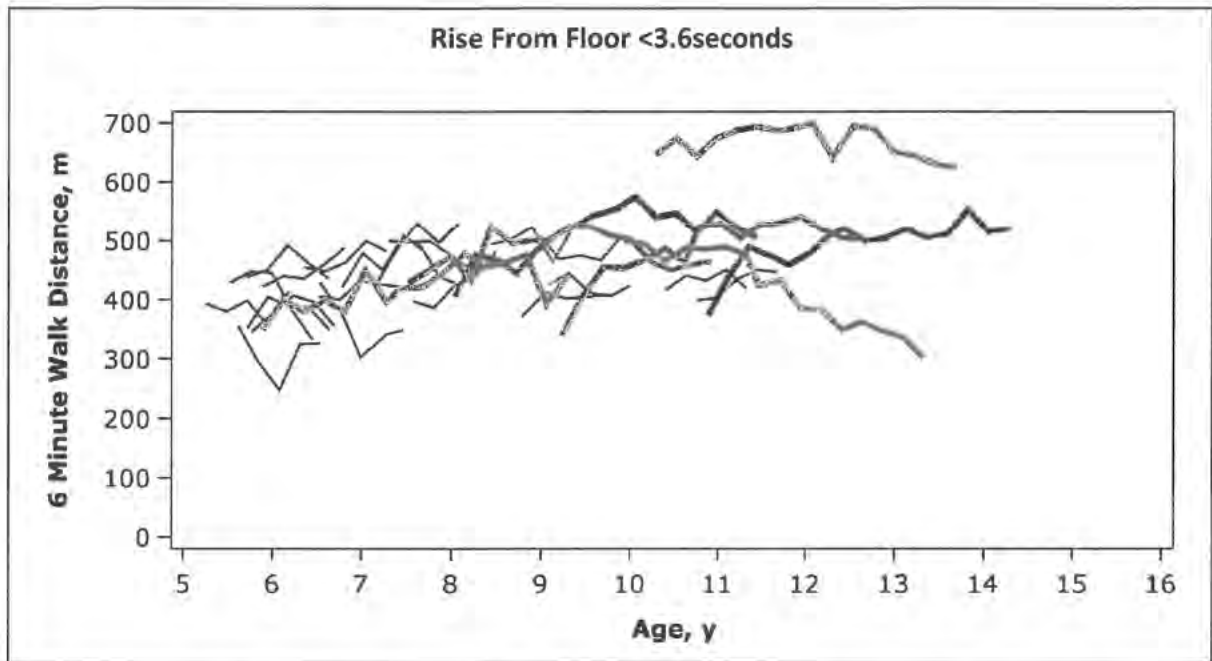
Figure 26 Comparisons of subjects with similar Time to Rise From Floor



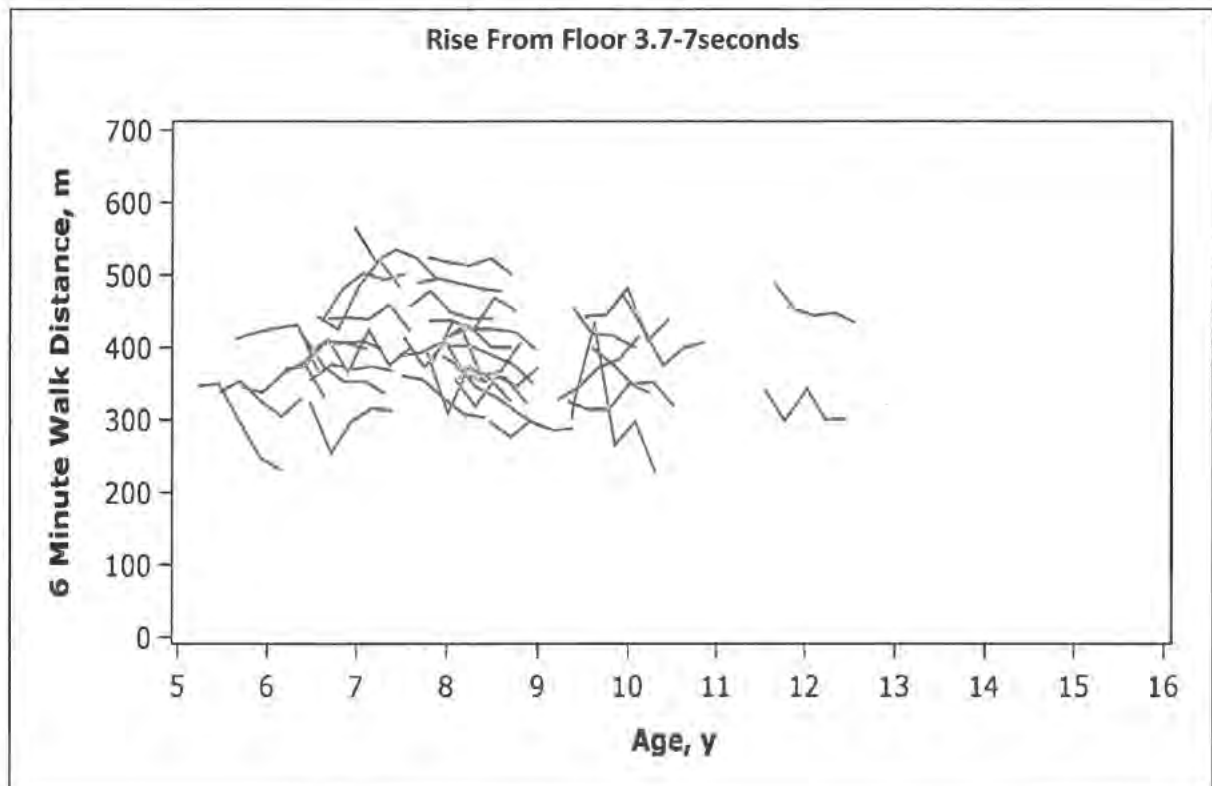
The 6MWD across all the placebo subjects from drisapersen studies, with Rise from Floor that match those from this Study DMD114673 was also looked at to evaluate the disease progression in these subjects. Rise from Floor from Study DMD114673 were lower than those found in the placebo subjects. The four different groups of baseline Rise from Floor were generated and the 6MWD was plotted as a function of age. The four groups were subjects with baseline Rise From Floor <3.6 seconds (to match the stable patients), 3.7-7 seconds, 7.1-11 seconds and >11 seconds. The 6MWD for each patient from this open label study was overlaid on the placebo subjects, to visualize the disease course of the subjects as shown in Figure 27. The figure shows that the disease progression of the subjects in Study DMD114673 is not different from placebo subjects from the drisapersen studies. The subjects that have higher function at baseline tend to show slower progression for few years.

Figure 27: 6MWD matching analysis with placebo subjects from drisapersen studies matched for baseline Rise From Floor Time

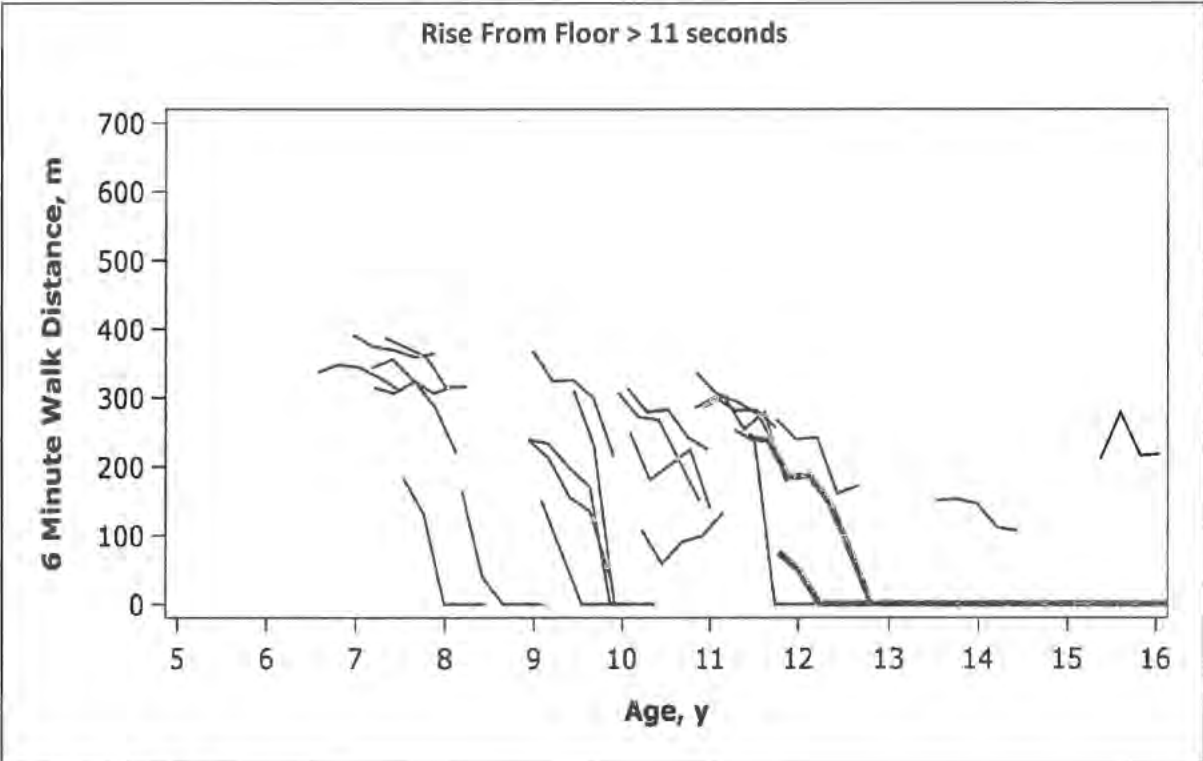
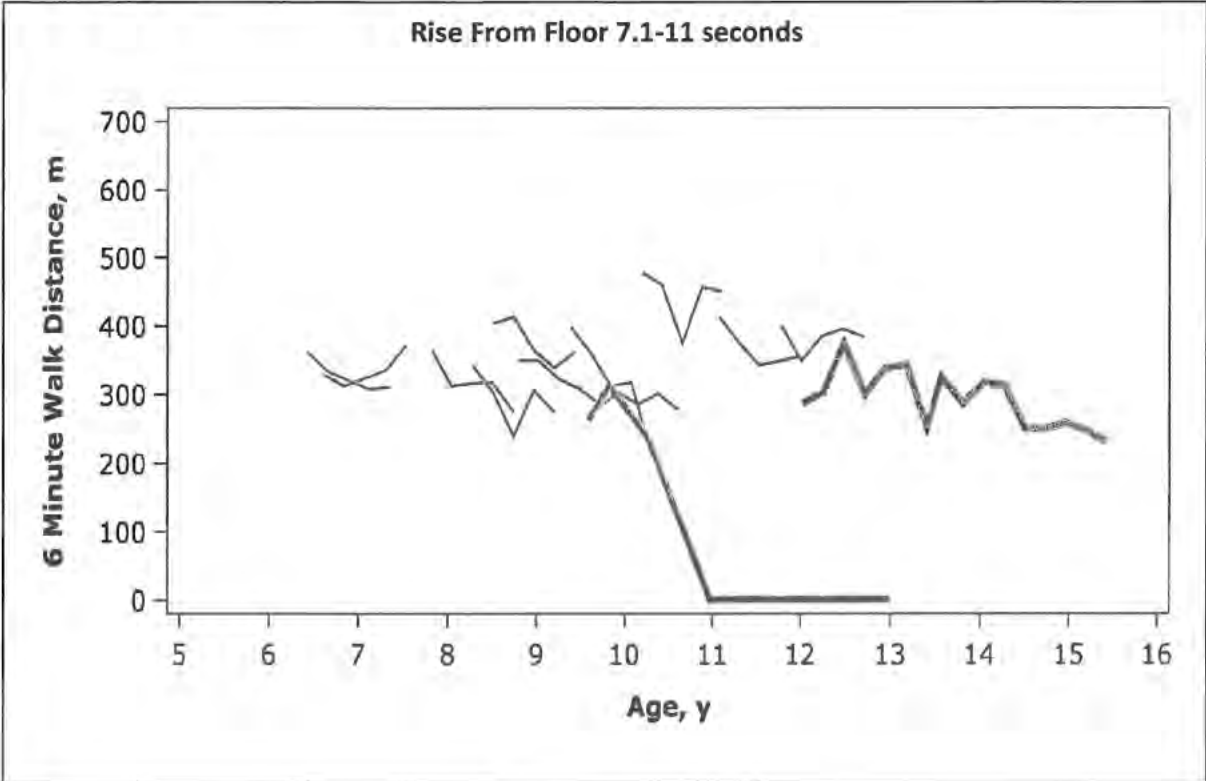
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Note: Placebo data are shown in grey lines and all subjects from Study DMD114673 are shown in colored lines



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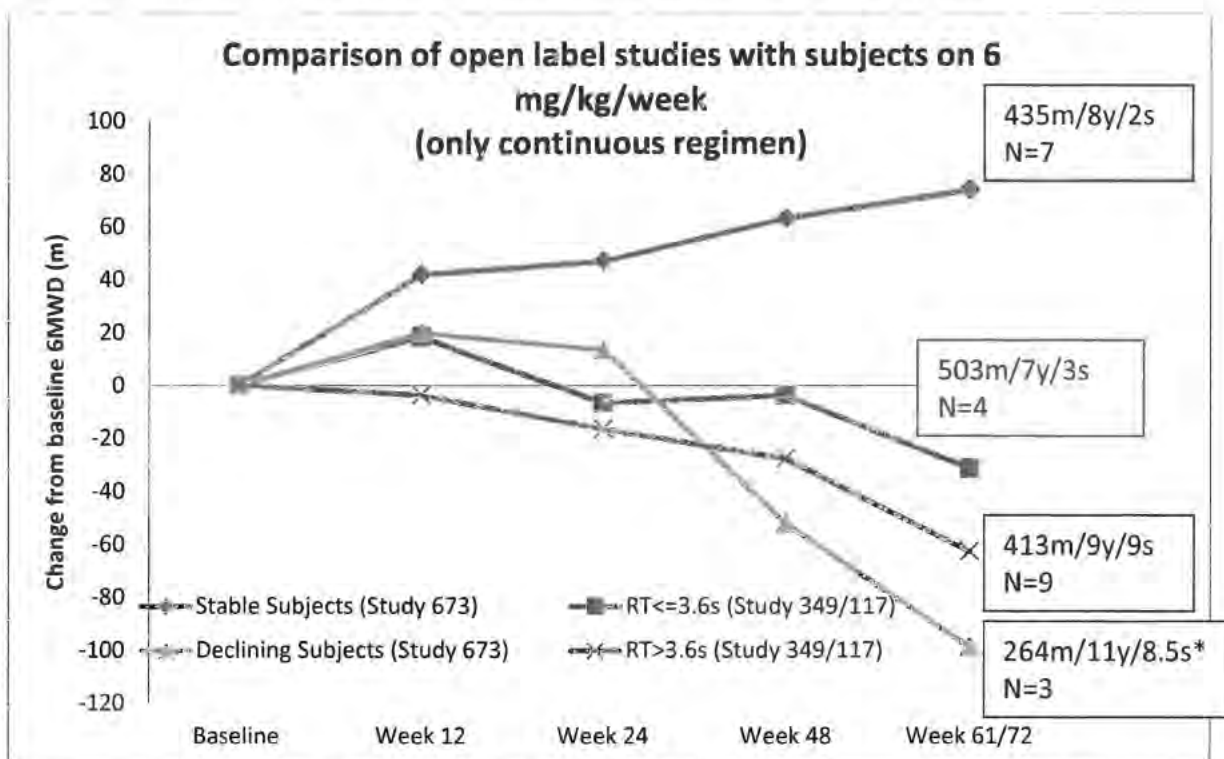
Source: Dr. Bhattaram

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In addition, I also explored the differences in disease progression across the two open label studies (Study DMD114349 and Study DMD114673). I graphically compared the means profiles of "Stable" and "Declining" subjects from Study DMD114673 to the subjects from the Phase 2 study DMD114117 that were evaluated for 2+ years in the open label extension study DMD11349. Baseline 6MWD, age and Rise from Floor are provided in boxes for each group of patients. Three observations were made in this comparison based on the mean data for each group:

1. Two small groups of patients in an open label setting can behave quite differently such as the interpretation of small open label studies may be problematic (Figure 28, blue and red profiles).
2. The disease progression appears to be dependent on the baseline Rise from Floor, 6MWD and age. Subjects with milder disease at baseline tend to have a slower progression, as shown by grouping subjects with Rise from Floor <3.6 and >3.6 seconds. This makes it difficult to conclude that the slow progression is due to drug effect and not due to the natural course of the disease in such patients. With the lack of adequate long term natural history data in such patients with mild disease at baseline, any conclusions of drug effect appears problematic (Figure 28 and Figure 29).
3. The magnitude of decline also depends on the composition of the patients in a group. When subjects from the continuous and intermittent regimens were combined the magnitude of decline was greater (Figure 29 and Figure 30).

Figure 28 Comparisons of open label studies with subjects on 6mg/kg/week



*Note: one subject was unable to Rise from Floor, two that lost ambulation not included, week 61 plotted for declining subjects

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Figure 29 Comparisons of open label studies (Study DMD114117 regimens combined)

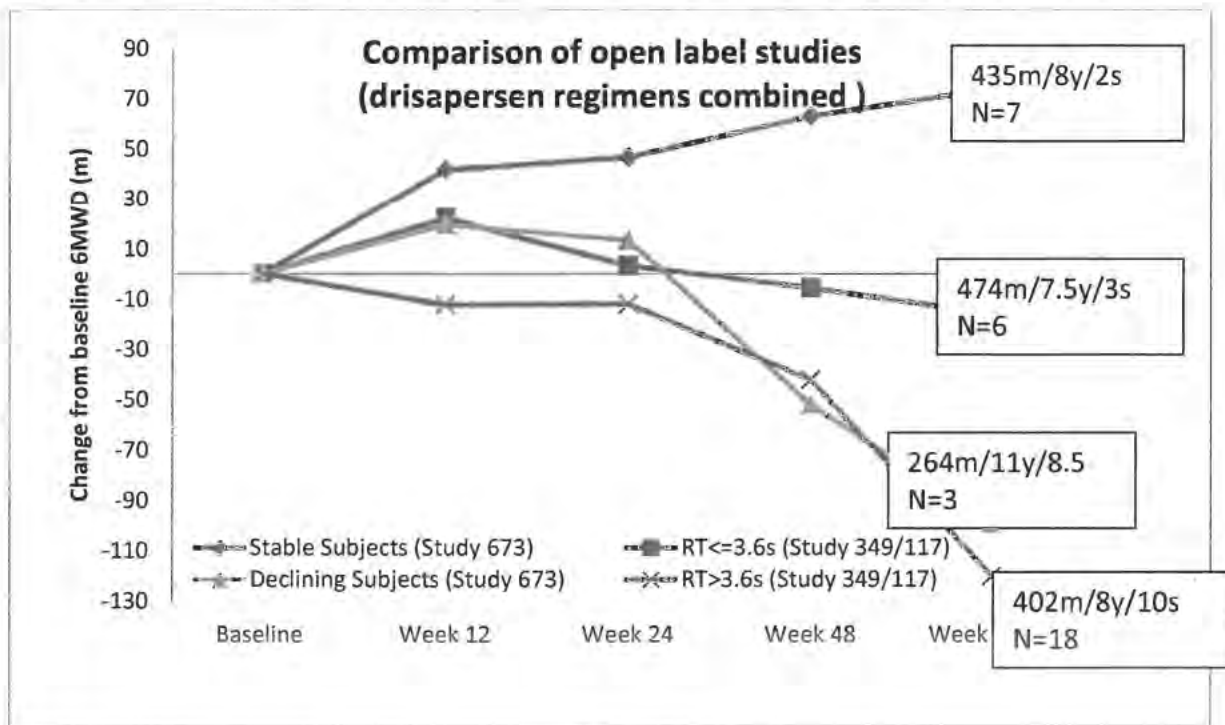
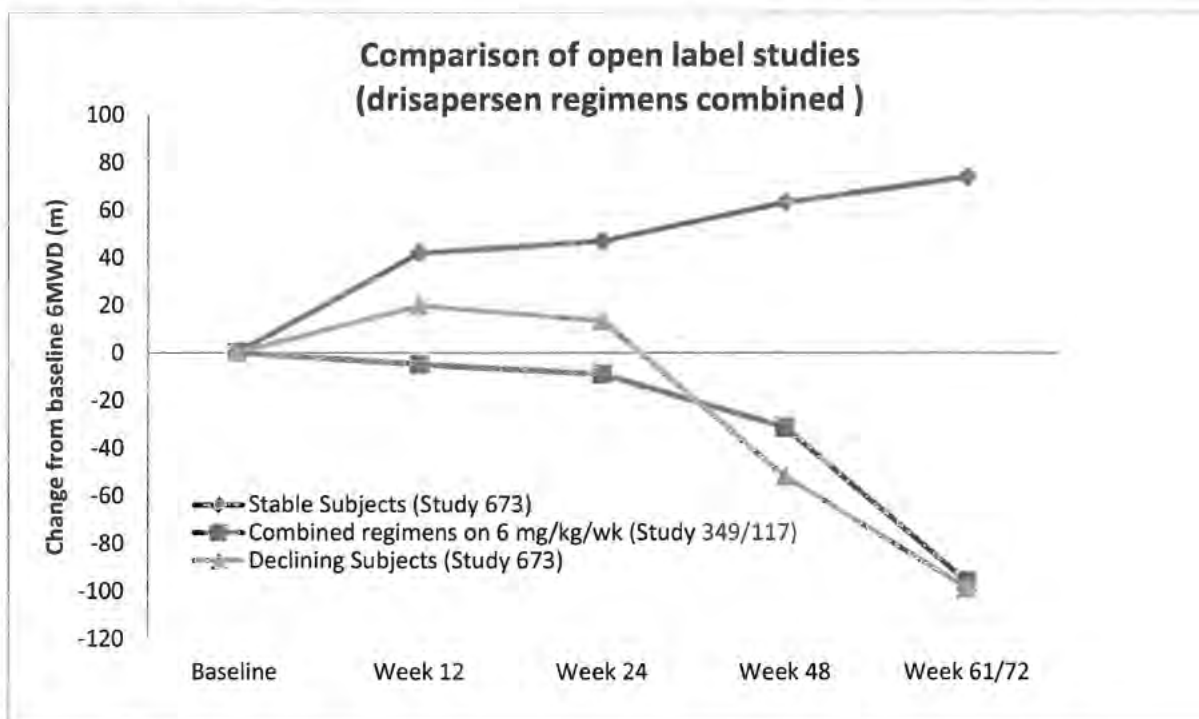


Figure 30 Comparisons of open label studies (Study DMD114117 regimens combined, not separated by Rise from Floor)



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Therefore, age, 6MWD and rise from floor time all are important factors to determining the disease trajectory of a given patient, in addition to many other known and unknown factors, genetic modifiers etc. The subjects in this study appear to have a better disease prognosis. In the absence of a control group, this study therefore, does not show any interpretable evidence of a benefit from treatment with drisapersen.

6.6. PRO051-02

6.6.1. Study Design

Overview and Objective

This was a phase I/II, open label, escalating dose pilot study to assess the effect, safety, tolerability and pharmacokinetics of multiple subcutaneous doses of PRO051 in patients with Duchenne muscular dystrophy.

Study Period: 25 March 2008 to 25 May 2009

Study Centers: UZ Leuven (campus Gasthuisberg), Leuven, Belgium
The Queen Silvia Children's Hospital, Goteborg, Sweden

Trial Design

Doses: Dose escalation study with subcutaneous injection of 0.5, 2, 4 and 6 mg/kg once per week (N=3 in each group)

Medication was injected in the abdominal subcutis by a maximum of two subcutaneous injections.

Population: 12 DMD boys with mutation correctable by skipping exon 51

- Ages 5-16 years that had a life expectancy of at least 6 months and were not on ventilator support.
- Glucocorticoid use was to be stable for at 2 two months prior to enrolment, and was to be kept constant during the study.

At screening, an MRI was performed to assess the quality of the muscle in which the biopsy was planned.

Duration/Assessments: Treatment: 5 weeks (Days 1, 8, 15, 22 and 29), Follow up: 13 weeks (Days 36, 43, 57, 78, 99 and 120)

In the 0.5 mg/kg dose group, a muscle biopsy was taken at Visit 1 (Screening) and at Visit 8 (Day 43). In the other dose groups, a muscle biopsy was taken at Visit 8 (Day 43) and at Visit 10 (Day 78).

Study Endpoints

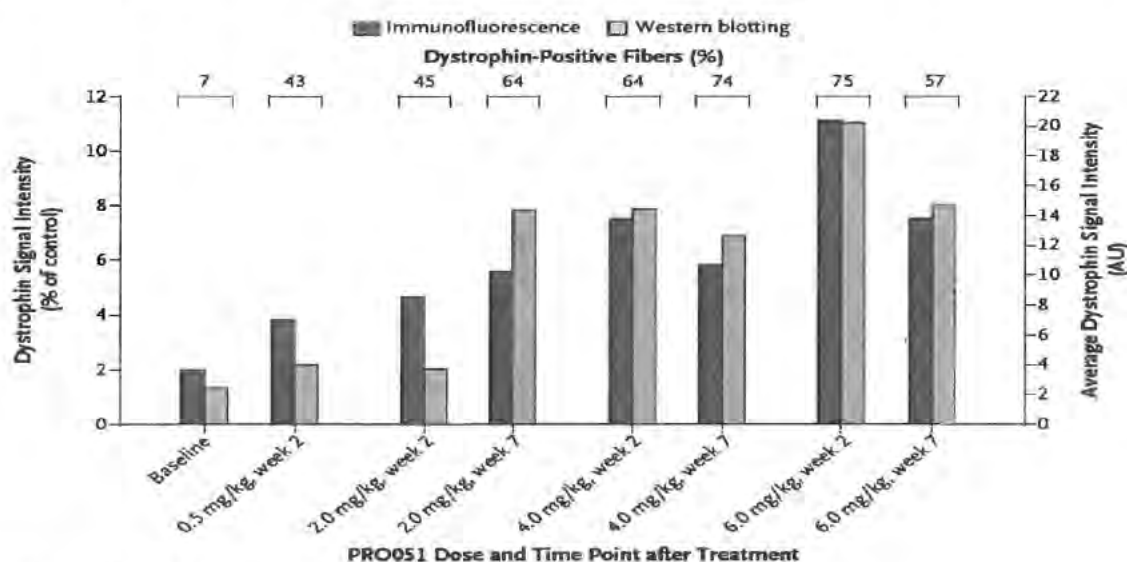
- Production of exon skip 51 mRNA and dystrophin expression by IFA and WB
- Presence of dystrophin expression (immunofluorescence analysis of cross-sections derived from muscle biopsy and Western blot analysis of total protein extracts from muscle biopsy)
- Muscle function (10m walk/run test, timed rising from floor, stair climb and 6MWT)
- Muscle strength

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 6.6.2. Study Results

In the 0.5 mg/kg dose group none of the subjects showed exon 51 skipping by RT-PCR. The effect in the 6 mg/kg dose group was not as prominent. Only the 4 mg/kg group showed exon 51 skip in all subjects. Average number of dystrophin positive fibers and average dystrophin signal intensity increased with increasing dose at 2 and 7 weeks after treatment.

The applicant refers to the published article by Dr. Goemans, which states that new dystrophin expression was observed between 60-100% of muscle fibers in 10 of the 12 patients, which increased in a dose dependent manner to up to 15.6% of the expression of healthy muscle.

Reviewer's Comment: It is unclear how dystrophin was detected 2 and 7 weeks after 5 doses in this study, when in no other study dystrophin was detected after 12 weeks of continuous dose of 6 mg/kg/week. The applicant has not provided individual raw data for this study to support the numbers for the dystrophin positive fibers, but refers only to the published article. There were no pre-treatment assessments at all doses, but only for the low dose (0.5 mg/kg) which is represented as the baseline in the above figure.



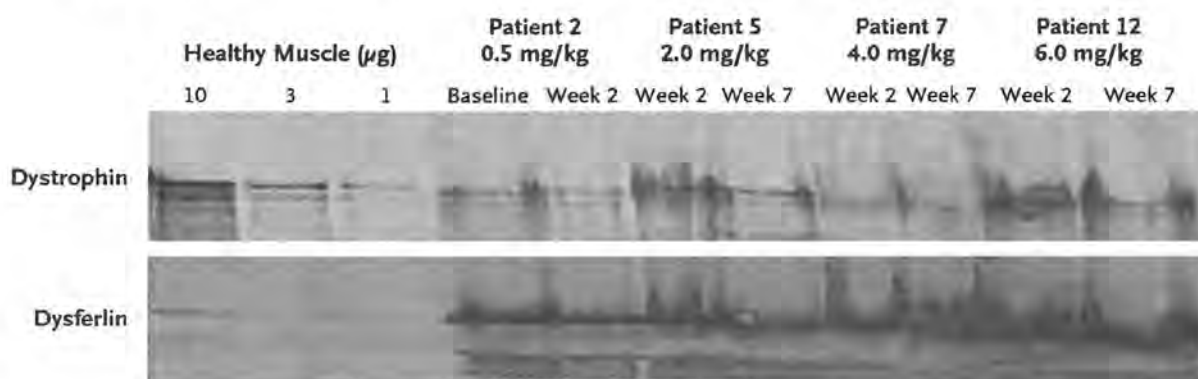
Source: Goemans NEJM 2010

OBP Reviewer Dr. Rao comment on methodology:

The publication states that “a signal intensity of 15.6% of the control intensity in Patient 8.” However, no raw data for patient 8 is provided in the publication. Overall, they comment that “The amount of dystrophin ranged from 17 to 35% of control levels.” However, a baseline sample was not tested in 9 out of the 12 patients. It is also noted that the western blot image in the NEJM publication is of *extremely poor quality* because the dystrophin bands are not clearly discernable, there is substantial smearing of the bands into other lanes, air bubbles or other artifacts, and the loading control (dysferlin) appears to be *unusable* for densitometric

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quantitation and normalization of dystrophin. While the healthy control dilutions appear to suggest that dystrophin levels comparable to or higher than these dilutions were observed in post-treated samples, the dilution factor between the healthy and DMD samples was between 300-500 fold, suggesting that post-treatment levels were extremely low compared to normal. Furthermore, linearity cannot be assumed at this high dilution.



6.7. Other Studies: DMD PRO051-01

Study PRO051-01 was an exploratory Phase 1 single dose, open label study in 4 ambulant and non-ambulant DMD subjects to evaluate the local dystrophin production after localized intramuscular injection. The primary data was not submitted to the NDA, and the following description is based solely on what was reported by the authors of the published report. Subjects were administered 0.8 mg drisapersen intramuscularly. The amount of dystrophin in total protein extracts ranged from 3 to 12% of that found in the control specimen and from 17 to 35% of that of the control specimen in the quantitative ratio of dystrophin to laminin $\alpha 2$.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy across Trials

7.1.1. Primary Endpoints

The Applicant conducted three randomized, double blind placebo controlled trials:

1. Study DMD114117 (n=53): evaluated two different regimens (continuous and intermittent) of the same dose (6mg/kg); Primary endpoint was change from baseline 6MWD at Week 25.
2. Study DMD11476 (n=51): evaluated two doses (3 mg/kg/week and 6 mg/kg/week); primary endpoint was at Week 24
3. DMD114044 (n=186): evaluated a single dose (6mg/kg/week), primary endpoint was at Week 48

In addition, the NDA included two open label extension studies Study DMD114349 (the 120 week extension of the placebo controlled studies: DMD114117 and DMD114044), and Study DMD114763

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(the 3.5 years extension of a 5 week proof of concept study PRO-051-02). In the extension studies subjects were given 6 mg/kg/week, but subjects had the option of moving to the intermittent regimen or to discontinue for safety related reasons.

6MWD is considered an effort dependent endpoint. The unblinding due to injection site reactions observed in the drisapersen treated subjects could potentially bias the results obtained from an effort dependent endpoint.

The strength and weaknesses of the analysis of the primary endpoint for the three placebo controlled studies are summarized below:

- Study DMD114117: The primary endpoint, change from baseline 6MWD at Week 25 was statistically significantly different from placebo for the continuous 6mg/kg/week dose with a treatment difference of 35 m ($p=0.01$) over placebo. Some of the weaknesses of the study include:
 - *Lack of treatment benefit with intermittent regimen*: a non-significant p-value of 0.80 at 24 weeks for the intermittent regimen which had comparable total doses and identical plasma concentration time profile and should seemingly produce similar response to treatment.
 - *Decline at Week 49*: The change from baseline in 6MWD of 31 m observed at Week 25 does not appear sustained at Week 49 with a decline to 11 m. Such differences could also be observed due to variability that may make the results look worse than they are (such as at Week 49) and make the results look better than they are (such as at Week 25). The improvement seen at Week 25 followed by a decline at Week 49 in the continuous drisapersen treatment group is concerning.

The subjects in the continuous treatment arm comprised of patients that were more functional at baseline compared to the intermittent and placebo arms as discussed in section 6.1.2. Differences in the baseline functional abilities of subjects in the treatment groups could bias the interpretation of the results. A small study increases the risk that efficacy may reflect baseline imbalances. Subjects with milder disease progression and younger age may remain stable or improve for the duration of 48 weeks or more. (McDonald 2013).

Since the continuous and intermittent regimen, both consisted of the same 6 mg/kg dose, a post-hoc analyses combining the two treatment regimen, showed a treatment difference over placebo of 31 m (nominal $p=0.05$) at Week 49, but a treatment difference of 20 m ($p=0.12$) at Week 25. This post-hoc analysis may suggest a lean towards treatment benefit at week 48 with drisapersen for a phenotypic heterogeneous DMD population, although unblinding due to injection site reaction remains a concern.

- Study DMD114876: The primary endpoint, change from baseline 6MWD at Week 24 for the 6mg/kg/week dose showed a treatment difference over placebo of 27 m ($p=0.07$) that was not statistically significantly different from placebo. Ordinarily this would be considered a negative study, but for a disease with no approved treatment, this could be considered as supportive evidence of benefit. Additional weaknesses of the study include:
 - In applicant's sensitivity analysis, removing a single placebo subject whose treatment was unblinded due to a hospital visit for flu-like symptoms, a treatment difference of 19 m ($p=0.21$) was observed, further weakening the confidence in the evidence towards efficacy.

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- A lower 3 mg/kg/week dose was worse than placebo. This suggests that the disease trajectory of patients with DMD is dependent on their baseline disease characteristics as discussed in section 6.2.2.
- This was a 24 week study. A 48 week Study DMD114117, showed a decline from baseline at Week 48. In Study DMD114876, the 6 mg/kg/week group showed stability in 6MWD up to Week 48, even when no treatment was given beyond 24 weeks. This could be due to variability or that subjects follow their own disease trajectories based on the baseline characteristics. Natural history studies by experts in the area suggest that earlier functional abilities can predict later functional abilities.
- **Study DMD114044 (2:1 randomization):** The change from baseline at week 48 for the 6 mg/kg/week dose was 10 m ($p=0.42$) that was not statistically significantly different from placebo. Applicant's discussion on the lack of response in study DMD11404 is given in section 6.3.3. Overall, this study was a well-designed and executed study with good statistical power to detect a small treatment effect.

The change from baseline and magnitude of treatment difference in these placebo controlled studies is summarized in Table 48 on page 116:

The open label studies with drisapersen are not supportive of treatment benefit.

- A 120 week open-label extension Study DMD114349 appears uninterpretable as many subjects dropped out either due to AE or the study being terminated early (4/18 on placebo and 5/35 on treatment from Study DMD114117). The decline in 6MWD in each treatment arm based on the parent study (DMD114117 and DMD114044) appears to be consistent with the phenotypic heterogeneity of each arm (see discussion in section 6.4.4), with the more functional subjects at baseline showing a slower progression and less functional patients at baseline showing a larger decline in a year. The applicant asserts a treatment difference of 50m at Week 96 for subjects on the continuous regimen compared to the placebo group that switched to treatment. The Applicant discusses the extension of DMD114117 only based on the subjects that were on continuous 6mg/kg/week regimen, that appeared more functional at baseline compared to the subjects on the intermittent regimen. The subjects on intermittent regimen when switched to the continuous regimen after 48 weeks show a treatment difference of 8m at Week 96 compared to the placebo group that switched to treatment. The subjects on intermittent regimen showed a mean decline in 6MWD of 63m at Week 96. It is known that the disease course is highly variable between affected individuals, a striking example being the age for the loss of ambulation, which can range from 6 to 15 years (Flanigan 2013, Hembertclaude 2102) and higher baseline function is associated with slower long-term decline in DMD (McDonald).
- A 3.5 years long open label study DMD114673 in 12 subjects showed that only 5 subjects did not decline during this study and 3 lost ambulation. The subjects that declined did not appear to be different from the typical natural history control. The subjects that did not decline in Study DMD114673 were atypical. They were highly functional at baseline with Time to Rise from Floor of <3seconds. **There were no other patients in the entire drisapersen development program with such low Time to Rise from Floor.** Consequently, it is entirely unconvincing that the stability observed in these 5 subjects is a treatment effect.

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Table 48 Primary endpoint analysis from the three placebo controlled studies (primary endpoint in orange colored boxes)

	Phase II studies						Phase III study	
	DMD114117			DMD114876			DMD114044	
	Placebo (combined) (N=18)	Dripersen 6 mg/kg/wk (N=18)	Dripersen 6 mg/kg intermittent (N=17)	Placebo (combined) (N=16)	Dripersen 3 mg/kg/wk (N=17)	Dripersen 6 mg/kg/wk (N=18)	Placebo (N=61)	Dripersen 6 mg/kg/wk (N=125)
Baseline, n Mean								
Week 24								
n	16	16	15	16	17	18	59	122
Mean change	-4	31	-0.1	-11	-20	16	-29	-24
Treatment difference p-value		35 0.01	4 0.80	- -	-9 0.55	27 0.07	- -	5 0.63
Week 48					←—————→			
n	17	18	15	15	17	18	59	117
Mean change	-25	11	2	-13.17	-38	15	-52	-42
Treatment difference p-value	- -	36 0.05	27. 0.15	- -	-25 0.24	28 0.18	- -	10 0.42
					No treatment			

Source: Adapted from Applicant's analysis with FDA re-evaluation

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The conflicting, results from Study DMD114044 diminish the strength of the smaller studies. One of the explanations by Applicant for this negative study has been the demographic and baseline population make-up of the Phase II and Phase III studies. As shown in the Table below, the smaller studies had a slight younger and more functional population in the continuous 6 mg/kg/week arm compared to the larger negative study.

Study	Prognostic Factor	Placebo	Drisapersen 6 mg/kg/week
DMD114117 (N=53)	Median Age (years)	7 years	6.5 years
	Baseline 6MWD (m)	403 m	428 m
DMD114876 (N=51)	Median Age (years)	8 years	6.5 years
	Baseline 6MWD (m)	416 m	396 m
DMD114044 (N=186)	Median Age (years)	8 years	8 years
	Baseline 6MWD (m)	348 m	337 m

Based on mean/median age and mean 6MWD at baseline, it appears true that the DMD subjects in Study DMD 114044 are likely to be more progressed in their disease. No restriction on the rise from floor was the only difference in the enrollment criteria between these studies. I looked at a subset of subjects from this study that had the similar age distribution (5-13 years), same range of 6MWD at baseline (330-561m) and subjects with rise time of ≤ 7 seconds as in the smaller studies to match the patient population characteristics in the Phase 2 and 3 studies. The MMRM analyses were conducted by Dr Sharon Yang (Statistician). The subjects in this subgroup of Study DMD114044 are balanced with regards to their age, baseline 6MWD and rise from floor time as shown below.

Study DMD114044 Subset with Subjects that meet the following criteria: Ages 5-13 years 6MWD 300-561m RT ≤ 7 sec	Prognostic Factor at baseline	Placebo N=27	Drisapersen 6 mg/kg/week N=59
		Median Age (years)	7 years
	Mean Age (years)	6.8 years	7.2 years
	Mean 6MWD (m)	401 m	402 m
	Median 6MWD (m)	399 m	402 m
	Mean Rise from Floor (s)	4.44 s	4.84 s
	Median Rise from Floor (s)	4.1 s	4.9 s

This subset of patients from Study DMD114044, showed a mean treatment difference of 5m, suggesting that the severity of the disease is not the reason for the negative results in study DMD114044 (Table 49). The results from this post-hoc analysis are contradictory to the results obtained from Study DMD114117. This also suggests that chance baseline imbalances, not drug effect, led to the positive findings in study 117.

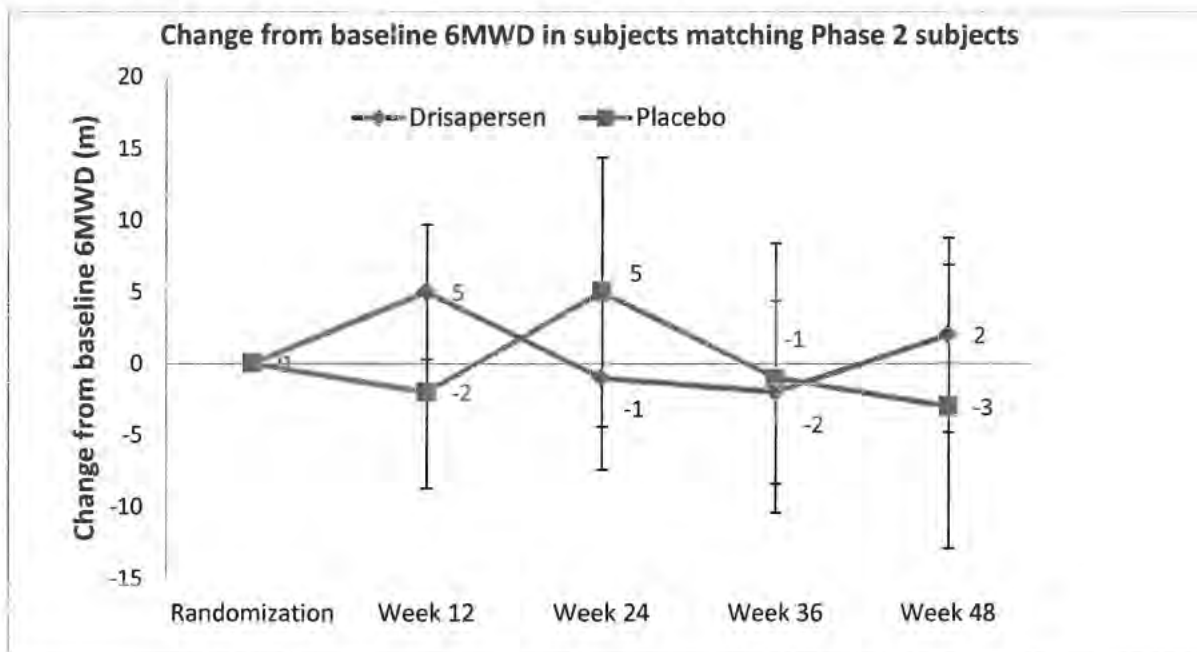
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Table 49 FDA analysis of subjects from Study DMD114044 that match the subjects from Studies DMD114117 and DMD114876

	Placebo (n=27)	Drisapersen 6 mg/kg/week (n=59)
Week 48		
Adjusted mean change	-3	2
Adjusted mean difference vs. placebo		5
p-value		0.71

Figure 31 shows the adjusted mean change from baseline in subset of subjects from Study DMD114044 that match the baseline characteristics of subjects from the Phase 2 studies.

Figure 31: FDA analysis of subjects from Study DMD114044 that match the subjects from Studies DMD114117 and DMD114876

I also conducted Kaplan-Meier analysis showing time to persistent 10% worsening in 6MWD in subjects with rise from floor ≤ 7 seconds. No meaningful differences between treatment groups were observed. Hence, the applicant's argument of a more functionally impaired population of the Phase III study as the reason for a negative study is not convincing.

The applicant presents the argument in the ISE that certain subgroups based on age ($\leq$ and > 7 years) and 6MWD (± 330) may respond differently. The applicant's post-hoc analyses showing the treatment

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differences in the four subgroups based on age and 6MWD are presented in Table 50.

Table 50 Mean/Median Change of baseline 6MWD by age group and 6MWD (applicant's post-hoc analysis of Study DMD114044)

	Age ≤ 7 years				Age > 7 years			
	6MWD ≤ 330 meters		6MWD > 330 meters		6MWD ≤ 330 meters		6MWD > 330 meters	
	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo	6 mg/kg	Placebo
N	17	4	33	25	33	17	34	13
Mean	11	-62	-12	-18	-124	-108	-25	-52
SD	49	99	63	51	94	108	61	70
Median	23	-55	-7	-26	-109	-109	-22	-55
Min	-109	-184	-215	-96	-303	-311	-194	-185
Max	68	42	112	106	48	89	102	48
Difference in Medians	+77 p=0.01		+20 p=0.66		-0.2 p=0.48		+33 p=0.24	
Difference in Means	+75 m		+6 m		-16 m		+27m	

Source: NDA module 2.5 Clinical Overview page 52

A treatment difference of 75 m ($p=0.012$) was observed for the sub-group age ≤ 7 years and 6MWD of ≤ 330 m. The treatment effect observed in the smaller studies was not likely driven by this subset of the patients, as there was only 1 subject each in the 6 mg/kg/week treatment group in both the Phase II studies with a baseline 6MWD of ≤ 330 m. Secondly, the median treatment difference of 75 m in Age ≤ 7 years + 6MWD of ≤ 330 m subgroup is driven by one placebo subject (#1256) with a baseline 6MWD of 184 m who could not perform the 6MWD due to gait loss after Week 12, hence at all subsequent visits the 6MWD was imputed to zero. Removing this subject, the treatment difference in the group of patients Age ≤ 7 years + 6MWD ≤ 330 m is 10 m. The other subgroups did not have a nominally positive p-value, including the subgroups that would likely have a milder progression (Age ≤ 7 years + 6MWD of > 330 m, Age > 7 years + 6MWD of > 330 m). Lastly a 6MWD of 330 m is a subjective cutoff. In the published literature some experts have presented natural history data in DMD with a cutoff of 350 m.

In an amendment to the ISE submitted on August 31st 2015, the applicant conducted additional analysis using an enhanced MMRM model including age and 6MWD subgroup and treatment by age and subgroup interaction as terms in the model. This analysis showed a treatment difference of 20 m ($p=0.12$) (Table 51). Baseline 6MWD was accounted for redundantly as terms in this model. Please refer to the statistical review for limitations on the statistical model.

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Table 51: Applicant's post-hoc analyses of Study DMD114044

Model	Population	Placebo (adjusted mean)	6mg/kg (adjusted mean)	Treatment effect vs. Placebo	P-value of Treatment Difference
MMRM	Overall*	-60 m	-40m	+20 m	0.12
MMRM	Overall ** minus older/more severe group based on 6MWD cut off of 330m	-44 m	-11m	+33 m	0.01

Source: Sponsor ISE amendment, Aug 31st 2015

The applicant asserts a treatment benefit of 33 m (nominal p-value 0.01) after removing subjects that are of Age > 7 years + 6MWD ≤ 330 m as it was the only subgroup that did not show a treatment benefit. By removing only one placebo subject that could not perform the test the p-value increases to 0.06. Using a 6MWD cutoff of 350m p-value increases to 0.06 with a treatment difference of 23 m and removing the single placebo subject (#1256) the p-value increases to 0.12 (Table 52), further suggesting that the results are dependent on the way the cutoff points are drawn are appear unstable.

Table 52 FDA Analysis with a 6MWD cutoff of 350m

Model	Population	Placebo (adjusted mean)	6mg/kg (adjusted mean)	Treatment effect vs. Placebo	Nominal P-value of Treatment Difference
MMRM	Overall ** minus older/more severe group based on 6MWD cut off of 350m	n=39 -33.8 m	n=81 -10.4m	+23.4 m	0.062
MMRM	Above population minus subject #1256	n=38 -26.9	n=81 -10.7	+16.3	0.196

Source: Dr. Sharon Yan

Hence, the sponsor's argument of removing a subgroup to show treatment benefit is subjective, as the effect size appears unstable and the p-value changes.

Overall, the evidence of efficacy from these studies based on the primary endpoint change from baseline 6MWD appears uncertain. The increase from baseline in 6MWD observed at Week 25 does not appear sustained at Week 49. The results from the other two studies further mitigate the positive findings from Study DMD114117, although a numerical advantage at Week 48 can be argued. It is difficult to separate a treatment effect from unblinding biases. Some of the many factors that could introduce bias studies could be clear unblinding due to injection site and physical training. Physical training might delay the functional deterioration caused by disuse in boys with DMD (Jansen 2013). From the open label studies, there is no reliable estimate of what happens to the subjects over several years due to dropouts. Overall, a precise estimate of treatment benefit cannot be established. Even if we assume a short term treatment benefit of 10-20m based on the overall results, there is no clear way to estimate whether this would delay the time to loss of ambulation. In addition, switching subjects from an intermittent regimen from Study DMD114117 to continuous regimen in the second year, subjects appear to be headed to losing ambulation at an age not older than expected from

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natural history. The prognosis of subjects is dependent on their baseline function.

Given the heterogeneity in disease progression, stratification of patients was important to ensure the groups were balanced not only for age, but for baseline 6MWD and corticosteroid use (McDonald 2103). It also appears that other factors such as Time to Rise from Floor, Ability to jump or hop clearing both feet up, ability to rise with gower's maneuver may also be important factors in predicting disease progression. The knowledge of these factors became apparent after these studies were initiated. In general, the pathophysiological mechanisms that underlie phenotypic variability are not fully understood. Recent publications also suggest genetic modifiers such as LTBP4 and osteopontin that could predict the disease trajectory in individual subjects. Such information is not available from the drisapersen program.

7.1.2. Secondary and Other Endpoints

None of the secondary endpoints showed statistically significant treatment difference at either Week 24 or 28 in the three placebo controlled studies. The secondary endpoints were not analyzed in a hierarchical manner in the small studies (DMD114117 and DMD114876) and no key secondary endpoint was identified. In the large Study DMD114044, NSAA, 4-stair climb-ascent and 10 m walk/run were assigned as key secondary endpoints. The applicant does not propose labeling claims based on any secondary endpoints. All conclusions from all secondary endpoints are briefly summarized below:

Timed Function tests (rise from floor, 10 m walk/run, and 4-stair climb/ascent-descent):

- In Study DMD114117, the timed function tests were in the same direction as the primary endpoint for the continuous 6 mg/kg/week group compared with placebo was observed at Week 25 and 49. The trend of improvement worsened at Week 49, but remained numerically better than placebo. The clinical meaningfulness of these trends is unclear as the changes in the Timed Function Tests were less than 1 second, with the exception of rise from floor where a treatment difference of 3 seconds was observed. The intermittent regimen showed a favorable trend only for the 10 m walk/run.
- In study DMD114876, the timed function tests were variable with no consistent dose trends and the treatment difference was <1 second.
- In Study DMD114044, no consistent trends in favor of drisapersen were observed across all tests that are correlated with each other.

NSAA

- In Study DMD114117, NSAA showed favorable trends at Week 25 for both continuous and the intermittent regimen, that worsened at Week 49. The change from baseline in favor of drisapersen was greater for the intermittent regimen at Week 25, which does not follow the same direction as that of the 6MWD. The changes are small at week 49 (-0.2 and -0.4, respectively for the continuous and intermittent) in a total NSAA score of 34, with higher scores being better). Mazzone et al 2013 have shown that younger subjects can remain stable in NSAA assessments in the first year and there were a larger number of younger subjects in this study. Therefore, it is unclear if the stability is related to treatment effect or the natural progression of the disease as measured by NSAA.
- In study DMD114876 and DMD114044, no significant or consistent treatment difference in favor of drisapersen was observed.

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Pulmonary Function Tests

- The changes in pulmonary function tests were small, not clinically meaningful in any study and not in favor of drisapersen. Changes in pulmonary function are not expected in early ambulant population.

Muscle Strength

- Unfavorable and variable trends in muscle tests were observed in all studies, with greater decline in muscle strength observed in the drisapersen group in Study DMD114044.

Serum Creatine Kinase:

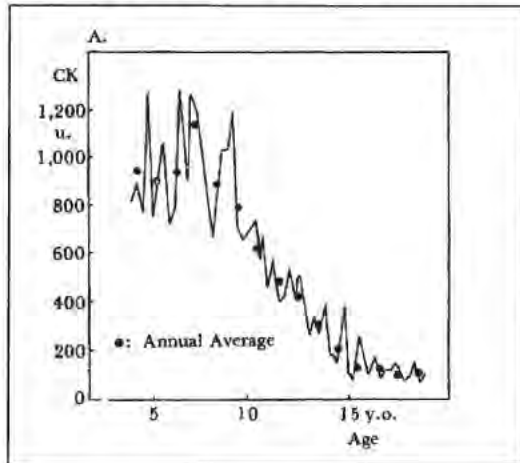
Serum creatine kinase, a marker of muscle cell injury was the only secondary endpoint that was consistently reduced by 30-40% across the three studies based on percent change from baseline with nominal p-values of 0.08, 0.53 and <0.001 for the Study DMD114117, DMD 114876 and DMD114044 respectively, suggesting a possible improvement in muscle cell integrity. However, this finding is associated with several confounders: CK levels are remarkably variable, with large within patient and between patient variability and are known to fluctuate day to day. It is reduced with inactivity, steroid use, advancing age of the DMD boys due to reduction in muscle mass as the muscle fibers are replaced with fat and fibrous tissue, clinical progression and diurnal variation (increase during the day and decrease at night) and inflammation. I will evaluate each of these factors as possible confounder of a treatment effect.

- *Effect of variability on CK:* Statistically significant reductions in CK were observed despite the variability. CK increases during the day and decreases at night. All CK assessments in the studies were generally conducted between 8 am to 5 pm.
- *Effect of inactivity on CK:* Florence et. al. (1985) have shown that on complete bed rest days the mean decrease in CK level was 13,000 IU/L compared to the active days in DMD boys. The mean decrease in the drisapersen treated subjects in all the three studies was between 4000-5000 IU/L. There was no evidence of inactivity of the subjects from the Patient or Parent reported outcomes but the activity level of subjects are hard to discern from such studies and activity levels were not recorded systematically. The greater number of subjects with injection site reactions in the drisapersen treated patients could plausibly make the subjects less active, but CK reduced in subjects with or without injection site reactions to the same extent of 30-40%.
- *Effect of steroids on CK:* Steroid use reduces CK. Both drisapersen and placebo subjects were on steroids for a minimum of 6 months. It is not known if the dose, regimen and duration of steroid use would impact the reduction in CK. The impact of these on the reduction in CK across treatment groups are difficult to discern from the studies. There were some differences in steroids use across studies as shown below, but the impact of these difference is unknown:

	Study DMD114044		Study DMD114117		Study DMD114876	
	Placebo	Drisapersen	Placebo	Drisapersen	Placebo	Drisapersen
Median Time on steroids (months)	19	27	23	14	39	19
Steroid Regimen:						
Continuous (%)	85%	86%	61%	67%	94%	100%
Intermittent (%)	15%	14%	39%	33%	6%	0%

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- *Effect of age on CK:* Published studies suggest that CK peaks at ages 3-5 years and declines with age with levels reduced to 50% by age 7 years.



Konagaya et. al. (Figure on the left) suggest that in the second half of the first decade, due to relatively higher rate of muscle degeneration, there is an abrupt drop of serum CK levels. Hence, CK decreases with age and disease progression. In study DMD114044, there were 17% subjects that were greater than 11 years in the drisapersen group compared to 11% in the placebo group. The Phase 2 studies had only couple subjects that were older than 11 years, about an age when there is an abrupt drop in CK levels. To explore if the statistically significant reduction in CK in Study DMD114044 was driven by the slightly higher

number of subjects >11 years in the drisapersen group, I also calculated the mean percent change from baseline in CK in subjects >7 to ≤11 years in both drisapersen and placebo groups. Irrespective of the age groups CK was consistently reduced in the drisapersen treated patients compared to placebo patients as shown:

Mean percent change from baseline in CK	Study DMD114044		Study DMD114117 At Week 48		Study DMD114876 At Week 24	
	Placebo	Drisapersen	Placebo	Drisapersen	Placebo	Drisapersen
≤ 7 years	4.5%	-19%	36%	-11%	-2%	-31%
>7 years	-2%	-41%	36%	-41%	5.7%	-16%
>7 to ≤11 years	0.4%	-43%				

There was no consistent trend in mean percent reduction of CK in subjects <7 or >7 years and ranged between 30-40% reduction in these groups with wide variability. The percent reduction in the >7 years of age was 40% in Studies DMD114117 and DMD114044, and was 11-19% in subjects ≤7 years of age. Opposite trend was observed in Study DMD114876 subjects where subjects ≤7 years of age had greater reduction in CK (30%) compared to 16% in subjects >7 years of age. In addition, impact of reduction in muscle mass due to muscle wasting with increasing age is unknown from these studies, but muscle mass will decline with age and disease progression.

Nevertheless, CK reduction was greater in the drisapersen treated subjects in all three subjects with nominal p-values of <0.001, 0.08 and 0.53 from Studies DMD114044, DMD114117 and DMD114876, respectively.

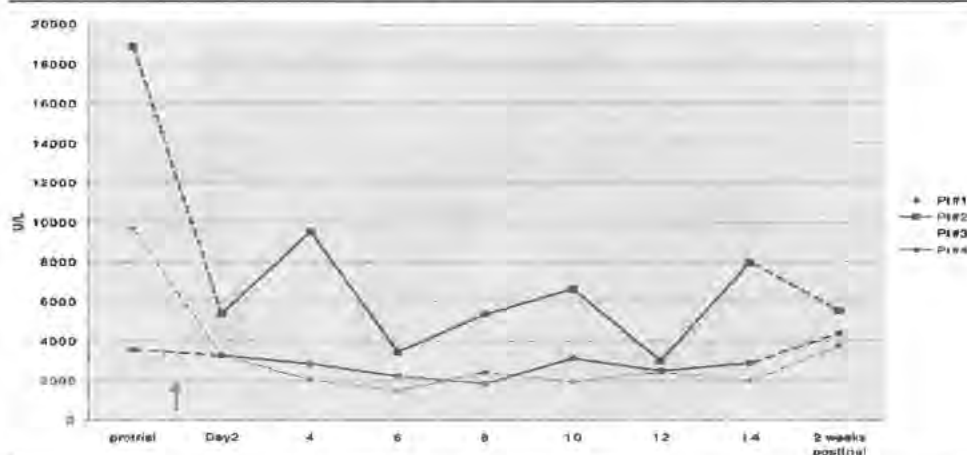
- *Effect of inflammation on CK:* Reduced CK activity in inflammatory diseases such as rheumatoid arthritis is linked to an inflammatory response, where an inverse correlation has been reported between CK activity and inflammatory markers (Lee 2000). I explored if the decrease in CK in the drisapersen treated subjects was due to an increase in inflammation and not an improvement in muscle cell integrity. Only ≤10% of subjects on drisapersen showed elevation in

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one of the inflammatory markers. The markers of inflammation, C-reactive protein and Complement C3 measured in the drisapersen program did not appear to be inversely correlated to CK. It is uncertain if the inflammatory response due to injection site reactions could be associated with a reduction in CK, although CK reduced by 30-40% in subjects with or without injection site reaction.

- In a 14-day study with gentamicin, CK dropped by 50% in DMD boys (Malik 2010), while dystrophin increased after 6 months of dosing. In another 14-day study the highest drop in CK with gentamicin was after 1 day of dosing (Wagner 2001).



Gentamicin has a short half-life of 2-3 hours, but uncertain is this reduction in one day is mechanistically plausible. CK was assessed at earlier time points in some subjects on drisapersen. The CK reduction appeared to be lower at Week 3 compared to Week 49, but there was a large variability between time points. This is somewhat reassuring given the long half-life of drisapersen. Therefore, it is uncertain to what extent these factors could play a role in reducing serum CK levels and if CK change are essentially caused by improvement in muscle integrity or due to other unknown factors such as an increase in metabolism of CK caused by the drug. While some factors could be explained by data, the others remain unknown. In addition, there was no correlation of 6MWD and CK, as in the Phase 3 study. Therefore, given all these caveats, a treatment effect due to reduction in CK is difficult to discern, but a plausible treatment effect cannot be ruled out.

MRI: Consult review of the MRI data conducted by Dr. Daniel Krainak (CDRH Imaging Division) concludes that the data presented in the application are unconvincing of treatment benefit.

Dystrophin:

The utility and caveats of dystrophin measurement in DMD:

Genetic mutation and deficiency of dystrophin leads to DMD in humans. Dystrophin has a structural role in the dystrophin-associated glycoprotein complex as a cytoskeletal stabilization protein and protects muscle fibers against contraction induced damage. Dystrophin also has a signaling role that includes mechanotransduction of forces and localization of proteins. Mutations in the DMD gene disrupt the open reading frame and prevent the full translation of dystrophin. Hence, there appears to

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an intrinsic biological reason to measure dystrophin in DMD patients. Drisapersen is designed and targeted to restore the open reading frame with the production of a truncated but functional dystrophin. However, in humans, a quantitative, linear, and direct correlation between restoration of functional dystrophin and treatment benefit in terms of muscle function has not been clearly established (see discussions by Wilton 2014 and Lu 2014). Qualitatively, the existence of Becker patients with detectable levels of dystrophin and milder phenotype than Duchenne patients suggests that dystrophin is, at least in part, related to the muscle function. Morandi and others have unsuccessfully attempted to establish this quantitative relationship using BMD cohorts (Morandi 1995).

In the mdx animal model for DMD, dystrophin restoration at levels of ~25-80% of normal have been achieved with antisense oligonucleotides (Gao 2014) or exon-skipping morpholino oligomers (Goyenvalle 2010). In these and other studies, dystrophin restoration was observed along with prevention of dystrophic pathology and restoration of muscle strength in the animal muscles examined.

In humans, some caveats that complicate a clear relationship between dystrophin protein and functional outcome are:

1. The presence of variable levels of trace and revertant fiber dystrophin. The low levels found in DMD also suggest that trace levels of dystrophin are unlikely to limit muscle degeneration.
2. The heterogeneity of the dystrophin between muscle sub-groups (e.g. biceps vs quadriceps) and within the same muscle biopsy.
3. The genotype and specific gene mutation of a BMD or DMD appears to impact basal levels of dystrophin but a systematic study hasn't been presented.
4. Inconsistent or heterogeneous measurement of dystrophin across laboratories that claim a quantitative relationship. Lack of a reference standard and proper control samples also make robust quantitative claims questionable.
5. The severity of the disease as a consequence of the chronic inflammatory environment. Lack of dystrophin also stimulates an inflammatory response that is an important mechanistic driver for the muscle degenerative process over time. With increasing age, the interplay between chronic activation of innate immunity and asynchronous bouts of degeneration/regeneration combine to yield a poorly orchestrated repair response that may itself drive disease progression (Rosenberg 2015). It is possible that the chronic inflammatory environment and repeated muscle damage over time presents a point-of-no-return that cannot be overcome simply based on restoration of extremely low levels of dystrophin.
6. Restoration of truncated dystrophin in DMD patients likely triggers an auto-immune response to the new protein in these patients. Even though these patients have revertant fibers, Flanigan and Mendel have previously published that these patients are not "tolerized" to novel dystrophin production and show dystrophin-specific T-cell immunity that increases with age (Flanigan 2013). In animal models, this was mitigated with administration of anti-inflammatory agents (Villalta 2014 and Rosenberg 2015). How the autoimmune response to the new dystrophin impacts its availability and function within muscle tissue is unclear.

Detection of dystrophin was assessed by exon 51 skipping by RT-PCR, qualitative IFA and WB in Study

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DMD114117, DMD114876, DMD114044, DMD114673 and PRO051-01. A small to non-existent dystrophin increase in dystrophin from baseline was observed; however, this increase was not consistent across all the placebo controlled studies. A relatively reasonable assessment of dystrophin increase was only obtained from Study DMD114117. The results across placebo controlled studies and methodologies are summarized below.

Dystrophin mRNA by PCR: The applicant provided a qualitative assessment of dystrophin mRNA by either nested, lab-on-chip, or droplet digital PCR. These methods do not indicate that mRNA was translated into functional protein.

- *Nested RT-PCR:* Nested RT-PCR assessments were qualitative with assessments of visual bands (yes/no). A small increase in exon 51 skipped dystrophin mRNA was observed only in some patients across studies with no consistent trend between treatment groups as summarized below.

Study	Number of subjects/total number analyzed		
	Placebo	6 mg/kg/week	6 mg/kg Inter OR 3 mg/kg/week
Study 114117 (Wk 24)	0/18	2/18	5/17
Study 114876 (Wk 24)	2/16	10/18	10/17
Study 114044 (Wk 48)	56/61	114/125	-

- *The Lab-on-chip capillary electrophoresis PCR:* This method showed some increase compared to baseline but the standard deviations were high. Due to several analytical deficiencies, this quantitation has limited reliability.

Study Treatment	Exon skip (a.u) (mean(SD))	
	Week 0	Week 25, 24 or 48
Study 114117		
Placebo	1.30 (1.01)	0.73 (0.41)
Weekly 6 mg/kg/week	1.29 (2.42)	1.30 (1.50)
Intermittent 6 mg/kg	1.72 (2.38)	2.60 (5.34)
Study 114876		
Placebo	2.01 (1.52)	1.53 (1.20)
Weekly 6 mg/kg/week	2.69 (4.09)	4.44 (3.55)
Weekly 3 mg/kg/week	2.41 (4.38)	4.37 (6.78)
Study 114044		
Placebo		1.45 (1.68)
Weekly 6 mg/kg/week		2.83 (5.21)

Dystrophin Protein by Immunofluorescence: Immunofluorescence assessments suggest small increases in mean membrane-associated dystrophin intensity in some treated patients from study 114117 but not from studies 114876 or 114044 as summarized below. IFA quantitation of dystrophin has high

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background and may increase more than linearly with small changes in dystrophin which could lead to an overestimation of amount of dystrophin compared to WB. The IFA method can suggest protein localization but is less meaningful for protein level quantitation.

Study	Number of subjects/total number analyzed		
	Placebo	6 mg/kg/week	6 mg/kg Inter OR 3mg/kg/week
Study 117 (Wk 24)	1/18	9/15	4/15
Study 876 (Wk 24)	7/12	1/18	5/11
Study 044 (Wk 48)	9/61	9/125	

Dystrophin Protein by Western Blot: Some patients in study 114117 showed a small increase compared to baseline but with very low dystrophin signal compared to healthy samples.

Study	Number of subjects/total number analyzed		
	Placebo	6 mg/kg/week	6 mg/kg Inter OR 3 mg/kg/week
Study 114117 (Wk 24)	0/14	5/17	5/16
Study 114876 (Wk 24)	0/5	0/1	1/5
Study 114044 (Wk 48)	-	-	-

The applicant's WB method was more quantitative than IFA because (1) a serial dilution of healthy tissue sample was used alongside test samples and control samples and (2) a reasonably muscle-specific α -actinin loading control was included.

Open-label studies: The dystrophin increase was unreliable and unimpressive from the open label studies as discussed below:

Study DMD114673: Dystrophin was assessed at Week 24 and Week 72 of this extension study.

- For IFA analysis, at week 24, no reliable estimate of dystrophin expression was obtained due to poor muscle biopsy quality in the 12 subjects. However, 8/12 subjects had additional biopsy at Week 72. Some subjects showed a slight increase (2 to 8%) in mean membrane intensity, while other showed a slight decrease (1 to 9%) at Week 72, leading to no consistent evidence of increase in dystrophin expression.
- For WB analysis, an increase of 21-46% at week 24 over previous time point was observed; however, at week 72 the same patients did not consistently show an increase. Upon request, the applicant clarified that, with the exception of one sample at 1.1% the dystrophin levels observed in this study were all below 1%, which is their lower limit of detection by WB.

Study PRO051-02: Dystrophin expression was evaluated 2 and 7 weeks AFTER a 5 week dosing period in 12 subjects.

- This study does not give reliable estimates of dystrophin. There were no baseline samples in 9/12 subjects. This is the only study where dystrophin expressions have been reported by

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the investigator after 5 weeks of dosing with drisapersen.

7.1.3. Subpopulations

Age:

No conclusive evidence of efficacy in any age group can be established from the placebo controlled studies. Age was post-hoc subgroup analysis for studies DMD114117 and DMD114876, but was pre-specified as a subgroup for Study DMD114044. The age groups evaluated were ≤ 7 years and > 7 years, as published data suggest that there are differences in disease progression among these subgroups, but these differences are also dependent on the baseline 6MWD.

McDonald et al and many other experts have shown that *“there is a trend for the 6MWD to improve or be stable over the first 7 years of age and patients who have lower initial 6MWD tend to show greater declines over the course of 48 weeks. Patients ≥ 7 year of age may also show stable function or even improving function, but they are almost those with higher levels of baseline function (6MWD $>350m$)”* (Excerpt from McDonald 2013). Please note that there are imbalances in the 6MWD between treatments in some of these age comparisons such that it complicates the interpretation of these age differences in treatment effect.

The age subgroup analyses in the placebo controlled studies are shown in Table 53. Age subgroup analysis was not nominally positive in any study. The age related differences seen in the post-hoc analyses of small phase II studies (DMD114117, DMD114876) are unreliable due to small number of subjects in each group and due to an imbalance in the baseline 6MWD in the treatment and placebo arm within some age comparisons.

Table 53: Age subgroup analyses in placebo controlled studies

Treatment	N	Baseline Mean (SD)	Adjusted Mean Change from Baseline (SE) at Week 48*	Treatment Difference	95% CI
Age ≤ 7 years at Baseline (Study DMD114044)					
Placebo	29	383 (66)	-25 (11)	21	(-6, 48)
Drisapersen 6 mg/kg/wk	51	368 (65)	-4 (8)		
Age ≤ 7 years at Baseline (Study DMD114117)					
Placebo	13	409 (40)	-13 (16.54)	38	(-12, 89)
Drisapersen 6 mg/kg/wk	11	413 (62)	25 (18.20)		
Age ≤ 7 years at Baseline (Study DMD114876)* 24 weeks					
Placebo	6	445 (63)	-14 (21)	31	(-29, 90)
Drisapersen 6 mg/kg/wk	10	385 (60)	17 (17)		
Age > 7 years at Baseline (Study DMD114044)					

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Placebo	32	316 (101)	- 84 (15)	7	(-29, 43)
Drisapersen 6 mg/kg/wk	74	316 (107)	-77 (11)		
Age >7 years at Baseline (Study DMD114117)					
Placebo	4	386 (57)	-61 (24)	56	(-6, 114)
Drisapersen 6 mg/kg/wk	7	450 (81)	-5 (18)		
Age >7 years at Baseline (Study DMD114876)* 24 weeks					
Placebo	10	399 (48)	- 16(12)	28	(-9, 64)
Drisapersen 6 mg/kg/wk	8	410 (62)	12 (14)		

In study DMD 044, the subjects ≤ 7 years had larger treatment benefit (21 m) than subjects > 7 years (6.9m). The applicant believes that younger subjects may have greater treatment benefit with drisapersen. In this comparison, one 7 year old subject (#1256) on placebo with a baseline 6MWD of 184m could not perform the test due to gait loss after Week 12. This inability to perform the test is not likely to do the lack of response to treatment after Week 12, but more likely to the disease condition of this subject. A treatment difference of 10 m was observed in subject's ≤ 7 years of age after removing this single subject. This further weakens the notion that younger subjects may receive greater treatment benefit.

In addition, pooling the two Phase II studies, which the applicant asserts was a more functional population, the treatment difference over placebo was greater for the older subjects (40m), compared to the younger subjects (27m) at Week 24, further weakening the notion that treatment effect is greater in the younger population.

Pooling the 48 week placebo controlled studies, a larger treatment difference of 24m was observed for the younger population compared to a 7m treatment difference in the older subjects. Pooling the 48 week studies, I also conducted an exploratory post-hoc analysis by age in subjects with Rise from Floor ≤ 7 seconds which is summarized in Table 54. Given the few number of subjects that were >7 years, the interpretation of the data across all ages are not reliable. Nevertheless, the 5-6 year old subjects showed greater treatment difference.

Table 54: Pooled 6MWD analysis by age for the 48 week studies in subjects with Rise from floor ≤ 7 s

Age	Drisapersen N	Placebo N	Mean Treatment Difference
5 years	12	10	67 m
6 years	23	11	28 m
7 years	14	12	12 m
8 years	14	6	2 m
9 years	7	5	31 m
10 years	2	1	-67 m
11 years	2	1	32 m

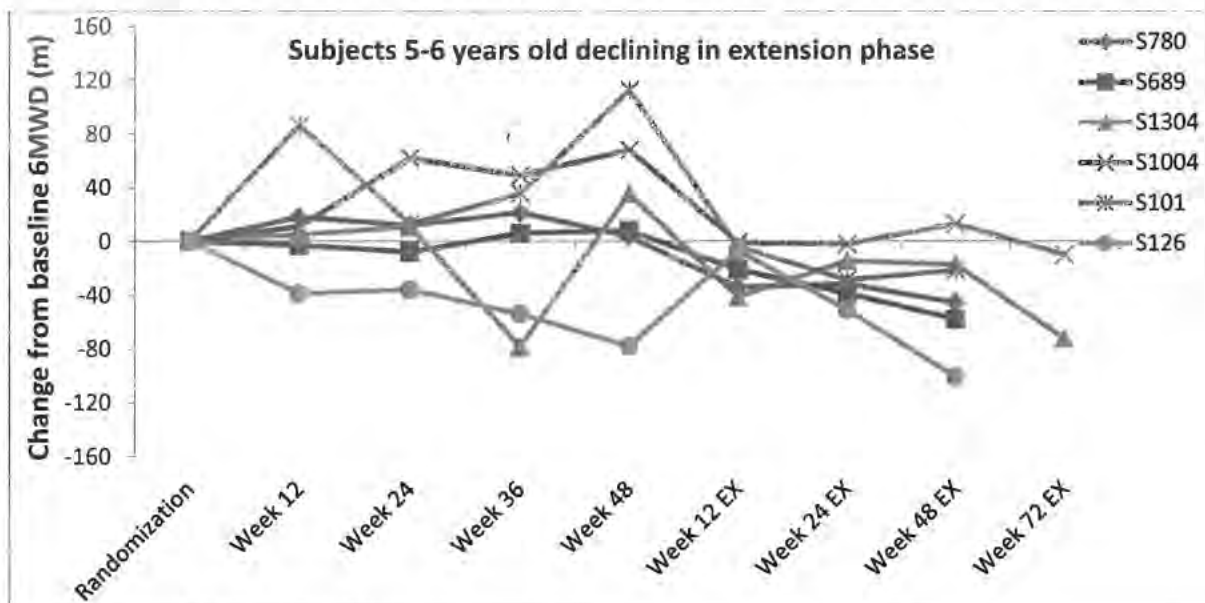
Note: The baseline 6MWD was lower by 8-20m in the drisapersen arm in the ages 5-7 years

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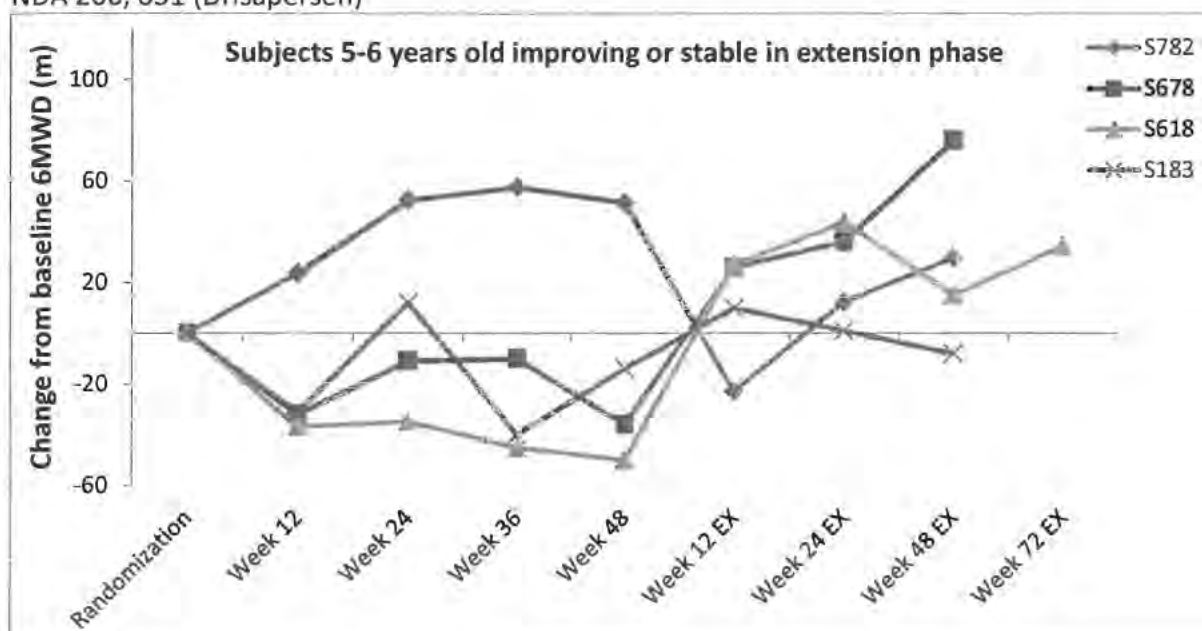
Experts have suggested that viable muscle fibers may be required to restore dystrophin and hence would seem logical to start treatment early for a treatment benefit in the long-term. Keeping this hypothesis in mind, I looked at the 6MWD time course in the open label extension phase for the 5-6 year old from Study DMD114044. There were 10 subjects on treatment of the ages 5-6 years that had ≥ 2 year data from the open label extension phase. Of these 10 subjects, 6 tended to decline in the 2nd year of treatment with continuous 6mg/kg/week drisapersen, 4 tended to improve. The data from a few of these 10 subjects could be considered random noise in the measurement. For ease of visual representation these 6MWD time course of these subjects have been categorized as those improving and declining in the extension phase (Figure 32). These figures suggest that some subjects tend to decline in the 2nd year of treatment with 6mg/kg/week drisapersen. Given the variability in the progression, it is difficult to get an estimate of the time to loss of ambulation in these young subjects.

Figure 32 Two year time course of 6MWD of 5-6 year old subjects from Study DMD114044



Note: EX stands for extension phase

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Overall, there is no compelling evidence that the subjects ≤ 7 years of age may benefit treatment with drisapersen, but a plausible biological argument can be logical.

Ethnicity and Race:

There is insufficient data on ethnic and race comparisons for efficacy. A total of 82-95% of the subjects were Not-Hispanic/Latino across the three studies. No interpretable differences can be obtained between ethnic groups. A total of 76% of the subjects were White Caucasian/European in Study DMD114044 and 88% in Studies DMD114117 and DMD114876. Due to the small number of subjects of the non-Caucasians, no interpretable treatment difference based on race can be obtained.

Country:

No reliable conclusions can be drawn with respect to efficacy in different countries. A Total of 23 countries participated in the placebo controlled studies. The number of subjects per treatment group was small in these countries. Only Canada, France, Italy, Germany and United States had more than 15 subjects.

7.1.4. Dose and Dose-Response

An initial loading dose of 6mg/kg drisapersen twice weekly for 3 weeks, followed by maintenance treatment with 6 mg/kg administered weekly is proposed. The loading regimen was evaluated in Study DMD114117, in which a statistical significant difference from placebo was observed for the primary endpoint 6MWD. Given, the long half-life of drisapersen (29 days), it is acceptable to initiate treatment with a loading dose for three weeks, as proposed by the Applicant.

6 mg/kg was considered to be the maximum tolerated dose by Applicant due to signs of potential subclinical nephrotoxicity (mild proteinuria) in the extension study DMD114673 after 6 months of

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treatment and due to preclinical pro-inflammatory findings (including the recent preliminary data from the 39 week monkey study). Drisapersen doses 0.5, 2, 4 and 6 mg/kg were evaluated in a 5 week proof of concept Study PRO-051. Due to the lack of significant safety findings and a pharmacodynamics effect (increase in dystrophin expression) with 5 weeks of dosing, the 6 mg/kg/week dose was given the open label extension Study DMD114673. A single dose of 9 mg/kg administered to 3 non-ambulant subjects was associated with renal toxicity and inflammatory reactions and self-limiting pyrexia and flu-like symptoms in all subjects. Doses higher than 6mg/kg/week were not evaluated in any other study.

A lower 3 mg/kg dose was evaluated in Study DMD114876 in only 18 subjects. In this study:

- 6 mg/kg/week was superior than placebo (27m)
- 3 mg/kg/week was worse than placebo (-9 m)

Given the variability in the assessment of 6MWD, this difference from placebo is not substantial and could be considered as indistinguishable from placebo at Week 24. The sample size of this study is small, hence difficult to conclude that 3 mg/kg/week as an ineffective dose. No clear dose-response was established.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Pharmacokinetic studies have shown that drisapersen concentrations reach steady state at 24-36 weeks and also likely the time it would take for dystrophin to accumulate in the muscles. None of the placebo controlled studies have shown any dystrophin expression at Week 12, but an exploratory published 5 week study showed an increase in dystrophin after 5 weeks of dosing. In many subjects a change from baseline in 6MWD of similar magnitude was observed both at Week 13 and Week 24. This could be due to the variability in the assessment of 6MWD.

The applicant asserts that there was maintenance of effect after further 24 weeks off treatment. In Study DMD114876, in which treatment was administered for only 24 weeks, change from baseline in 6MWD at Week 24 was 16 m and 15 m at Week 48, after a drug free period. This would suggest that treatment effect is maintained. Given the turnover half-life of dystrophin this may be physiologically possible as well. In this study the treatment difference from also remained similar (27m) at Week 24 and 48. This is because the placebo group also did not decline in the 48 week period. Similar treatment effect was also observed at Week 12, but not certain if the effect at Week 12 is due to increase in dystrophin as no dystrophin was measurable at week 12 in any study. Therefore the maintenance of change from baseline in the 6MWD at Week 48 appears less convincing of a persistence of effect from this study.

The evidence for durability of response is unclear. In Study DMD114117, a mean change from baseline in 6MWD was 31 m at Week 24 and 11 m at Week 48, suggesting a decline in 6MWD of about 20 m. A treatment difference from placebo of 35 m was observed on both Week 24 and Week 48. This probably was due to a decline in the placebo group of about 20 m in this study at Week 48, driven by a few subjects in the study.

The applicant asserts that a difference of ~30 m was observed in subjects who received continuous 6

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mg/kg/week for 96 weeks in the extension study of DMD114044 compared to those subjects that received placebo in the parent study for 48 weeks followed by 48 weeks of continuous 6 mg/kg/week regimen. The sample size was reduced to almost 50% of the parent study in each arm; hence the observed difference of ~30 m is uninterpretable, even though it is plausible.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Drisapersen could be used in the ambulant patients with exon-51 skip amenable DMD, if efficacy were to be established. Effectiveness of drisapersen in non-ambulant patients has not been evaluated. Postmarketing considerations are premature at this time.

7.2.2. Other Relevant Benefits

There are no other relevant benefits at this time.

7.3. Integrated Assessment of Effectiveness

In this section, I discuss the various options of regulatory pathways for drisapersen.

As required by the law under 21CFR 314.126 (a) (b), substantial evidence of effectiveness for drug approval is based on the requirement of independent substantiation of evidence of effectiveness. Drisapersen development program has 3 adequate placebo controlled studies with a single primary endpoint and several non-specific secondary clinical endpoints.

There is no substantial evidence of efficacy for drisapersen from the adequate and well controlled studies based on a clinical endpoint, change from baseline 6MWD.

There was a statistically significant treatment difference for drisapersen 6 mg/kg/week over placebo ($p=0.01$) at week 25 for the primary endpoint change from baseline 6MWD in only one small Phase 2 Study DMD114117. The change from baseline in 6MWD observed at Week 25 does not appear sustained at Week 49. An intermittent regimen of the same 6mg/kg dose with identical plasma exposure showed no statistically significant ($p=0.80$) difference over placebo in this study. The known and unknown biases from this study such as unblinding due to injection site skin reactions and baseline imbalances in prognostic factors due to chance alone could be mitigated if these findings are replicated in independent studies. It is disappointing that there is no independent substantiation of these results from the second Phase 2 Study DMD114876 ($p=0.07$) and the large Phase 3 DMD114044 ($p=0.42$) to rule out the possibility of a false positive finding due to chance alone. Removing one placebo subject from the analysis of the Phase 2 Study DMD114876 because the subject was unblinded increased the p-value to 0.21, further weakening the confidence in the evidence towards efficacy from Study DMD114117. Applicant's argument of a more functionally impaired population of the Phase 3 study DMD114044 contributing to a lack of treatment response was not substantiated by a FDA post-hoc analysis of subjects with similar baseline age, 6MWD and rise from floor time as in the Phase 2 studies.

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There was no statistically significant treatment difference ($p=0.71$) or even a larger numeric treatment difference in this subgroup of patients, suggesting that the disease severity of the subjects was not the reason for the negative results from Study DMD114044.

Although a numeric advantage for drisapersen over placebo was observed in the three placebo controlled studies, a precise estimate of possible effect size cannot be established for drisapersen. An aggregate of the data across studies and all post-hoc analyses suggest that if it were to be concluded that the result was due to drug, there was a numerical advantage with drisapersen of approximate 10-20 m over placebo over 24-48 weeks. The clinical meaningfulness of this short term numeric advantage with drisapersen in the overall prognosis remains uncertain.

A number of secondary endpoints were assessed without control for multiplicity. None of the secondary endpoints were nominally positive in any study. Secondary endpoints such as Timed Function Tests (rise from floor, 10m walk/run, 4-stair climb/ascent –descent) and NSAA are also measures of lower limb strength like the 6MWD and are highly correlated to each other. These secondary endpoints were in the same direction as the primary endpoint in only Study DMD114117. There were no consistent trends in favor of drisapersen in other studies. The differences in the Timed Function Tests were mostly <1 second between treatment and placebo in all three studies. Muscle strength measure by myometry and pulmonary function tests did not favor drisapersen. The changes were small across treatment groups. These secondary endpoints analyses do not contribute to the assessment of efficacy.

Even if one were to consider the results of Study DMD114117 bereft of uncertainties, there is no independent substantiation of these findings. A single study approval could be argued for a rare disease with no approved treatments. Single study approvals are generally limited to situations in which the study has demonstrated a clinically meaningful effect on mortality or irreversible morbidity and in which a second trial would be ethically impossible. For this application, we have 2 other adequate controlled studies which cannot be ignored and the endpoint is not mortality or irreversible morbidity. In addition, the study was smaller than a large well powered study that failed to show effectiveness. Given the above concerns from the placebo controlled studies, I do not recommend standard full approval of drisapersen in the treatment of exon 51-skip amenable DMD.

The law under 21CFR 314.500 further provides the regulations for approval under Subpart H- Accelerated approval of new drugs for serious and life threatening disease. DMD is a severe disease in which progressive loss of muscles lead to loss of ambulation, respiratory and cardiac complications and ultimately death. There are no approved treatments of DMD in the United States.

Under Subpart H, approval can be based on either on a “surrogate endpoint” that is reasonably likely based on epidemiologic, therapeutic, pathophysiologic or other evidence to predict clinical benefit at some later time OR on an “intermediate clinical endpoint” that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.

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I will first consider 6MWD as an "intermediate clinical endpoint". 6MWD is a clinically meaningful endpoint in DMD as it is a measure of how a patient functions. It measures how much a subject can walk (in meters) in a fixed time of 6 minutes. While being able to walk more is certainly meaningful in the day-to-day activities of the patient, an improvement in measure of a distance could predict an effect on irreversible morbidity or mortality, which is time to loss of ambulation or death, i.e. could affect the ultimate rate of decline. If we were to consider 6MWD as an intermediate clinical endpoint, it would be on the basis of the short-term benefit of walking more reasonably likely to have an effect on the rate of decline of walking performance and thus influence the time to loss of ambulation. Drugs granted accelerated approval MUST meet the same statutory standards of effectiveness and safety as those granted traditional approval. As discussed in the previous paragraphs, the clinical evidence of efficacy for drisapersen does not meet the statutory standard and remains inconclusive based on 6MWD and other clinical secondary endpoints. An aggregate of the data across studies and all post-hoc analyses suggest a relatively short-term numerical advantage with drisapersen of approximately 10-20m over placebo. These differences were not statistically significant, hence no persuasive treatment effect size can be established between drisapersen and placebo. Based on natural history studies in DMD, a 10-20m treatment difference between drisapersen and placebo is also not likely to have a large effect on delaying the time to loss of ambulation (Natural history studies have suggested decline in 6MWD of 22-58 m in a year). The open label studies in the application, though not completely interpretable, do not suggest that the rate of decline in the walking performance was different from that of natural history. Hence, based on the unpersuasive results of 6MWD from studies presented in this application, it is uncertain if 6MWD can serve as an intermediate clinical endpoint reasonably likely to predict an effect on irreversible morbidity for this application.

Therefore, the threshold for accelerated approval based on 6MWD as an intermediate clinical endpoint reasonable likely to predict benefit on time to loss of ambulation or the rate of decline appears unmet.

Lastly, I will discuss the regulatory pathway of accelerated approval based on a surrogate endpoint reasonable likely to predict clinical benefit. Creatine kinase, a marker of muscle cell integrity at a molecular level could serve as a surrogate endpoint reasonable likely to predict clinical benefit. CK was reduced by 30-40% across the three studies based on percent change from baseline with nominal p-values of 0.08, 0.53 and <0.001 for the Studies DMD114117, DMD 114876 and DMD114044 respectively, suggesting a plausible improvement in muscle cell integrity. While the reduction CK was consistent across studies, the effect of confounders such as inactivity, reduced muscle mass, steroids use and inflammatory processes cannot be completely understood from the data. There was obviously no correlation of reduced CK to the clinical endpoint 6MWD based on the studies in the Application. A statistically significant ($p < 0.001$) reduction in CK was observed despite of no difference in walking ability between drisapersen and placebo ($p = 0.42$). Given this, the clinical meaningfulness of the observed reduction in CK is uncertain from the studies in this application. Hence, the reasonable likelihood of a reduction in serum creatine kinase to predict a clinical benefit in function or time to loss of ambulation appears uncertain. An increase in dystrophin protein expression could reflect biological activity and can be considered a surrogate endpoint. It is disappointing that the dystrophin protein expression data were equivocal. The changes in dystrophin were minimal and reliable only in one study.

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Therefore, the threshold for accelerated approval based on creatine kinase or dystrophin as a surrogate endpoint reasonable likely to predict clinical benefit of drisapersen of this application appears unmet as well.

One can argue a numerical advantage on the subjective endpoint 6MWD and on an objective endpoint such as CK in favor of drisapersen in all studies is suggestive that drisapersen is better than placebo. Although, these two together also do not meet the threshold for being reasonably likely to predict an effect on irreversible morbidity or mortality.

The development program for drisapersen is extensive for a rare disease and exemplary. It is very disappointing that that both clinical and biomarker data for drisapersen are inconclusive at this time.

8 Review of Safety

Safety Review Approach

The safety of drisapersen is reviewed by Dr. Evelyn Mentari, MD in a separate review.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was held on November 24th, 2015. In general, the committee agreed that the efficacy of drisapersen as a treatment for patients with Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping has not yet been demonstrated by the data from the clinical program so far.

10 Labeling Recommendations

Labeling recommendations are deferred until Advisory Committee meeting.

11 Risk Evaluation and Mitigation Strategies (REMS)

REMS are not proposed for this application. The reader is referred to Dr. Mentari's safety review.

12 Postmarketing Requirements and Commitments

Postmarketing requirements are deferred until Advisory Committee meeting.

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13 Appendices

13.1. References

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13.2. Financial Disclosure

Covered Studies: 3

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>78</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> Note: There are 33 sub-investigators whose financial disclosure information could not be obtained despite due diligence efforts by the sponsor. These sub-investigators could not be located.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>NA</u> Significant payments of other sorts: <u>NA</u> Proprietary interest in the product tested held by investigator: <u>NA</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>NA</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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Appendix A

North Star Ambulatory Assessment Scale

Activity	2	1	0	Comments
1. Stand	Stands upright, still and symmetrically, without compensation (with heels flat and legs in neutral) for minimum count of 3 seconds	Stands still but with some degree of compensation (e.g. on toes or with legs abducted or with bottom stuck out) for minimum count of 3 seconds	Cannot stand still or independently, needs support (even minimal)	
2. Walk	Walks with heel-toe or flat-footed gait pattern	Persistent or habitual toe walker, unable to heel-toe consistently	Loss of independent ambulation – may use KAFOs or walk short distances with assistance	
3. Stand up from chair	Keeping arms folded Starting position 90° hips and knees, feet on floor/supported on a box step.	With help from thighs or push on chair or prone turn	Unable	
4. Stand on one leg - right	Able to stand in a relaxed manner (no fixation) for count of 3 seconds	Stands but either momentarily or needs a lot of fixation e.g. by knees tightly adducted or other trick	Unable	
5. Stand on one leg – left	Able to stand in a relaxed manner (no fixation) for count of 3 seconds	Stands but either momentarily or needs a lot of fixation e.g. by knees tightly adducted or other trick	Unable	
6. Climb box step – right	Faces step – no support needed	Goes up sideways or needs support	Unable	
7. Climb box step – left	Faces step – no support needed	Goes up sideways or needs support	Unable	
8. Descend box step –right	Faces forward, climbs down controlling weight bearing leg. No support needed	Sideways, skips down or needs support	Unable	
9. Descend box step –left	Faces forward, climbs down controlling weight bearing leg. No support needed	Sideways, skips down or needs support	Unable	
10. Gets to sitting	Starts in supine – may use one hand to assist	Self assistance e.g. – pulls on legs or uses head-on-hands or head flexed to floor	Unable	

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Activity	2	1	0	Comments
11. Rise from floor	From supine – no evidence of Gowers' manoeuvre*	Gowers' evident	(a) NEEDS to use external support object e.g. chair OR (b) Unable	Time (00.0s)
12. Lifts head	In supine, head must be lifted in mid-line. Chin moves towards chest	Head is lifted but through side flexion or with no neck flexion	Unable	
13. Stands on heels	Both feet at the same time, clearly standing on heels only (acceptable to move a few steps to keep balance) for count of 3	Flexes hip and only raises forefoot	Unable	
14. Jump	Both feet at the same time, clear the ground simultaneously	One foot after the other (skip)	Unable	
15. Hop right leg	Clears forefoot and heel off floor	Able bend knee and raise heel, no floor clearance	Unable	
16. Hop left leg	Clears forefoot and heel off floor	Able bend knee and raise heel, no floor clearance	Unable	
17. Run (10m)	Both feet off the ground (no double stance phase during running)	'Duchenne jog'	Walk	Time (00.0s).....
				TOTAL= /34

Grading for Timed Function Tests

Grading of rising from floor (supine to stand)

1. Unable to stand from supine, even with use of a chair.
2. Assisted Gower's – requires furniture for assist in arising from supine to full upright posture.
3. Full Gowers – rolls over, stands up with both hands "climbing up" the legs to achieve full upright posture.
4. Half Gowers – rolls over, stands up with one hand support on leg.
5. Rolls to the side and/or stands up with hand one or both hands on the floor to start to rise but does not touch legs.
6. Stands up without rolling over or using hands.

Clinical Review (Efficacy)

NDA 206, 031 (Drisapersen)

Grading of 10 m walk/run test

1. Unable to walk independently.
2. Unable to walk independently, but can walk with full leg calipers (KAFOs) or with support from a person.
3. Highly adapted wide based lordotic gait. Cannot increase walking speed.
4. Moderately adapted gait. Can pick up speed but cannot run.
5. Able to pick up speed, but runs with a double stance phase, i.e. cannot achieve both feet off the ground.
6. Runs and gets off both feet off the ground (with no double stance phase).

Grading of 4-stair climb

1. Unable to climb 4 standard stairs
2. Climbs 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step). Uses both arms on one or both handrails.
3. Climbs 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step). Using one arm on one handrail.
4. Climbs 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step). Not needing handrail.
5. Climbs 4 standard stairs alternating feet, needs handrail for support.
6. Climbs 4 standard stairs alternating feet, not needing handrail support.

Grading of 4-stair descend

1. Unable to descend 4 standard stairs.
2. Descends 4 standard stairs "marking time" (descends one foot at a time, with both feet on a step before moving to next step). Requires both arms on one or both handrails.
3. Descends 4 standard stairs "marking time" (descends one foot at a time, with both feet on a step before moving to next step). Requires one arm on one handrail.
4. Descends 4 standard stairs "marking time" (descends one foot at a time, with both feet on a step before moving to next step). Not needing handrail.
5. Descends 4 standard stairs alternating feet in both directions, needs handrail for support.
6. Descends 4 standard stairs alternating feet, not needing handrail support.

Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

Appendix B [Additional Dystrophin bioassay-related reviewer comments]

RT-PCR measurement of dystrophin exon 51-skipped mRNA:

While the exact cause for these spontaneous exon skipping is unknown, alternative splicing events and skip frame-shifting that restore the open reading frame (ORF) for dystrophin might result in the spontaneous internally-deleted dystrophin in these fibers. No comprehensive study in boys with DMD has been conducted to characterize the extent of baseline revertant dystrophin but smaller studies have suggested that at least 50-62% of DMD cases show some baseline dystrophin-positive fibers and that the percentage of revertants or trace dystrophin fibers within these samples ranged from 0.01 to 25%. The reason for these baseline exon skipped mRNA and their correlation to protein levels after treatment has not yet been clearly defined in published studies. Emerging literature suggests that the *stability* of the transcript (skipped mRNA) is an important factor for determining ultimate dystrophin protein expression, rather than the *amount* of transcript. As their proposed mechanism of action, exon 51 skipping therapies should result in an increase in overall percentage of fibers with stable exon 51 skipped products when compared to a patient-matched baseline sample from the same muscle sub-group. The data is not adequate to demonstrate an increase in skipped product because it is a qualitative assay with no internal controls for reference. An intensity measurement of the PCR fragment(s) at multiple time-points could add some confidence, as attempted by the applicant with the nested RT-PCR approach.

The stability of the exon skipped transcript detected is also not apparent from the nested/lab-on-chip analysis. Any proposed correlation between dystrophin mRNA and protein levels is complicated by the known instability of the mRNA. Spitali et al (2013) have reported that Becker patients and mdx mice show significant transcript instability that obscures a clear correlation between transcript and protein levels. Anthony et al (2014) reported transcript instability in DMD patient samples with out-of-frame deletions compared to in-frame deletions. They suggest that measuring transcript stability by covering multiple exon junctions for dystrophin might indicate stability, which may be more important for predicting protein levels than measuring amounts of transcript. By using a nested PCR approach, the applicant may have hypothetically enhanced specificity for the target sequences on dystrophin but their exact primers were not described or whether their method captures transcript stability. Specifically, the applicant did not use multiple primers to cover additional regions of the target dystrophin skipped product to be able to predict stability of the transcript, as suggested by the literature cited above, which may be a better predictor of pharmacodynamic activity. While their lab-on-chip capillary electrophoresis/nested PCR method is a reasonable qualitative method for detecting dystrophin transcript, it may not provide the most accurate representation of exon skip that would be predictive of dystrophin protein expression. Additionally, no reference standard or calibration curve was used so it is not possible to interpret the applicant's data as reflective of absolute copy numbers of dystrophin transcript.

Assay cut-offs and scoring approach for the IFA and WB methods:

According to the applicant, for IFA, an increase in dystrophin was defined as an increase in mean membrane intensity of more than 4% at week 25 compared to pre-treatment biopsy. A strong increase in dystrophin was defined as an increase in dystrophin intensity by $\geq 9\%$ for the mean or $\geq 4\%$ for the mean accompanied by an increase of $\geq 15\%$ for the 10th quartile of most intensive pixels and confirmed by visual inspection of the images. A decrease was $\leq -4\%$ for the mean membrane intensity. For WB, an increase was defined as a $>30\%$ increase in densitometric value of the ~ 427 kDa dystrophin band (post treatment -pre-treatment/pre-treatment)*100.

The 4% assay cutoff for an IFA score of "increase" and $>9\%$ for "strong increase" appears reasonable from a purely analytical standpoint because the inter- and intra-assay variability observed by the applicant is between 2-5% for this immunofluorescence assay. The Applicant also cited an mdx mouse model study where motor function was improved when levels of dystrophin were $>4\%$ compared to healthy control muscle. However, no

Clinical Review (Efficacy)

NDA 206, 031 (Drisapersen)

correlative human endpoint data (e.g. muscle function or DAPC protein co-localization) has been presented to support the biological significance of this scoring. Therefore, it cannot be concluded that the applicant's assay assay cut-offs are biologically meaningful.

Correlation between IFA, WB, and RT-PCR methods:

A clear, consistent, and positive correlation between all three assays - IFA, WB, and Exon skip -has not been established by the Applicant or published literature in the field using appropriate positive/negative controls (e.g. with BMD, DMD, healthy samples in the linear range). As presented by the applicant, the WB data is likely to be most reliable because a serial dilution with a healthy positive control was used for comparison and pre-treatment and post-treatment samples were run on the same gel in most instances. The IFA can suggest protein localization but is likely to be less meaningful for protein level quantitation.

Taylor et al have reported a correlation between immunofluorescence-based intensity ratios of dystrophin/spectrin and dystrophin protein levels measured by Western blotting and normalized to actin. In the article, data have been presented, suggesting a strong correlation between Western blotting and IFA (Anthony 2014 and Kevin Flanagan, Nationwide Children's Hospital, Columbus, OH, at the FDA-NIH Dystrophin Workshop 2015). However, the data presented also had an inter-laboratory variability CV of 22-67% for IFA, which lowers the confidence in the quantitative abilities of IFA and reproducibility of the findings.

The correlation between IFA and WB methodologies likely depends on several factors including, but not limited to, (1) the differences in the basic assay methodologies (e.g. single cell-based microscopy versus homogenized lysate-based WB), (2) the antibodies used, the epitopes being targeted, as well as the exposure of those dystrophin epitopes to the antibodies in its intracellular or lysate state (3) the staining controls used (e.g. spectrin versus actin), (4) the measurement controls used (e.g. a negative DMD or positive healthy sample), (5) operator bias in the absence of automated image capture or analyses, (6) distribution and localization of dystrophin within the muscle fiber, (7) heterogeneity in the levels of revertant dystrophin between and within individual DMD patients, (8) sensitivity of the detection systems (e.g. fluorescence-tagged antibodies or densitometer instrument used), and (9) the limits of detection and quantitation for either methods. While it may be challenging to establish a strong quantitative correlation between WB and IFA, the protein levels observed the two methods for an appropriately designed experiment should trend in the same direction.

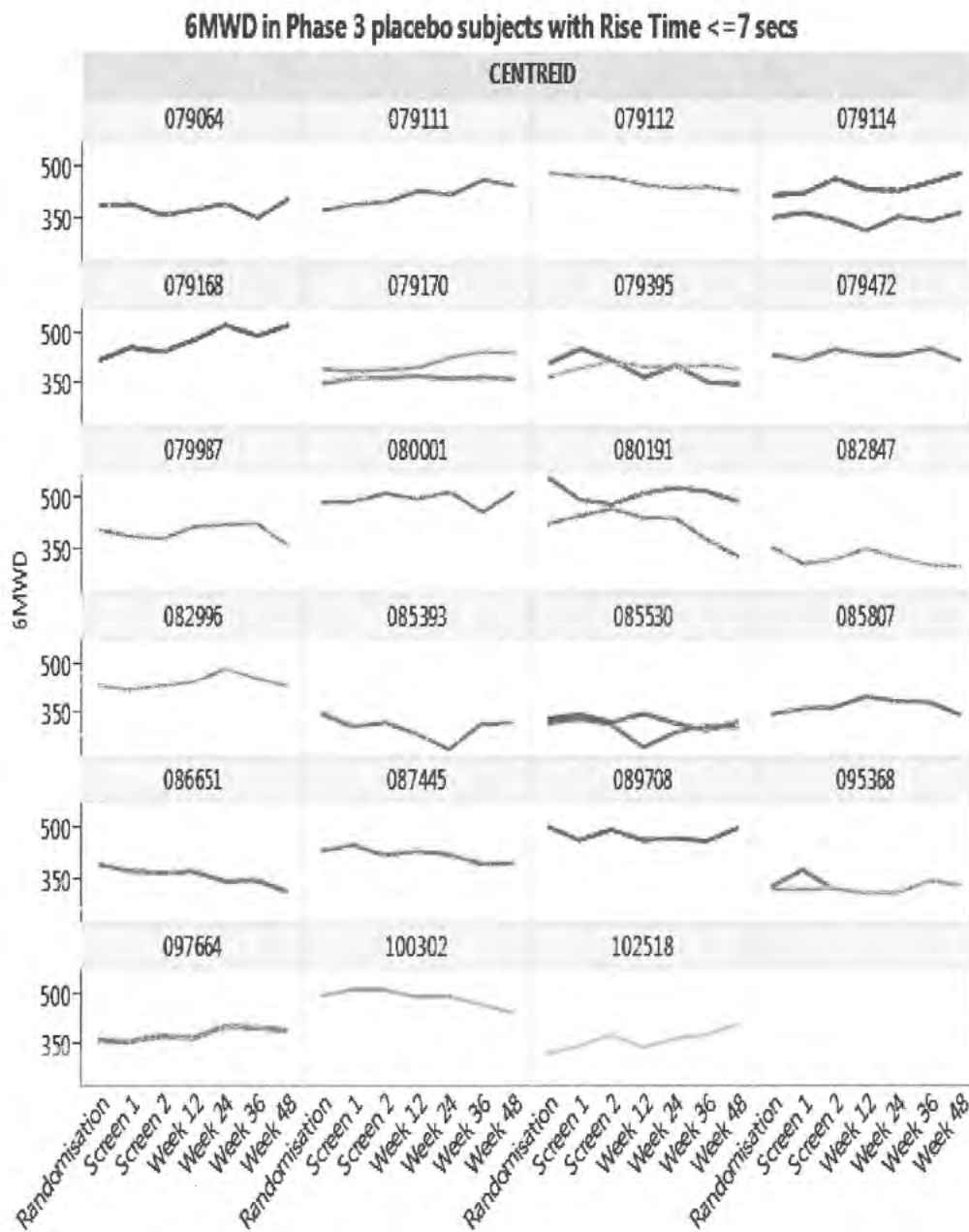
Additional comments on the deficiencies with the IFA methodology used in study 114876:

The applicant states that the inter-assay reproducibility of their IFA assay between experiments for placebo and drisapersen-treated subjects combined was 5% and ranged between 0-16% for the study. It is not clear if the mean values reported in Table 26 that are below 5% represent biologically-relevant responses or expected assay variability. There also appear to be several critical deficiencies in the applicant's analytical approach that preclude an interpretable assessment of dystrophin increase.

The Applicant states that a large change in spectrin (>20%) was observed between Week 24 and baseline biopsies, it is not clear whether and how this impacted dystrophin intensity measurements. However, it may suggest that either spectrin or the way spectrin was analyzed was not suitable for the intended purpose of being a muscle fiber co-stain. This could have been addressed by conducting adequate assay validation prior to clinical sample testing.

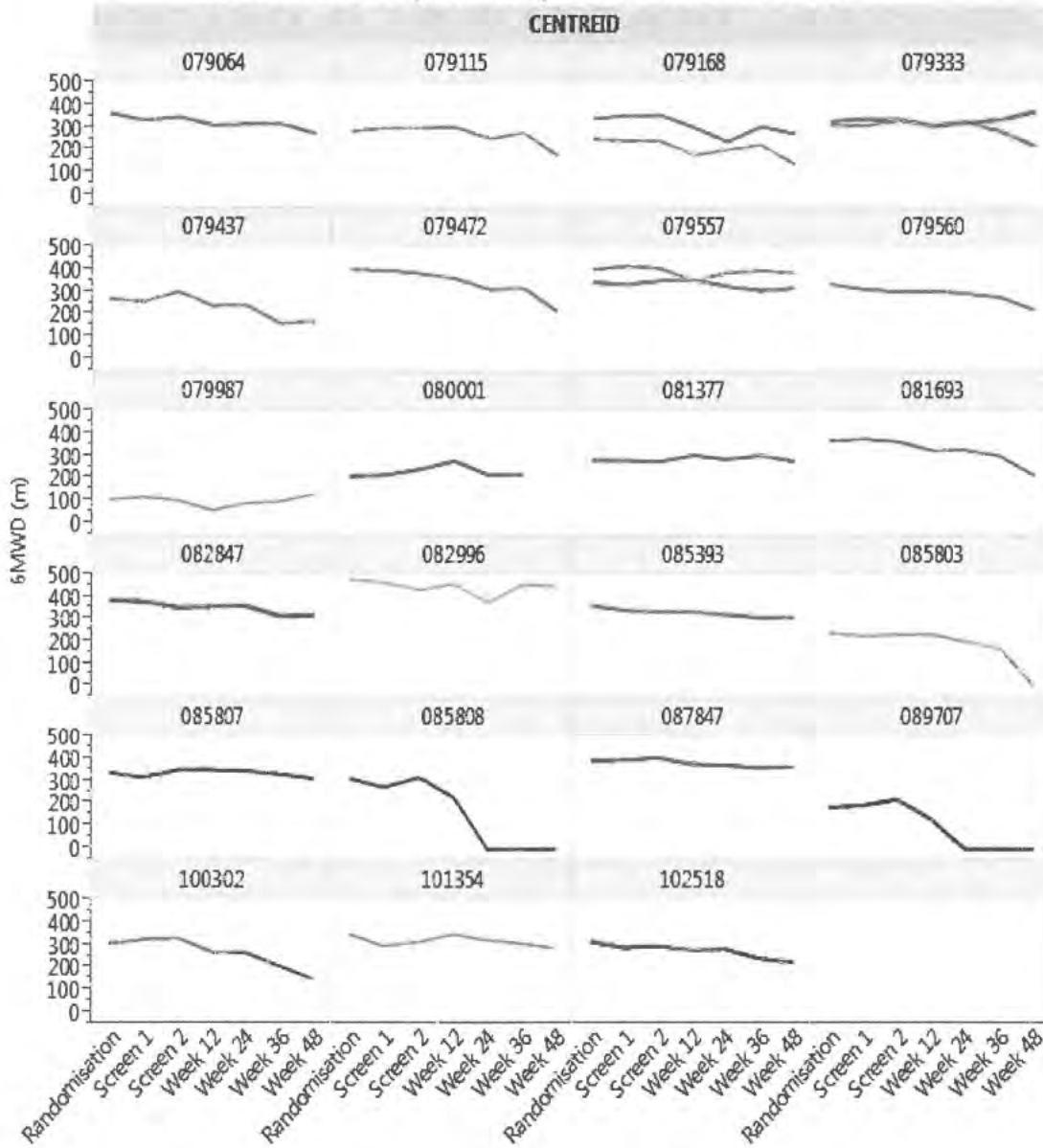
The number of subjects with sufficient quality, size, and muscle fiber content for each group was low (12, 11, and 13 for placebo, Week 24-3 mg/kg, and wk24- 6 mg/kg).

Appendix C

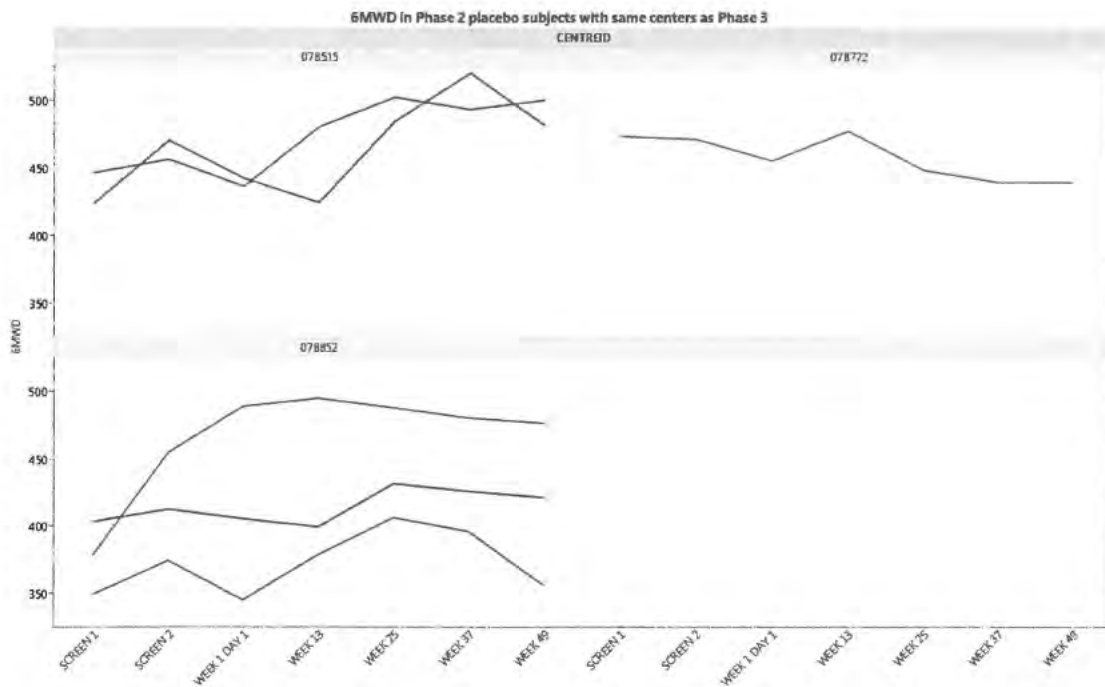
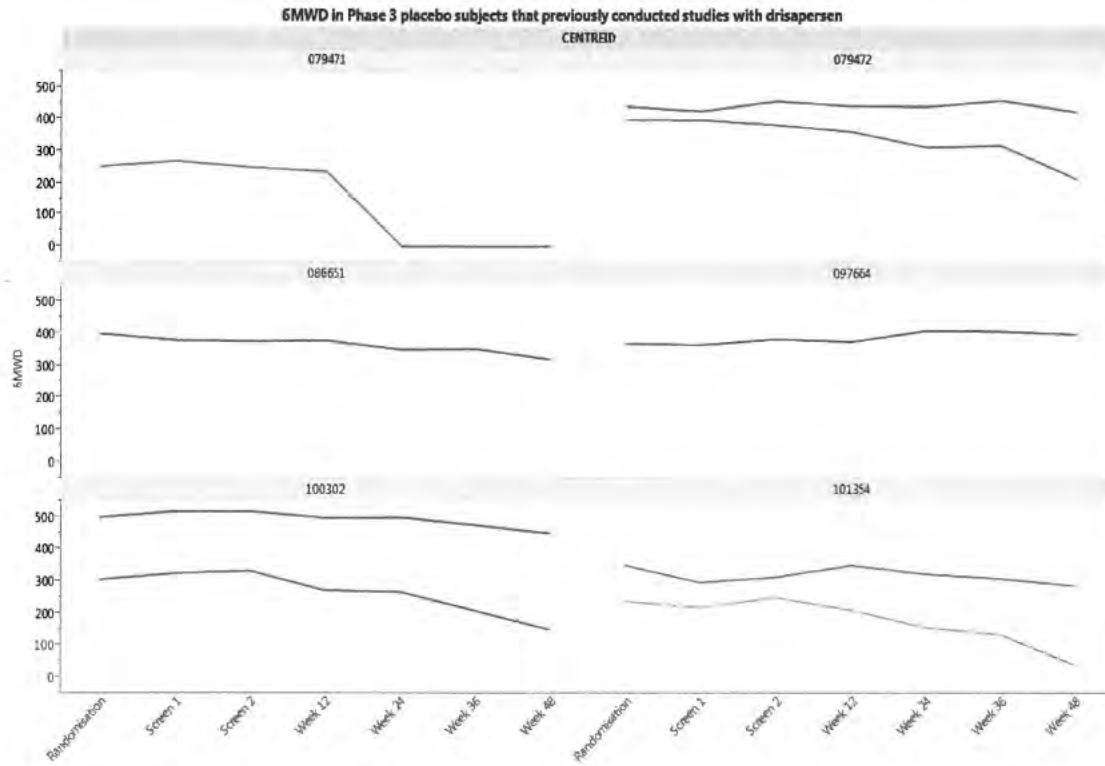


Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

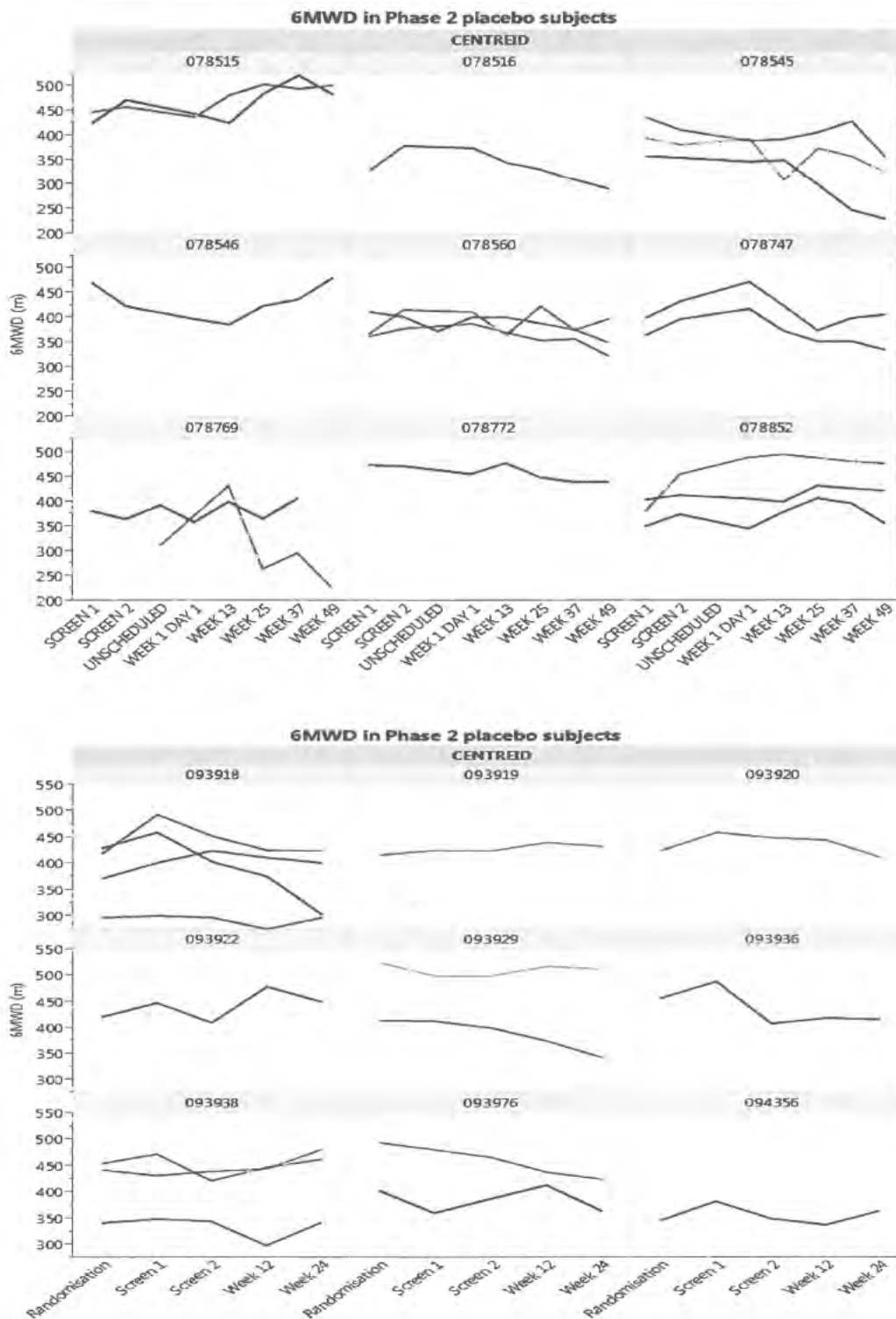
6 MWD in Phase 3 placebo subjects with Rise Time > 7 secs



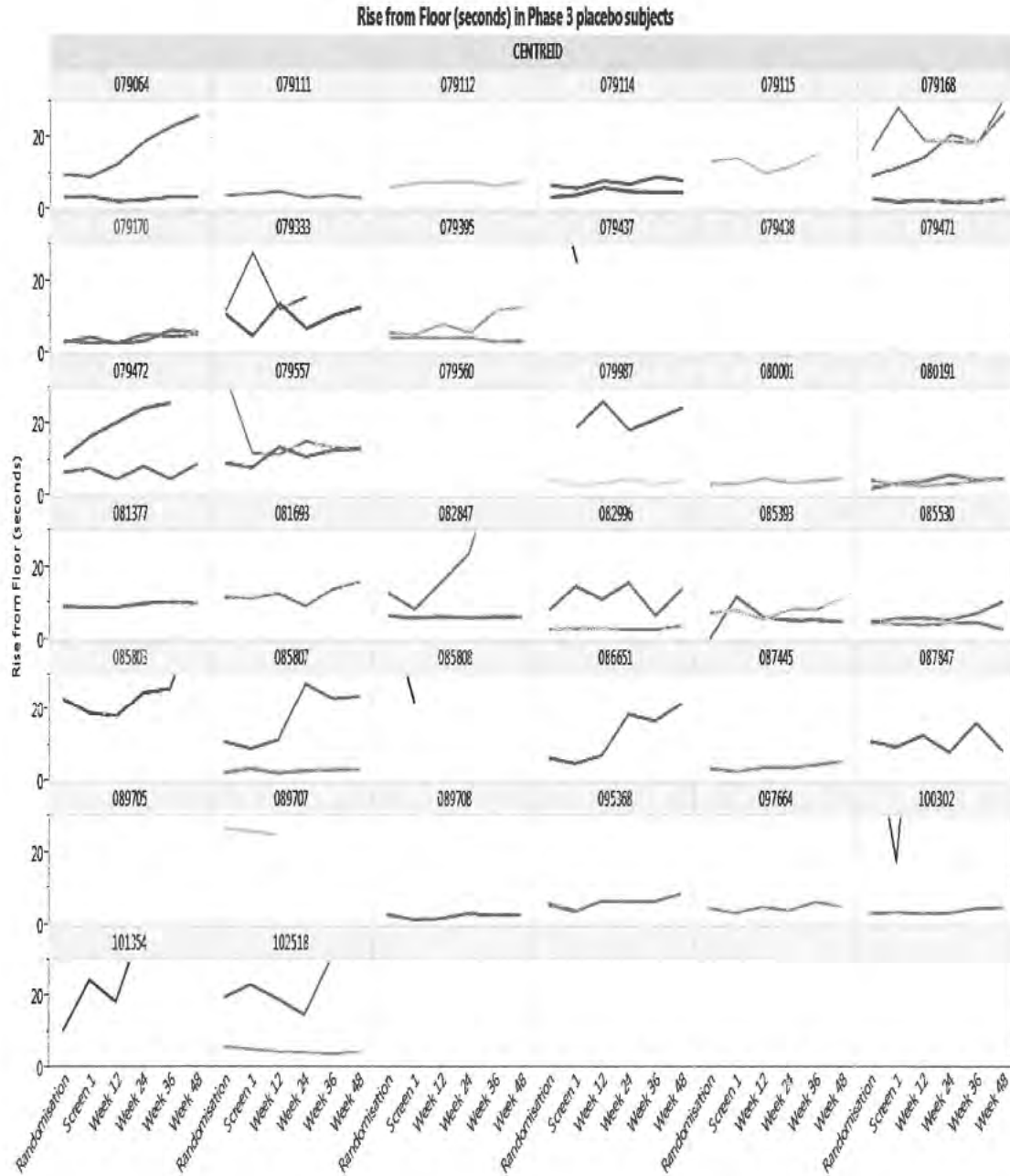
Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)



Clinical Review (Efficacy)
 NDA 206, 031 (Drisapersen)

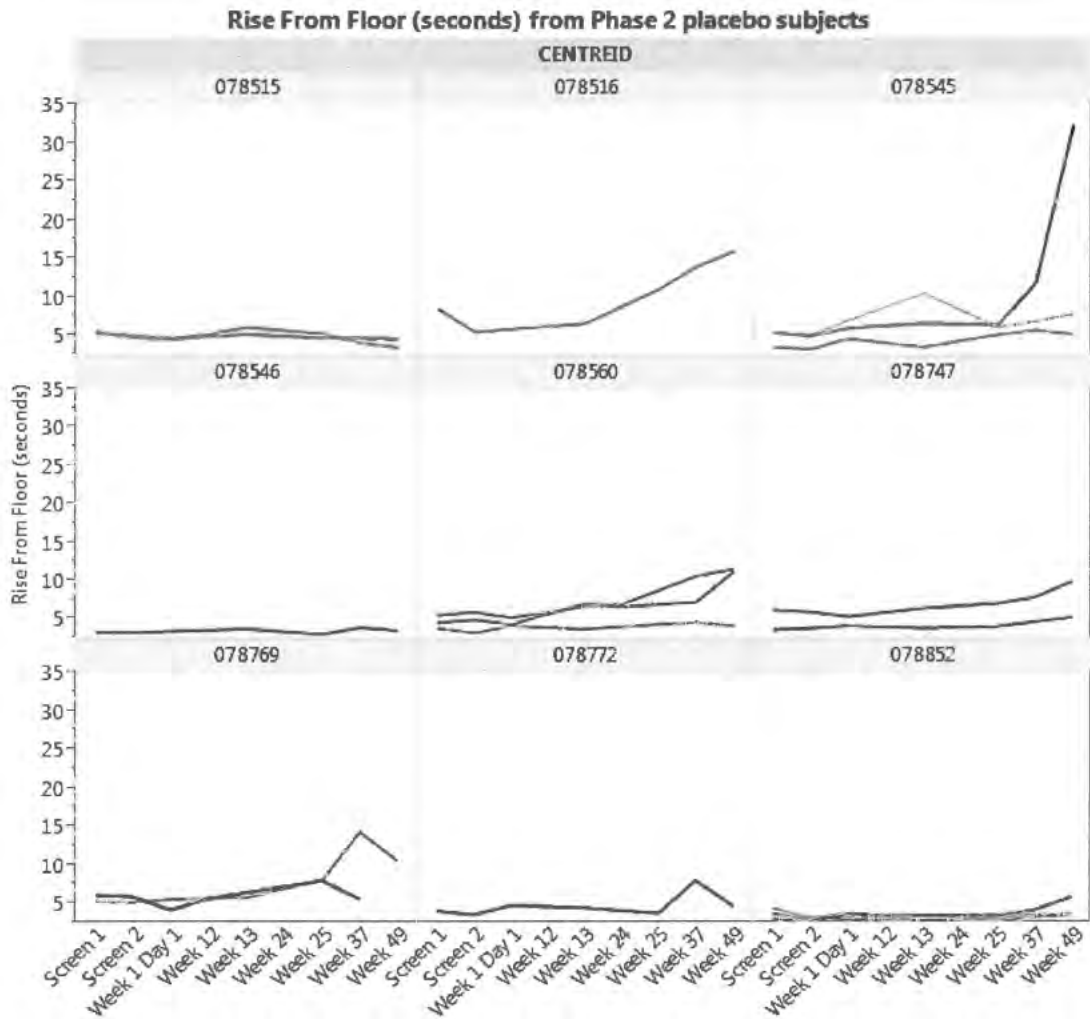


Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)

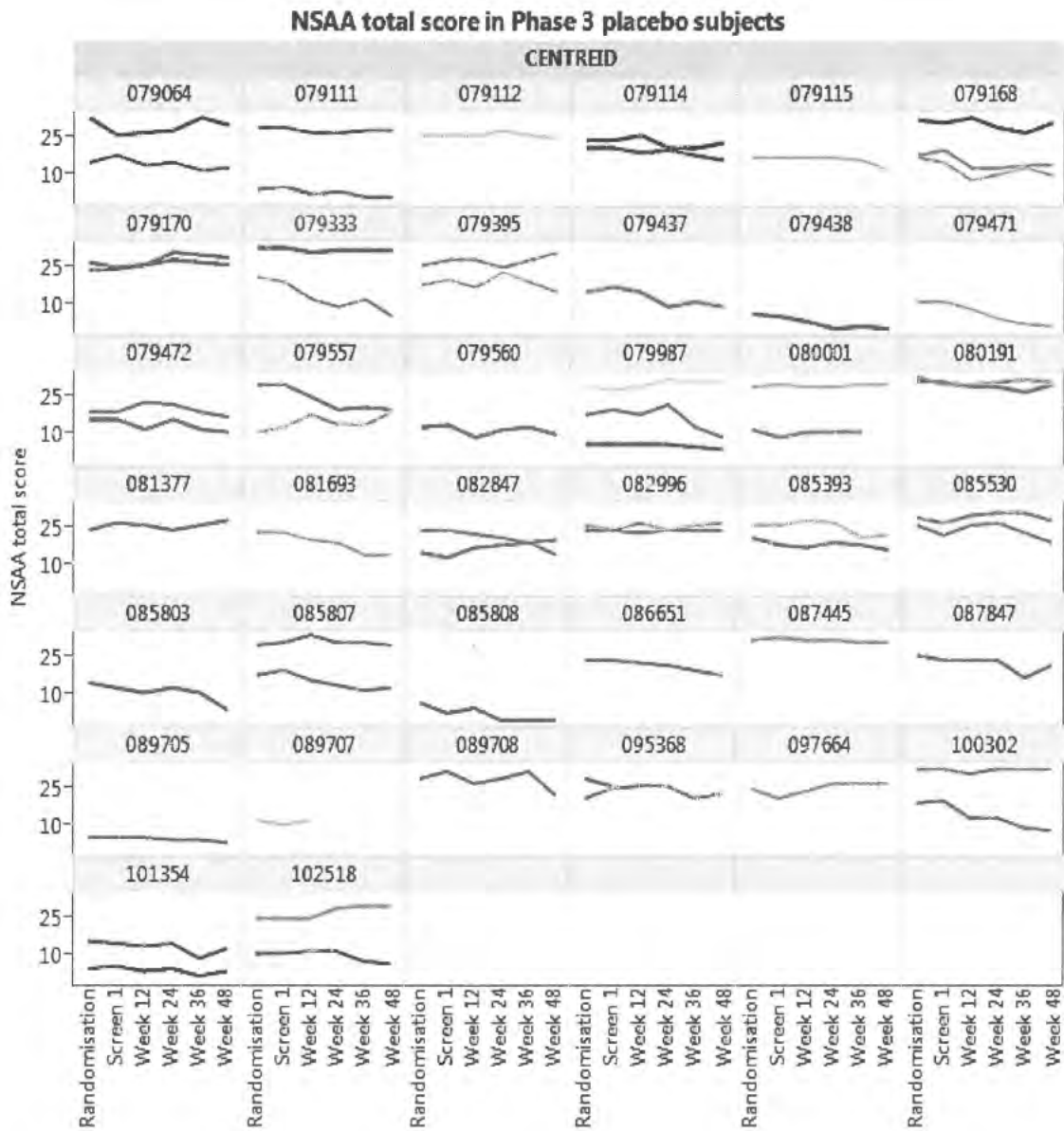


Note: The Y-axis has been truncated to 30 seconds

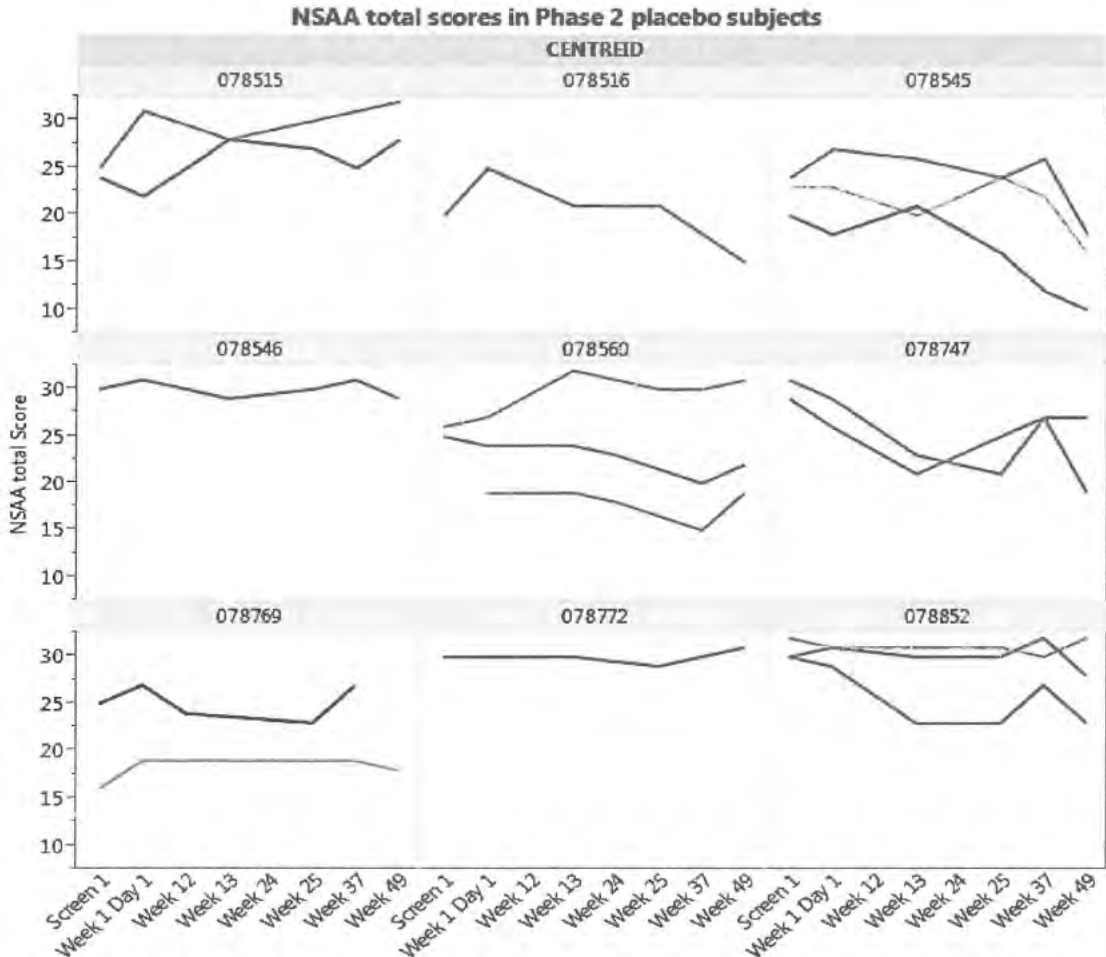
Clinical Review (Efficacy)
NDA 206, 031 (Drisapersen)



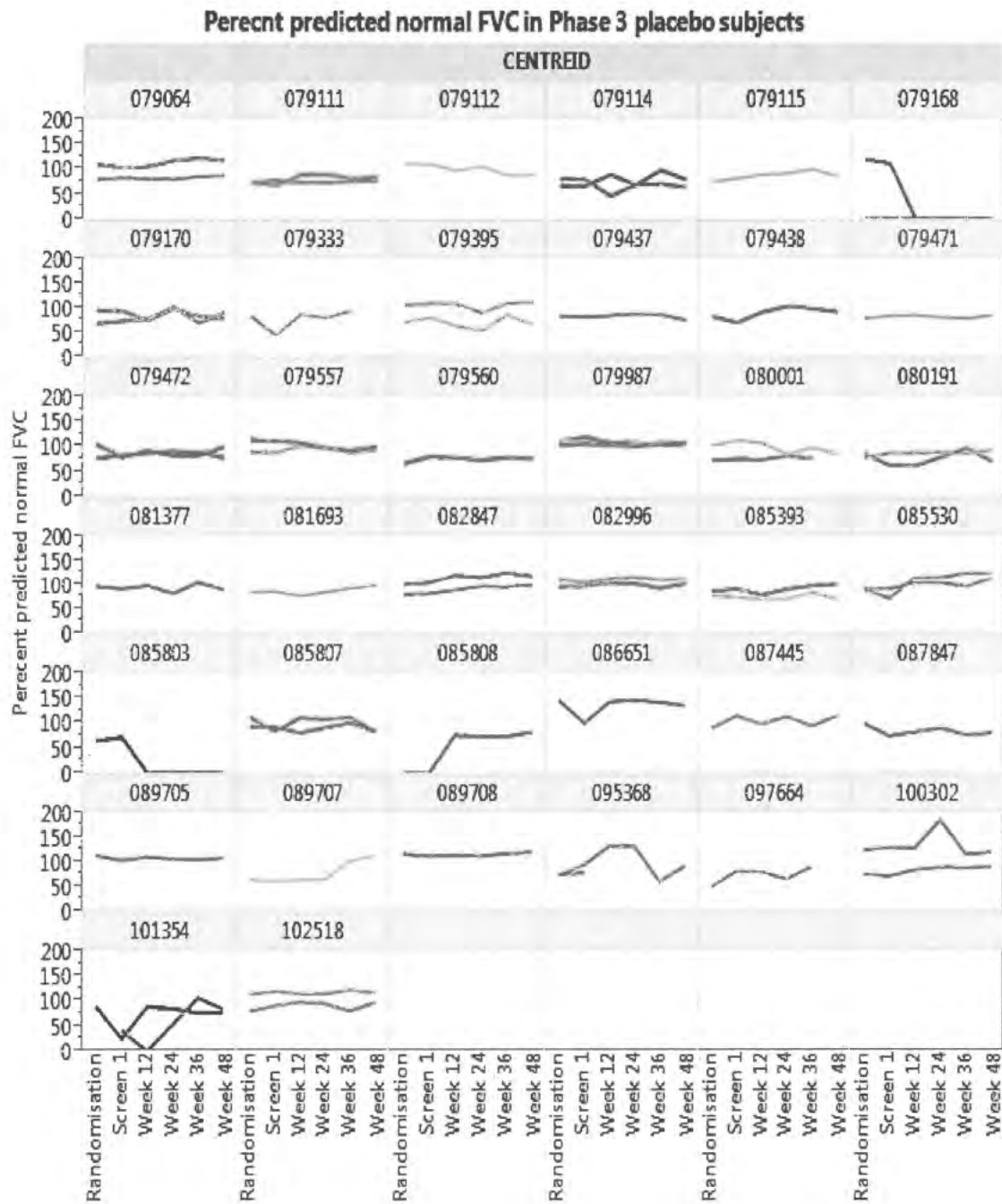
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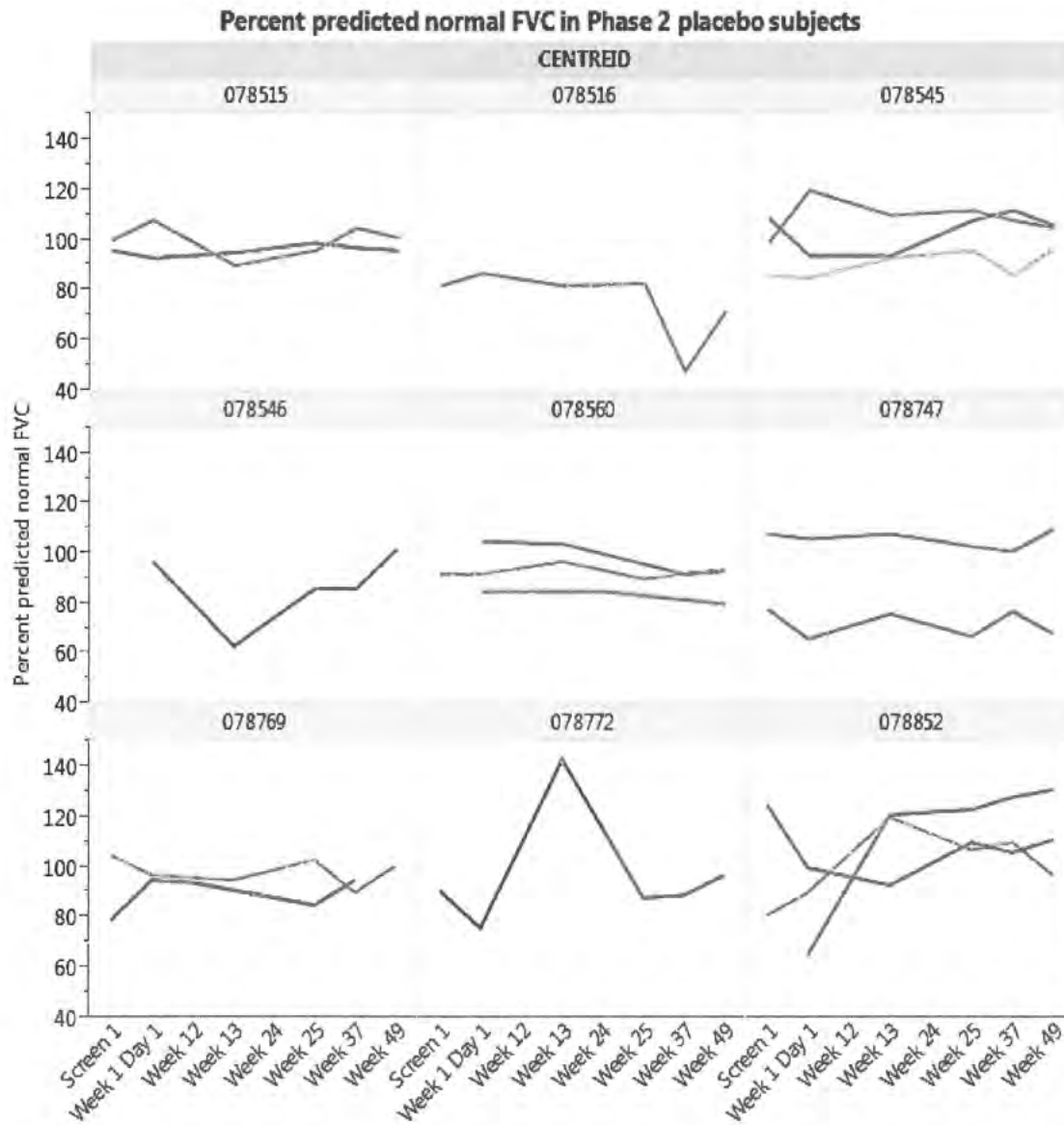
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NDA 206, 031 (Drisapersen)



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

/s/

VEENEETA TANDON
12/03/2015

V ASHUTOSH RAO
12/04/2015

RONALD H FARKAS
12/04/2015

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 1:36 PM
To: DeMarco, Devota R
Subject: RM FW: Discussion with PHRMA CEOs and the establishment of a recruitment/retention fund at FDA

From: Califf, Robert
Sent: Thursday, April 14, 2016 5:54 AM
To: Mullin, Theresa; Moscicki, Richard; Woodcock, Janet
Subject: RE: Discussion with PHRMA CEOs and the establishment of a recruitment/retention fund at FDA

Sounds ok to me. We should have more discussion internally about what our limits may be with regard to incentives and creation of disparities for career FDA folks vs those who come in. not easy, but I sure appreciate the creative options.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Mullin, Theresa
Sent: Wednesday, April 13, 2016 7:05 PM
To: Moscicki, Richard; Califf, Robert; Woodcock, Janet
Subject: RE: Discussion with PHRMA CEOs and the establishment of a recruitment/retention fund at FDA

I can add that due to the schedule conflict with the AC meeting on eteplirsen for DMD on April 25th, the meeting with the PhRMA and BIO CEOs has just been rescheduled to July 12th. While I am sorry about the delay for other PDUFA topics, this would also allow more time for any further internal discussion or putting together talking points that FDA would want to share. Thx, Theresa

Theresa M Mullin, PhD
Director, Office of Strategic Programs
FDA Center for Drug Evaluation and Research

From: Moscicki, Richard
Sent: Wednesday, April 13, 2016 4:55 PM
To: Califf, Robert; Woodcock, Janet
Cc: Mullin, Theresa
Subject: Discussion with PHRMA CEOs and the establishment of a recruitment/retention fund at FDA

Dear Rob and Janet, I recently spoke to both of you about an idea to help us recruit and hire executive level people from industry for key positions that we have had difficulty filling due to conflict of interest. I initially approached Bill Chin at PHRMA to see what could be done to encourage companies to accelerate unvested options or RSUs for senior execs who were coming to FDA as a public service gesture. Admittedly the optics for that may not be great if companies were seen as doing special financial favors for those coming to FDA. An alternative proposed for our consideration is to create the equivalent of an "ALTIP" fund. This would be a fund that we could use to draw on to mitigate the losses that executives might take if they have to renounce these options or RSUs. The fund could draw from user fees. Ideally all user fees, would contribute a small portion for the fund. I suspect a fund of \$5 million should be sufficient. The award for each person involved would be paid out as a

retention bonus, say over 5 years. Reasonable limits would be placed on the awards granted from the fund. Of course, we already have the ability to give retention bonuses but I suspect this would need legislative effort to make real. We are meeting with the PHRMA executives soon, Therese Mullin suggested we may wish to put this on our agenda to discuss with them if we wish to pursue this. I think the PHRMA staff will be open to this discussion. Rich.

From: [Bernstein, Jessica](#)
To: [Moran, Kristy](#)
Cc: [JW Direct Reports & Deputies](#); [CDER-EOS](#); [Behr, Virginia L](#); [Peterson, Jayne E](#); [MedWatch Safety Alerts](#); [Drug Safety Web](#); [Meister, Karen G](#); [Walsh, Sandy](#); [Sherwood, Edward M](#); [Thomas, Kimberly K \(ORP\)](#); [Helmanis, Lisa M](#); [Sullivan, Diane](#); [Stowe, Ginneh D.](#); [Baumgartner, Kristofer](#); [OPO Policy](#); [CDER-OPO-Inquiries](#); [Choi, Moon Hee](#); [Ngo, Diem-Kieu \(CDR,USPHS\)](#); [Farkas, Ronald](#); [Bastings, Eric](#); [Chov, Fannie \(Yuet\)](#); [Dunn, Billy](#); [Ware, Jacqueline H](#); [Unger, Ellis](#); [Locicero, Colleen L](#); [Vail, Victor H](#); [Peddicord, Sarah](#); [Walsh, Sandy](#); [Bolek, Michelle](#); [Rawlings, Kimberly](#); [Kremzner, Mary E](#); [Rausch, Paula \(FDA\)](#)
Subject: Information Advisory (UPDATED): FDA to Announce a RESCHEDULED Meeting of Peripheral and Central Nervous Systems Drugs Advisory Committee to Discuss Eteplirsen to Treat Duchenne Muscular Dystrophy
Date: Tuesday, February 23, 2016 3:59:14 PM
Attachments: [IA_Public_Mtg_PCNS_AC_Eteplirsen_to_Treat_DMD_New_Date_022316_DNP_ODEI_DEO_OEP_CDOR_cleared.doc](#)

Good Afternoon Kristy,

In late February or early March, FDA will announce a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. The Committee will meet on April 25, 2016 to discuss a new drug application for eteplirsen injection for treatment of Duchenne muscular dystrophy (DMD) in patients who have a specific mutation of the DMD gene. FDA expects the meeting announcement will be of interest to patients with DMD and their families, advocacy groups, industry, health care professionals (including neurologists and therapists working with people with DMD), researchers, and those working in regulatory science. FDA will not issue a press release. FDA will include the meeting information in the weekly tip sheet that is sent to all reporters who are on the FDA media list. The attached updated IA reflects the new meeting date.

*****PLEASE NOTE THAT THIS INFORMATION IS NOT RELEASABLE TO THE PUBLIC UNTIL ACTION TAKES PLACE*****

Regards,

Jessica

Jessica Bernstein, MPH

Writer-Editor

Division of Executive Operations

Office of Executive Programs

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

(240) 402-0524

jessica.bernstein@fda.hhs.gov

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 4:36 PM
To: DeMarco, Devota R
Subject: RM

From: Unger, Ellis
Sent: Monday, January 11, 2016 5:56 PM
To: Diggs, Felicia; Woodcock, Janet; Moscicki, Richard; Throckmorton, Douglas C; Temple, Robert; Guidos, Robert; Jenkins, John K; Kweder, Sandra L
Cc: Ligon, Sharnell (CDER)
Subject: RE: Written Submission for Congressman Fitzpatrick - Duchenne Muscular Dystrophy

In case no one has responded, he says in the final paragraph that he is looking forward to our reply. So I think we need to craft one.

From: Diggs, Felicia
Sent: Friday, January 08, 2016 7:50 PM
To: Woodcock, Janet; Unger, Ellis; Moscicki, Richard; Throckmorton, Douglas C; Temple, Robert; Guidos, Robert; Jenkins, John K; Kweder, Sandra L
Cc: Ligon, Sharnell (CDER)
Subject: Written Submission for Congressman Fitzpatrick - Duchenne Muscular Dystrophy
Importance: High

Dear all,

Please see attached a written letter from Congressman Fitzpatrick (Pa) addressed to Dr. Woodcock, who would like for this correspondence to be included as a written record in addition to his oral testimony at the January 22nd PCNS advisory committee. PCNS acknowledged receipt of the letter and have forward it to OL. Please advise if a formal response is required.

<< File: Letter for the Record to FDA re FDASIA and duchenne treatments FINAL 1.7.16.pdf >>

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: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 10:23 AM
To: DeMarco, Devota R
Subject: RM Patient Advocacy Group request for time during eteplirsen AC

From: Jenkins, John K
Sent: Sunday, January 10, 2016 2:21 PM
To: Diggs, Felicia; Woodcock, Janet
Cc: Unger, Ellis; Temple, Robert; Moscicki, Richard
Subject: RE: Patient Advocacy Group request for time during eteplirsen AC

No objection or comment from me.

From: Diggs, Felicia
Sent: Friday, January 08, 2016 2:29 PM
To: Woodcock, Janet
Cc: Unger, Ellis; Temple, Robert; Moscicki, Richard; Jenkins, John K
Subject: Patient Advocacy Group request for time during eteplirsen AC

Dear all,

The attached letter was addressed to Dr. Woodcock with a courtesy copy to you regarding the Jett Foundation (patient advocacy group) request for 10 minutes of Sarepta (sponsor of eteplirsen) agenda time during the January 22nd advisory committee. Please see the response attached that was cleared by Eric Basting and Jayne Peterson. If you have any objections to the document could you let me know by 4pm today if possible?

<< File: Doc - Jett Foundation12-28-15 3-48 PM (2).pdf >> << File: Jett_Foundation_Reply_PCNS_AC_Jan2016.pdf >>

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: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 4:37 PM
To: DeMarco, Devota R
Subject: RM

From: Unger, Ellis
Sent: Friday, January 08, 2016 2:34 PM
To: Diggs, Felicia
Cc: Temple, Robert; Moscicki, Richard; Jenkins, John K; Woodcock, Janet
Subject: RE: Patient Advocacy Group request for time during eteplirsen AC

No objections.

From: Diggs, Felicia
Sent: Friday, January 08, 2016 2:29 PM
To: Woodcock, Janet
Cc: Unger, Ellis; Temple, Robert; Moscicki, Richard; Jenkins, John K
Subject: Patient Advocacy Group request for time during eteplirsen AC

Dear all,

The attached letter was addressed to Dr. Woodcock with a courtesy copy to you regarding the Jett Foundation (patient advocacy group) request for 10 minutes of Sarepta (sponsor of eteplirsen) agenda time during the January 22nd advisory committee. Please see the response attached that was cleared by Eric Basting and Jayne Peterson. If you have any objections to the document could you let me know by 4pm today if possible?

<< File: Doc - Jett Foundation12-28-15 3-48 PM (2).pdf >> << File: Jett_Foundation_Reply_PCNS_AC_Jan2016.pdf >>

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: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 5:08 PM
To: DeMarco, Devota R
Subject: RM
Attachments: Doc - Jett Foundation12-28-15 3-48 PM (2).pdf; Jett_Foundation_Reply_PCNS_AC_Jan2016.pdf

-----Original Message-----

From: Diggs, Felicia
Sent: Friday, January 08, 2016 2:29 PM
To: Woodcock, Janet
Cc: Unger, Ellis; Temple, Robert; Moscicki, Richard; Jenkins, John K
Subject: Patient Advocacy Group request for time during eteplirsen AC

Dear all,

The attached letter was addressed to Dr. Woodcock with a courtesy copy to you regarding the Jett Foundation (patient advocacy group) request for 10 minutes of Sarepta (sponsor of eteplirsen) agenda time during the January 22nd advisory committee. Please see the response attached that was cleared by Eric Basting and Jayne Peterson. If you have any objections to the document could you let me know by 4pm today if possible?

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

December 27, 2015

Janet Woodcock, MD
Director of the Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Woodcock:

As you know, the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) of the U.S. Food and Drug Administration (FDA) will review Sarepta's New Drug Application (NDA) for eteplirsen, on January 22, 2016. On behalf of the Jett Foundation and the patients and families suffering from Duchenne muscular dystrophy, I am writing to request that you and the Division of Neurology Products consider the sponsor's intention to donate to Jett Foundation ten minutes of their presentation time during their PCNS advisory committee meeting. Jett Foundation has proposed to Sarepta that this time be used to present the Patient Reported Outcome (PRO) report previously presented to FDA on July 7, 2015.

I anticipate that Sarepta will negotiate between 60 to 90 minutes to present their phase IIb eteplirsen data. If Sarepta is granted the full 90 minutes from the review division to present their data, the company has agreed to yield 10 minutes to the Jett Foundation for presentation of this important PRO report.

As noted on the federal registry, FDA has graciously allowed the community a full two hours during the open public hearing (OPH) so patients and families with Duchenne can tell their stories. However, given the high profile of the drug and the disorder, the OPH will be filled quickly with testimony of far traveled, deserving, patients and families.

Additionally, this quantitative report was received positively by the division and prepared and developed specifically for this drug at the request of FDA. This report is consistent with the Duchenne DRAFT guidance (Food and Drug Administration, pg. 7) recently published by FDA, and assesses the meaningfulness of eteplirsen's clinical data by capturing the trial participants response to the drug in their activities of daily living.

The report includes specific, quantifiable data that was systematically collected through the input of patients and caregivers in the eteplirsen trials. It includes measurable and precise evidence that will provide the panel members with a more complete picture of the benefits – or lack thereof – of eteplirsen on the day-to-day lives of those with Duchenne. As you know, the "six-minute walk test" is currently the only validated clinical endpoint measured as part of the clinical trial. The PRO data goes beyond the limitations of the six-minute walk test to access the clinical meaningfulness of eteplirsen's study findings.

Further, as you know, Congress has repeatedly – in FDASIA, in pending legislation, and in hearings and testimony – urged FDA to take into account patient-generated information that may be important to benefit-risk considerations, and how input from patients and caregivers can contribute to drug development. The inclusion of Jett Foundation's PRO report during Sarepta's presentation lends an opportunity to FDA to demonstrate their commitment to patient focused drug development.

The Jett Foundation  *Fighting Duchenne Muscular Dystrophy*

I appreciate the time the review division dedicates to the process of reviewing a drug through an advisory panel committee meeting, and I understand, truly, that January 22nd 2016 will be a long day for everyone involved. However, I feel strongly that allowing the sponsor 90 minutes to present, ensuring that 10 minutes are donated to PRO's, will add to the scientific discussion among the panel members, and reaffirm the commitment FDA and industry have to giving prominence to the voice and the views of patients.

Thank you for your ongoing engagement with the Duchenne patient community. I look forward to a favorable response to this modest request.

Sincerely,



Christine McSherry
Executive Director
Jett Foundation
68 Evergreen Street, Suite One
Kingston, MA 02364

Cc: Robert Temple, M.D., Deputy Director for Clinical Science, CDER
Richard Moscicki, M.D., Deputy Director for Science Operations, CDER
John Jenkins, M.D., Director, Office of New Drugs, CDER
Ellis Unger, M.D., Director, Office of Drug Evaluation I, CDER
John Whyte, M.D., Director, Professional Affairs & Stakeholder Engagement, CDER

The Jett Foundation  Fighting Duchenne Muscular Dystrophy



January 08, 2016

Christine McSherry
Executive Director
Jett Foundation
68 Evergreen Street, Suite One
Kingston, MA 02364
Via: Electronic Mail
Christine@jettfoundation.org

Dear Ms. McSherry:

Thank you for your recent letter to Dr. Janet Woodcock on behalf of the Jett Foundation regarding Sarepta Inc.'s intention to donate 10 minutes of their presentation time during the January 22, 2016 Peripheral and Central Nervous System Drugs Advisory Committee meeting. Your letter was referred to me for a response.

FDA does not object to Sarepta giving the Jett Foundation 10 minutes of their presentation time to present the patient reported outcome report that was presented to FDA on July 7, 2015.

Thank you for contacting the FDA regarding this matter.

Sincerely,

**Felicia
Diggs -A**

Digitally signed by Felicia Diggs -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=CMS, ou=People, cn=Felicia Diggs -A,
0.9.2342.19200300.100.1.1=2001164960
Date: 2016.01.08 14:21:02 -0500

Felicia M. Diggs, RN, BSN, MSN
Consumer Safety Officer
Center for Drug Evaluation and Research

Cc: Robert Temple, MD
Richard Moscicki, MD
John Jenkins, MD
Ellis Unger, MD
John Whyte, MD

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Friday, July 14, 2017 10:23 AM
To: DeMarco, Devota R
Subject: RM: videos and data from the DMD mothers

From: Dunn, Billy
Sent: Tuesday, November 10, 2015 3:49 PM
To: Moscicki, Richard
Subject: RE: videos and data from the DMD mothers

Rich,

I don't remember such a pledge. I will check with the team and get back with you. My understanding is they are planning on presenting this during the public comment period at the AC. I suppose it might be reasonable to wait until the eteplirsen AC.

Billy

From: Moscicki, Richard
Sent: Tuesday, November 10, 2015 3:46 PM
To: Dunn, Billy
Subject: videos and data from the DMD mothers

Hi Billy, I know that there is a lot of stress at DNP right now but this is minor I hope. Christine McSherry from the Jett Foundation, an organizer of the video data on DMD kids on eteplirsen, approached me at a Patient Advocacy meeting to ask when they could publically release the data. She said that they had pledged not to until we told them they could as to not put pressure on the situation. She did indicate that they would like to show the data at the AC (I presume for eteplirsen). Janet thinks its ok to let them use the information publically but I thought I would check in with you and your team. Rich.

From: [Leptak, Christopher](#)
To: [Moscicki, Richard](#)
Subject: FW: Dystrophin LOI
Date: Thursday, May 14, 2015 9:47:47 AM
Attachments: [26170dfc1n2_ORP_OTs.doc](#)
[DDT-FDA-LOI-Aug2013-Submission.pdf](#)
[CHNMC Dystrophin LOI Letter 2.11.2014.pdf](#)
[DMD dystrophin quantification.doc](#)

Rich, per the email below, it sounds like PPMD's interest in qualification has not been shared with OTS and it is unclear if they are willing to/working with CHNMC. As part of your ongoing dialogue with PPMD, can you see if they are willing to submit an LOI and figure out what their relationship is with CHNMC (if any)?

From: Leptak, Christopher
Sent: Thursday, May 14, 2015 9:42 AM
To: Moscicki, Richard; Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: Dystrophin LOI

Rich, John, Billy, and Eric,

In follow-up to Monday's dystrophin discussion, below is a summary of key points as well as some additional information for continued discussion/consideration:

- * Dystrophin Workshop follow-up: Once cleared by FDA and NIH, a Workshop Summary will be posted to the workshop's webpage. In addition, there was discussion of a White Paper (or equivalent) which would outline specific recommendations/considerations RE dystrophin detection methodologies.
- * DMD Indication-specific Guidance: The draft guidance (attached) is nearing final version and is planned to be cleared/published in the near future. Prior to publication, a meeting with PPMD will take place as a planned outreach effort.
- * DMD NDAs: Review of data in progress. Dystrophin will likely contribute to the "totality of evidence" evaluation, although the type of dystrophin information collected and the approach to analysis differs between the trials/companies.
- * Letters of Intent (LOSs) and dystrophin qualification: As background, CHNMC approached BQP last year RE qualification of dystrophin as a surrogate (LOI attached below). Based on input from OND/OTS, the decision was made not to move forward for reasons stated in the attached letter. Of note, the team met internally and produced advice (also attached) but that advice was not shared in its entirety with CHNMC since the project did not move forward.

Presently, there are two groups (CHNMC and PPMD) that have recently expressed interest in dystrophin qualification; to our knowledge, the two groups are not working together in this goal. I checked with OTS and only Children's has been in communication with OTS and neither have formally submitted an LOI. For CHNMC, OTS shared that they have backed off of their initial "surrogacy or nothing" stance and are now considering a step-wise approach (one option put forward is considering qualification of dystrophin as a nonclinical PD biomarker for POC).

I recommended and OTS agreed that the groups should formally submit a LOI so that we see what is being proposed for COU, giving us specifics rather than guessing at what appears to be a moving target. As we discussed on Monday and once the LOSs are in house, we could set up meetings (or meeting if the two groups are in fact willing or are working together) to have further discussions (if needed) with the outside groups including options (LOS, qualification, other?). That will keep us engaged (optics) while still not committing us to a given path without specific information upon which to make decisions.

Sound like a plan?

Best,
Chris

Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Colleen Locicero 301-796-1114.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

(b) (5)

Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry

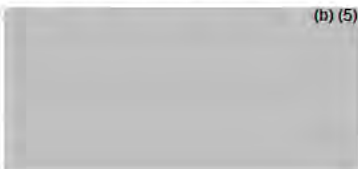
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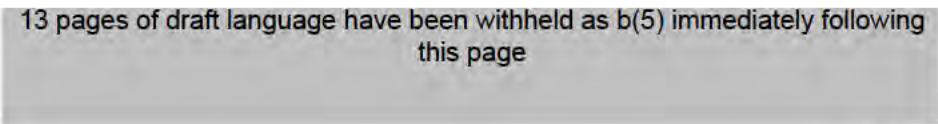
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Center for Drug Evaluation and Research (CDER)**

(b) (5)



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



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Cover Letter Accompanying Biomarker Qualification Submissions

Date: August 16, 2013

Subject: DRUG DEVELOPMENT TOOL (DDT) QUALIFICATION SUBMISSION

DDT Type: BIOMARKER

DDT Tracking Record Number: (none)

Submission Type: LETTER OF INTENT

DDT Name(s): DYSTROPHIN PROTEIN

Context of Use: Accurate quantification of dystrophin protein in skeletal muscle biopsies to be qualified as a surrogate endpoint in phase II and III clinical trials aiming to restore full length or truncated dystrophin protein in Duchenne Muscular Dystrophy patients.

Complete submitters contact information:

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kristy.brown@childrensnational.org

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Biomarker Qualification Letter of Intent

Description of Submitters (Principal Investigators):

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A. Introduction

Restoration of missing dystrophin protein in Duchenne muscular dystrophy (DMD) patients is perhaps one of the most promising therapeutic strategies that exists today for this devastating muscle disease. Potential therapies aiming to restore either full-length or Becker-like truncated dystrophin are currently entering phase II and III clinical trials with many more in the pipeline. These include mutation specific exon skipping with antisense oligonucleotide [1, 2], stop codon read-through [3], gene therapy [4] and stem cell therapy [5]. Unfortunately, these trials are hampered by a lack of a robust surrogate endpoint

to determine efficacy. The most widely used clinical endpoint in DMD clinical trials is the 6 minute walk test [6]. However, significant changes in walking speed may take a year or more to develop, and there is significant test to test variation. Thus, relying on functional outcome measures such as the 6 minute walk require a large cohort for adequate statistical powering, as well as an increased length of trial and also additional costs for conducting trials. This is a particularly significant barrier to phase II trials where a more rapid read-out showing a proof-of-principle of the therapeutic approach is desired. A biomarker surrogate endpoint would enable faster trials that are compatible with the small patient sets as well as minimize costs. The ideal surrogate endpoint to monitor restoration of dystrophin protein is dystrophin protein itself since it is directly linked to the pathophysiology of the disease. Dystrophin represents only 0.002% of total striated muscle protein making it challenging to measure in muscle tissue. Current methods using immunohistochemistry and western-blotting have proven laborious and often inconsistent from run to run. We have recently developed an unbiased mass spectrometry method to accurately and simultaneously quantify dystrophin protein and several other muscle proteins in a muscle biopsy (Brown et al., 2013) [7]. The method was found reproducible and linear over wide dynamic range, detecting and quantifying as low as 5% of the normal levels of dystrophin found in healthy skeletal muscle.

B. Proposed context of use

The goal of this LOI is to qualify quantitative levels of dystrophin protein as a surrogate endpoint to determine response to therapy for use in clinical trials aiming to restore full length or truncated Becker-like dystrophin in Duchenne muscular dystrophy patients. A surrogate endpoint for these trials will speed analysis, reduce costs and aid FDA evaluation of these potential therapies. Restoration of dystrophin protein to accurately detectable levels (approximately 10% of normal) is indicative of an improved clinical outcome. The method can be also extended to measure the levels of dystrophin and other muscle proteins deemed to be therapeutically valuable in other muscular dystrophies such as Becker muscular dystrophy and congenital muscular dystrophies.

C. High-level data description

The correlation between the amount of dystrophin protein and improved clinical outcome is well known based on the improved clinical presentation of BMD patients compared to DMD patients [8, 9]. The presence of truncated dystrophin in BMD patients at levels approximately equal to or greater than 10% of the levels found in healthy individuals greatly improves their clinical phenotype and quality of life [7, 8, 10, 11]. Additionally, multiple animal studies of dystrophin restoration in mouse and dog models of DMD show profound clinical responses upon restoration of dystrophin [12-16].

Therefore, measuring the amount of restored dystrophin is an ideal surrogate endpoint to monitor efficacy. Dystrophin is a low abundant protein, accounting for approximately 0.002% of the total striated muscle protein [17] and traditional methods for dystrophin quantitation such as western blots and immunohistochemistry are notoriously difficult and inconsistent [18, 19]. Alternatively, mRNA quantitation is often used to evaluate the levels of exon skipped products [20]. But, mRNA expression does not always correlate with protein levels [21] and amplification saturation can be problematic. Finally, both antibody based assays and mRNA approaches as surrogate biomarkers suffer from limited reliability and sensitivity.

Recently, our lab developed an alternative approach to quantitate dystrophin protein using a targeted mass spectrometry in combination with stable isotope spike-in strategy [7]. Protein extract from human muscle biopsy tissue is spiked with $^{13}\text{C}_6$ -Lys fully labeled mouse muscle extracts. Spiked samples are further fractionated by SDS-PAGE and the dystrophin band including other muscle proteins are digested with trypsin. Human muscle proteins, including dystrophin, are quantitated through mass spectrometry signal comparison of the isotopically heavy labeled mouse peptides that share 100%

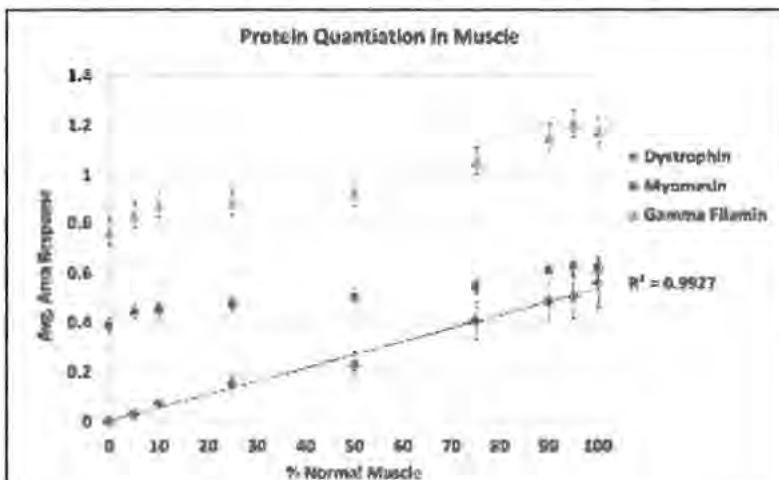


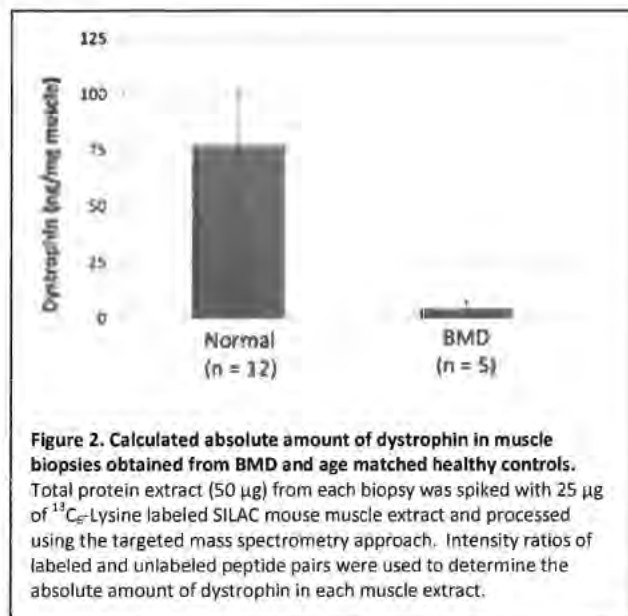
Figure 1. Titration curve of dystrophin protein and other muscle specific proteins using targeted MS approach with SILAC mouse spike-in. Dystrophin protein, as well as myomesin and filamin c, were quantitated in different combination mixtures of muscle extracts from DMD and age matched healthy donors at ratios leading to 0, 5, 10, 25, 50, 75, 90, 95 and 100% of dystrophin relative to normal. Each final mixture contained 50 μg of total muscle protein and was spiked with 25 μg of $^{13}\text{C}_6$ -Lysine labeled SILAC mouse muscle extract. Transition ion intensities obtained at the MS/MS level for the targeted labeled and unlabeled peptide pairs generated from the spike-in standard and endogenous human dystrophin were used to determine the relative amount of dystrophin and other muscle proteins (myomesin and filamin c). Standard deviation at each data point represents average ratios obtained from labeled and unlabeled peptide pairs: 5 pairs for dystrophin protein (QAPIGGDFPAVQK, VLSQIDVAQK, IFLTEQPLEGLEK, TLNATGEEIIQQSSK, VHALNNVNK); 3 pairs for filamin c (SPFVVNVAPPLDLSK, EVGEHVVSVRK, HIGISFTPK) and two pairs for myomesin (VSEPVAALDPAEK, VLGGLPDWTIQEGK). These peptides have 100% sequence homology between human and mouse and were used for ratio measurements. As expected, dystrophin protein increased with increasing relative amount of normal muscle extract while myomesin and filamin c remained unchanged.

sequence homology with the human counterpart peptide.

Muscle biopsies, from normal or from patients with dystrophinopathies, are very heterogeneous containing varying proportions of myofibers, connective tissue (fibrosis) and adipose tissue (fatty replacement). Depending on the biopsy location and disease state, the proportion of myofibers (cell type expressing dystrophin) can vary significantly. Therefore, this targeted mass spectrometry technique can simultaneously quantitate dystrophin as well as other myofiber-specific proteins for use as internal controls enabling normalization to correct for muscle tissue heterogeneity thus providing precise and specific quantitation of dystrophin protein associated with muscle (Figure 1) [7].

The limit of detection (LOD) and limit of quantification (LOQ) was better than 10% (e.g. as low as 5%) of the normal amount of dystrophin, making the assay sensitive enough to measure dystrophin in clinical specimens (Figure 1) [7]. The targeted mass spectrometry assay routinely measures dystrophin content in 50 µg total muscle protein extract from roughly 0.5 mg of frozen biopsy. This amount of muscle is readily available from diagnostic needle biopsies, which are in the range of 20 mg [22], and much less invasive than open biopsies.

As shown in Figure 2, the absolute amount of dystrophin in normal muscle (n=12) as determined using the targeted mass spectrometry assay was approximately 0.001 to 0.004% of total striated muscle (75 ± 15 ng per mg of muscle), consistent with previous findings [7, 17]. BMD muscle biopsies (n = 5) showed a wide range of dystrophin expression at approximately 10% of the level found in normal muscle (0 to 7 ng per mg of muscle), Figure 2 [7]. Other studies have shown dystrophin levels in BMD patients to range from 7-71% as determined by western blot [8].



The ability to accurately and routinely quantitate dystrophin levels and muscle biopsy tissue is now possible using the targeted mass spectrometry approach. This will enable the use of dystrophin protein levels to monitor response to therapy. DMD patients lack dystrophin protein and even partial restoration is expected to improve clinical outcome. Additionally, current trials are limited to ambulatory participants due to relying on the 6 minute walk. Using dystrophin as the surrogate endpoint would make trials more inclusive.

In conclusion, quantification of dystrophin is the ideal surrogate biomarker to monitor the efficacy or failure of therapies aiming to restore its expression in DMD patients. This surrogate is clinically meaningful and will aid the development of multiple therapeutic approaches. This technique is more specific and accurate than current assays.

D. Additional resources that support the context of use as well as data the submitter plans to obtain from ongoing or future studies.

Our lab continues to evaluate the targeted mass spectrometry assay for quantitation of dystrophin. We currently plan to apply this assay to quantitate dystrophin tissues in pre-clinical studies performed on mouse and dog models of DMD. We plan to offer this service to assist current and future clinical trials.

We are currently submitting a funding application to the MDA to cover costs associated with these studies.

In the Fall of 2013 an international symposium will be held to discuss possible community consensus of biomarkers for DMD response to therapies.

E. Indicate if there are plans to submit the biomarker for qualification by other international regulatory agencies

None at this time.

F. Process-related questions for FDA

None at this time.

G. References:

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From: [Bernstein, Jessica](#)
To: [Salerno, Mary Jo](#)
Cc: [JW Direct Reports & Deputies](#); [CDER-EOS](#); [Behr, Virginia L](#); [Peterson, Jayne E](#); [MedWatch Safety Alerts](#); [Drug Safety Web](#); [Meister, Karen G](#); [Walsh, Sandy](#); [Sherwood, Edward M](#); [Thomas, Kimberly K \(ORP\)](#); [Helmanis, Lisa M](#); [Sullivan, Diane](#); [Stowe, Ginneh D.](#); [Baumgartner, Kristofer](#); [OPO Policy](#); [CDER-OPO-Inquiries](#); [Choi, Moon Hee](#); [Ngo, Diem-Kieu \(CDR,USPHS\)](#); [Farkas, Ronald](#); [Bastings, Eric](#); [Choy, Fannie \(Yuet\)](#); [Dunn, Billy](#); [Ware, Jacqueline H](#); [Unger, Ellis](#); [Locicero, Colleen L](#); [Vail, Victor H](#); [Peddicord, Sarah](#)
Subject: Information Advisory: FDA to Announce a Meeting of Peripheral and Central Nervous Systems Drugs Advisory Committee to Discuss Eteplirsen to Treat Duchenne Muscular Dystrophy
Date: Friday, November 20, 2015 12:13:51 PM
Attachments: [IA Public Mtg PCNS AC Eteplirsen cleared DNP ODE-I DEO OEP ToFDAES 112015.doc](#)

Good Afternoon Mary Jo,

In November or December 2015, FDA will announce a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. The Committee will meet on January 22, 2016 to discuss a new drug application for eteplirsen injection for treatment of Duchenne muscular dystrophy (DMD) in patients who have a specific mutation of the DMD gene. FDA expects the meeting announcement will be of interest to patients with DMD and their families, advocacy groups, industry, health care professionals (including neurologists and therapists working with people with DMD), researchers, and those working in regulatory science. FDA will not issue a press release. FDA will include the meeting information in the weekly tip sheet that is sent to all reporters who are on the FDA media list.

*****PLEASE NOTE THAT THIS INFORMATION IS NOT RELEASABLE TO THE PUBLIC UNTIL ACTION TAKES PLACE*****

Regards,

Jessica

Jessica Bernstein, MPH

Writer-Editor

Division of Executive Operations

Office of Executive Programs

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U.S. Food and Drug Administration

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From: [Gross, Mary](#)
To: [Ienzi, Georgiann](#); [Kaiser, James](#); [Borges, Silvana](#); [Leptak, Christopher](#)
Cc: [Rao, Ashutosh](#); [Moscicki, Richard](#); [Nuckolls, Glen H \(NIH\)](#); [Farkas, Ronald](#)
Subject: Dystrophin Meeting - Instructions for Tomorrow
Date: Thursday, March 19, 2015 4:44:40 PM

Hi – the slides are preloaded and the room is ready; we are in 1503 B and C. The slide presentations are numbered and will need to be pulled up according to number; the speakers can advance them from there, except for Glenn Morris who will need the slides advanced. Other duties include helping speakers register and be seated, passing out and collecting note cards with questions and I'll manage the timer clock. Chris will manage the webcast questions and will triage the questions collected from the audience. I'll bring the agenda, speaker sign in sheet, name tags and tent cards with me. I plan on getting here by 7 am.

Thanks so much to the volunteers who are helping to keep this running smoothly. Looking forward to seeing everyone by 7:45 am. Thanks again.

Mary

From: [Gross, Mary](#)
To: [Rao, Ashutosh](#)
Cc: [Moscicki, Richard](#)
Subject: RE: dystrophin wkshp.ppt
Date: Thursday, March 19, 2015 2:53:04 PM

Thank you.

From: Rao, Ashutosh
Sent: Thursday, March 19, 2015 2:29 PM
To: Gross, Mary
Cc: Moscicki, Richard
Subject: RE: dystrophin wkshp.ppt

Hi Mary and Rich,
Please see attached slides. Rich, I used the newer version to make changes.
Thanks
Ash

From: Gross, Mary
Sent: Thursday, March 19, 2015 1:56 PM
To: Rao, Ashutosh
Cc: Moscicki, Richard
Subject: FW: dystrophin wkshp.ppt
Importance: High

Ash – please see Rich’s note about slides and please make the changes you suggested and send back to me, cc Rich too. Thanks.

Mary

From: Moscicki, Richard
Sent: Thursday, March 19, 2015 1:55 PM
To: Gross, Mary
Subject: RE: dystrophin wkshp.ppt

Yes Ash can finish them. just send me final copy, Did Ash see my second set as I sent him an earlier version. Rich.

From: Gross, Mary
Sent: Thursday, March 19, 2015 12:05 PM
To: Moscicki, Richard
Subject: RE: dystrophin wkshp.ppt

Can Ash fix them for you? Loading all presentations up this afternoon. Thanks.

From: Moscicki, Richard
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Subject: Re: dystrophin wkshp.ppt

Just saw it so no slides aren't final, but not sure when.

From: Gross, Mary
Sent: Thursday, March 19, 2015 11:59 AM
To: Moscicki, Richard
Subject: RE: dystrophin wkshp.ppt

Ash said he sent you comments this morning (an hour ago). Did you get them?

From: Moscicki, Richard
Sent: Thursday, March 19, 2015 11:59 AM
To: Gross, Mary
Subject: Re: dystrophin wkshp.ppt

yes.

From: Gross, Mary
Sent: Thursday, March 19, 2015 11:52 AM
To: Moscicki, Richard
Subject: FW: dystrophin wkshp.ppt

Are your slides final? Thanks.

Mary

From: Moscicki, Richard
Sent: Wednesday, March 18, 2015 9:48 PM
To: Gross, Mary; Rao, Ashutosh
Subject: dystrophin wkshp.ppt

Here are my slides

From: Rao, Ashutosh
To: Unger, Ellis; Gross, Mary; Leptak, Christopher; Ienzi, Georgianni; Farkas, Ronald; Nuckolls, Glen H (NIH); Moscicki, Richard
Subject: RE: Washington Weather Alert - Dystrophin Meeting.
Date: Thursday, March 19, 2015 2:52:34 PM

Sounds good.

Unless the weather predictions are wildly off-base, we shouldn't have much trouble getting in as originally planned.

From: Unger, Ellis
Sent: Thursday, March 19, 2015 2:48 PM
To: Rao, Ashutosh; Gross, Mary; Leptak, Christopher; Ienzi, Georgianni; Farkas, Ronald; Nuckolls, Glen H (NIH); Moscicki, Richard
Subject: RE: Washington Weather Alert - Dystrophin Meeting.

If there's a 2-hour delay, I'd think we'd start with opening remarks at 10:30. And if we lose 2 of our 9 hours, we should shorten everything by 22%. So...

15 minutes → 12 minutes.

10 → 8

40 → 35

Etc.

From: Rao, Ashutosh
Sent: Thursday, March 19, 2015 2:42 PM
To: Gross, Mary; Leptak, Christopher; Ienzi, Georgianni; Farkas, Ronald; Nuckolls, Glen H (NIH); Moscicki, Richard; Unger, Ellis
Subject: FW: Washington Weather Alert - Dystrophin Meeting.

What is our policy on public meetings if government opening is delayed? Although not very likely, if we do open late, how should we "delay" the workshop?

Would be good to have a plan in mind, in case we need to make a last-minute call.

From: Gross, Mary
Sent: Thursday, March 19, 2015 10:39 AM
To: Louise.Rodino-Klapac@nationwidechildrens.org; Austin, Christopher P (NIH); 'jervasti@umn.edu'; 'jsc5@uw.edu'; 'David.Rimm@Yale.edu'; (b) (6) 'c.beekman@prosensa.nl'; 'zarife.sahenk@nationwidechildrens.org'; 'ehoffman@childrensnational.org'; 'isweeney@mail.med.upenn.edu'; John Porter; 'Rabi_Tawil@urmc.rochester.edu'; Rao, Ashutosh; Moscicki, Richard; Unger, Ellis; 'wagnerk@kennedykrieger.org'; 'psazani@sarepta.com'; Hathout, Yetrib; Sebahattin Cirak; Babiak, John; Flanigan, Kevin; Sardone, Valentina; Pat Furlong; Farkas, Ronald; Nuckolls, Glen H (NIH); Leptak, Christopher; Polovoy, Alyssa
Cc: Ienzi, Georgianni; Kaiser, James; Borges, Silvana; Quartey, Elizabeth O (NIH); Reid, Kelli W (NIH); Gibson, Jackie J (NIH)
Subject: Washington Weather Alert - Dystrophin Meeting.

Dear Speakers – the possibility of inclement weather has been forecast for Washington DC and surrounding suburbs beginning early morning on March 20. If the government announces a delayed opening (2 hours for example), the meeting time will also be delayed that amount of time. If the government opens on time, the meeting will begin on time. For the latest information on government closings or delays, please check the opm.gov website early tomorrow morning. I've asked the meeting page to be updated with this information as well. I'm including driving and parking directions for you. Parking can be challenging on campus so if you plan to drive and park, I suggest you get here early.

Thanks.

Mary

<http://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241748.htm>

From: [Leptak, Christopher](#)
To: [Rao, Ashutosh](#); [Gross, Mary](#); [Ienzi, Georgiann](#); [Farkas, Ronald](#); [Nuckolls, Glen H \(NIH\)](#); [Moscicki, Richard](#); [Unger, Ellis](#)
Subject: Re: Washington Weather Alert - Dystrophin Meeting.
Date: Thursday, March 19, 2015 2:47:03 PM

Don't know about a policy per se. If we are on a delayed start, tough for us to extend beyond 5:30 given planned travel arrangements. Also tough to reduce speaking times even further. My vote would be to start as scheduled at 8:30.

Chris

From: Rao, Ashutosh
Sent: Thursday, March 19, 2015 02:41 PM
To: Gross, Mary; Leptak, Christopher; Ienzi, Georgiann; Farkas, Ronald; Nuckolls, Glen H (NIH); Moscicki, Richard; Unger, Ellis
Subject: FW: Washington Weather Alert - Dystrophin Meeting.

What is our policy on public meetings if government opening is delayed? Although not very likely, if we do open late, how should we "delay" the workshop?

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To: Louise.Rodino-Klapac@nationwidechildrens.org; [Austin, Christopher P \(NIH\)](mailto:Austin, Christopher P (NIH)); jervasti@umn.edu; jsc5@uw.edu; David.Rimm@Yale.edu; c.beekman@prosensa.nl; zarife.sahenk@nationwidechildrens.org; ehoffman@childrensnational.org; isweeney@mail.med.upenn.edu; John Porter; Rabi_Tawil@urmc.rochester.edu; Rao, Ashutosh; Moscicki, Richard; Unger, Ellis; wagnerk@kennedykrieger.org; psazani@sarepta.com; Hathout, Yetrib; Sebahattin Cirak; Babiak, John; Flanigan, Kevin; Sardone, Valentina; Pat Furlong; Farkas, Ronald; Nuckolls, Glen H (NIH); Leptak, Christopher; Polovoy, Alyssa
Cc: Ienzi, Georgiann; Kaiser, James; Borges, Silvana; Quartey, Elizabeth O (NIH); Reid, Kelli W (NIH); Gibson, Jackie J (NIH)
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From: [Rao, Ashutosh](#)
To: [Gross, Mary](#)
Cc: [Moscicki, Richard](#)
Subject: RE: dystrophin wkshp.ppt
Date: Thursday, March 19, 2015 2:28:44 PM
Attachments: [Moscicki dystrophin wkshp.ppt](#)

Hi Mary and Rich,
Please see attached slides. Rich, I used the newer version to make changes.
Thanks
Ash

From: Gross, Mary
Sent: Thursday, March 19, 2015 1:56 PM
To: Rao, Ashutosh
Cc: Moscicki, Richard
Subject: FW: dystrophin wkshp.ppt
Importance: High

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Here are my slides



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

www.fda.gov

Welcome remarks: FDA-NIH workshop on Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data

Richard Moscicki, M.D.
Deputy Center Director for Science Operations
CDER/FDA

March 20th 2015.
Dystrophin Methodology Workshop
[Co-chairs: Glen Nuckolls (NINDS/NIH) and Ashutosh Rao (CDER/FDA)]



Outline of presentation

- The scientific importance and need for reliable measurement of dystrophin protein
- Goals of the workshop
- Ground Rules



Importance of dystrophin protein measurement and need for reliable measurement



Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 24 (2014) 463–466



www.elsevier.com/locate/nmd

Personal Comment

Dystrophin as a therapeutic biomarker: Are we ignoring data from the past?

Steve D. Wilton^{a,*}, Sue Fletcher^a, Kevin M. Flanigan^b

^a Western Australian Neuroscience Research Institute and Centre for Comparative Genomics, Murdoch University, Murdoch, Western Australia, Australia

^b Center for Gene Therapy, The Research Institute, Nationwide Children's Hospital, Columbus, OH, USA

Received 12 January 2014; received in revised form 11 March 2014; accepted 13 March 2014



United Parent Projects
Muscular Dystrophy

Biomarkers and surrogate endpoints in Duchenne

There is a lot of discussion ongoing in the DMD community about biomarkers and surrogate endpoints as was pointed out by Patient representatives during an ENMC meeting on biomarkers for DMD (Jan 24-26 2014, Naarden, the Netherlands). On their request this document will explain what biomarkers are and will address questions about biomarkers and surrogate endpoints.

Cluster: Molecular Therapy—Nucleic Acids (2014) 3, e152; doi:10.1038/mtna.2014.6
© 2014 The American Society of Gene & Cell Therapy. All rights reserved 2152-9531/14
www.nature.com/mtna

COMMENTARY

What Can We Learn From Clinical Trials of Exon Skipping for DMD?

Qi-long Lu¹, Sebahattin Cirok² and Terence Partridge²

Molecular Therapy—Nucleic Acids (2014) 3, e152; doi:10.1038/mtna.2014.6; published online 11 March 2014



Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 25 (2015) 5–13



www.elsevier.com/locate/nmd

Special report

European Medicines Agency review of ataluren for the treatment of ambulant patients aged 5 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene

Manuel Haas^{a,*}, Viktor Vlcek^a, Pavel Balabanov^a, Tomas Salmonson^b, Serge Bakchine^c, Greg Markey^d, Martina Weise^e, Gabriele Schlosser-Weber^c, Henning Brohmann^c, Concepcion Prieto Yerro^f, Macarena Rodriguez Mendizabal^f, Violeta Stoyanova-Beninska^g, Hans L. Hillege^g

^a European Medicines Agency, London, United Kingdom

^b Läkemedelsverket, Medical Products Agency, Uppsala, Sweden

^c Hôpital Motron Blanche, CHU de Reims, Reims, France

^d Medicines and Healthcare Products Regulatory Agency, London, United Kingdom

^e Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany

^f Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain

^g Medicines Evaluation Board, Leidsch, The Netherlands

Received 15 September 2014; received in revised form 17 November 2014; accepted 18 November 2014



Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data:

- **Goals of the workshop:** Recent advances in drug development for Duchenne Muscular Dystrophy (DMD) present an opportunity for the development and validation of robust methods for the objective, reliable, and quantitative measurement of dystrophin and related muscle proteins. This workshop, cosponsored by the Food and Drug Administration and the National Institutes of Health was convened in order to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development.



Science and Quantitation

- To be truly useful in drug development, methodologies must be trusted
 - Robust /Reproducible
- Operating characteristics in the context of use must be understood
- Today we hope to survey the state of the art of the best methods for quantification of dystrophin and potential paths forward towards assay and drug development
- Scientific methodology
 - Not regulatory or surrogacy or endpoints
 - Not clinical meaningfulness
 - Not about one company vs another or one product vs another



Ground Rules: Do's

1. Focus on an open scientific discussion to foster reliable applications of current dystrophin methodologies
2. Expect highly-technical presentations from scientists directly performing or experts who lead other scientists directly performing dystrophin measurement
3. Disclose conflicts of interest
4. Share your own scientific experience regarding challenges and opportunities
5. Share technical details, such as antibody specificity, range of detection, variability, full-length gels, controls, etc
6. Reference appropriate scientific articles
7. Provide lessons learned
8. **Stay within the allotted time slot**



Ground Rules: Questions

- 8 Ask technical questions to the speakers about the science
9. Hold questions for the speakers for the open Q&A time at the end of each session
10. If possible, use the note cards in the back of the room to post questions to the speakers
11. Keep the questions brief and within the technical scope of this workshop



All Together

16. Listen for potential opportunities to collaborate and contribute
17. Identify opportunities that might require a consortia or group effort
18. Critique scientific concepts, not people/drugs/sponsors/organizations
19. Be respectful and constructive with your participation



Don't

1. Discuss or compare specific drugs, applications, Sponsors, or regulatory pathway
2. Expect a regulatory discussion of biomarkers, surrogate endpoints, or clinical meaningfulness



An Ideal Outcome

- Sharing in an open forum of information without self interest and defensiveness
- Identification of best practices
- Consensus on optimal current approaches to dystrophin measurement available today
- What can yet be done to make it better tomorrow



Thank you

- Scientific co-chairs [Ashutosh Rao (CDER/FDA) and Glen Nuckolls (NINDS/NIH)]
- Food and Drug Administration - Christopher Leptak (Office of New Drugs/CDER/FDA), Mary Gross, Georgiann Ienzi (Office of Executive Programs, CDER/FDA), Ronald Farkas, William Dunn, and Eric Bastings (Division of Neurology Products, CDER/FDA), Ellis Unger (ODE1/OND/CDER/FDA), Jim Kaiser (OTS/CDER/FDA), Hobart Rogers (Office of Clinical Pharmacology, OTS/CDER/FDA)]
- National Institutes of Health - Amanda Boyce (NIAMS/NIH), Petra Kaufmann (NCATS/NIH)]
- Supporters of the FDA-NIH interagency agreement and workshop (Janet Woodcock (CDER/FDA), Chris Austin and Pamela McInnes (NCATS/NIH), Walter Koroshetz (NINDS/NIH), Robert Carter (NIAMS/NIH))
- Sponsors of DMD therapies
- Parent Project Muscular Dystrophy (PPMD)
- DMD patients, families, and advocates

From: [Leptak, Christopher](#)
To: [Unger, Ellis](#); [Moscicki, Richard](#); [Temple, Robert](#); [Dunn, Billy](#); [Bastings, Eric](#); [Farkas, Ronald](#); [Rao, Ashutosh](#); [Kaiser, James](#); [Rogers, Hobart](#)
Cc: [Gross, Mary](#)
Subject: Re: March 20 Dystrophin Scientific Workshop Planning Meeting
Date: Thursday, March 19, 2015 11:24:36 AM

Ellis, most helpful. Consider less focus on the speaker (name and presentation title slide) and perhaps group by method (summary points for IHC etc)

Chris

From: Unger, Ellis
Sent: Thursday, March 19, 2015 10:58 AM
To: Moscicki, Richard; Temple, Robert; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh; Kaiser, James; Rogers, Hobart; Leptak, Christopher
Cc: Gross, Mary
Subject: RE: March 20 Dystrophin Scientific Workshop Planning Meeting

All,

I took some time last night and went through the first 8 talks, trying to glean the main points. Could you take a quick look at these (i.e., 2 minutes) and let me know if you think this approach will be helpful for the wrap-up? In part, I want to make sure I cover everything and stay on track. Obviously, I'll revise these slides during the presentations to better reflect what people actually say, and also try to summarize the panel discussions.

Ellis

<<Unger_Wrap-up.ppt>> -----Original Appointment-----

From: Gross, Mary
Sent: Tuesday, March 03, 2015 9:20 AM
To: Gross, Mary; Moscicki, Richard; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh; Kaiser, James; Rogers, Hobart; Leptak, Christopher; Ienzi, Georgiann; CDER WO 1315 conf rm Bldg22 - AR
Subject: March 20 Dystrophin Scientific Workshop Planning Meeting
When: Wednesday, March 18, 2015 3:00 PM-4:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: CDER WO 1315 conf rm Bldg22 - AR ; TCON 877 704 7717; PC (b) (4)

<< File: Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx >> << File: Registrant List.doc >> << File: Speaker Lis1.doc >>

From: Rao, Ashutosh
To: Moscicki, Richard
Subject: RE: dystrophin wkshp.ppt
Date: Thursday, March 19, 2015 9:56:53 AM

Hi Rich,

I thought the slides looked good overall. Here are some suggested minor modifications.

1. Title slide: I would change the title to "Welcome remarks: FDA-NIH workshop on **Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data**" or something like that.
2. Slide #2: Importance of dystrophin protein measurement- It's okay with me if you also want to show this. I'll move over this slide quickly during my presentation if you have introduced it. I'd still like to have it in my presentation because I will be referencing data from these papers in subsequent slides.
3. Slide #5: I would modify "Today we hope to survey the state of the art of the best methods for quantitation of dystrophin" to "Today we hope to survey the state.....quantitation of dystrophin and potential paths forward towards drug development" I thought adding the phrase "path forward" might make it a bit forward-looking in addition to wanting to openly discuss the current state of methods.
4. Slide #10: I would suggest modifying "dystrophin" to "dystrophin measurement" so it doesn't suggest that we want a consensus on *whether* dystrophin is an appropriate endpoint.
5. It would be good if at the end you could say a quick thanks to NIH for co-sponsoring, PPMD for helping to moderate, the speakers, participants, and patients. I would tailor this depending on who is in the audience that morning.

Best,
Ash

From: Moscicki, Richard
Sent: Wednesday, March 18, 2015 9:49 PM
To: Rao, Ashutosh
Subject: dystrophin wkshp.ppt

Hi Ash I was waiting for your call. I had some thoughts but wanted to foremost discuss my using some of your slides in my intro as attached and giving you more time to get into the actual technical concerns. Honestly let me know what you think. Rich.

From: [Gross, Mary](#)
To: [Nuckolls, Glen H \(NIH\)](#)
Cc: [Rao, Ashutosh](#); [Moscicki, Richard](#); [Leptak, Christopher](#); [Farkas, Ronald](#)
Subject: Dystrophin Meeting Planning
Date: Thursday, March 19, 2015 9:09:21 AM

Hi Glen – The travel was split up among the two federal agencies – Georgi arranged for a shuttle to take the FDA travelers to the meeting and I suggested the same thing be done from NIH. But I don't know where your travelers are staying or what arrangements have been made to get them to the meeting. Also, the weather may get a little dicey overnight, so we need to keep an eye out for a delayed opening. If there is one, the meeting will also be delayed 2 hours. I will be posting something on the website and alerting speakers to the possibility later today.

Mary

PS – Ash – I need your slides this morning. Thanks.

Mary

From: Nuckolls, Glen (NIH/NINDS) [E] [<mailto:nuckollg@ninds.nih.gov>]
Sent: Thursday, March 19, 2015 9:03 AM
To: Gross, Mary
Subject: shuttle from hotel

Mary,
Is there a shuttle from the Hotel to the meeting? What time will it leave the hotel? Thanks

Glen

From: [Rao, Ashutosh](#)
To: [Moscicki, Richard](#)
Subject: Fw: Draft dystrophin workshop slides
Date: Wednesday, March 18, 2015 3:20:49 PM
Attachments: [DRAFT_DW_2015_AR.ppt](#)

From: Rao, Ashutosh
Sent: Wednesday, March 11, 2015 01:48 PM
To: Moscicki, Richard; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Kaiser, James; Rogers, Hobart; Leptak, Christopher
Subject: Draft dystrophin workshop slides

Hi all,

Please find attached my draft slides for the dystrophin workshop on the 20th. Please provide your input to me by next Tuesday the 17th.

Talking points or detailed scripts for what I could say for each slide are included in the notes section of each slide. There is a lot more to say on each topic but I've tried my best to prioritize relevant points from previous discussions that can be delivered in 15 minutes and keeping in mind the diversity of this audience. You can send comments and suggested talking points by email or we can set up time to talk, whichever works best for you. I will try to give this group a practice talk on the 18th during the last planning meeting after incorporating feedback.

Thanks very much.

Ash



Background and workshop objectives related to analytical challenges and opportunities with dystrophin methodologies

Ashutosh Rao, Ph.D.
Office of Biotechnology Products
CDER/FDA

March 20th 2015.

Dystrophin Methodology Workshop

[Co-chairs: Glen Nuckolls (NINDS/NIH) and Ashutosh Rao (CDER/FDA)]

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

DRAFT VERSION – Do not share

From: [Gross, Mary](#)
To: [Moscicki, Richard](#); [Nuckolls, Glen H \(NIH\)](#); [Farkas, Ronald](#); [Leptak, Christopher](#)
Cc: [Rao, Ashutosh](#)
Subject: FW: Final call for Dystrophin agenda comments - due by 4:00 pm today
Date: Tuesday, March 17, 2015 2:57:00 PM
Attachments: [Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx](#)
Importance: High

May I have comments on Dystrophin Agenda by 4:00 pm this afternoon? I plan to finalize this afternoon and send on to be posted. Ash has provided comments. Thanks.

Mary

From: Gross, Mary
Sent: Monday, March 16, 2015 6:01 PM
To: Moscicki, Richard; Nuckolls, Glen H (NIH); Rao, Ashutosh; Farkas, Ronald; Leptak, Christopher
Cc: Gross, Mary
Subject: Final call for Dystrophin agenda comments - please send me any comments by tomorrow, March 17. I'd like to finalize and post to meeting page tomorrow.

From: [Rao, Ashutosh](#)
To: [Kweder, Sandra L](#)
Cc: [Moscicki, Richard](#)
Subject: FW: Notice of Scientific Workshop on March 20; Dystrophin Methodologies
Date: Tuesday, March 17, 2015 12:20:00 PM
Attachments: [Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx](#)
[FDA-NIH Dystrophin Workshop abbreviated.pdf](#)

Dear Sandy,

Rich Moscicki suggested that I forward this dystrophin workshop email to you to see if others from EMA might be interested in attending. The latest version of the agenda is attached. I got an out-of-office response from Sabine Haubenreisser.

Thanks

Best regards,
Ash
Ashutosh Rao, Ph.D.
CDER/OPQ/OBP

From: Rao, Ashutosh
Sent: Monday, March 02, 2015 3:38 PM
To: Haubenreisser, Sabine *
Cc: Gross, Mary; Farkas, Ronald; Bastings, Eric
Subject: FW: Notice of Scientific Workshop on March 20; Dystrophin Methodologies

Dear Dr. Haubenreisser,

The FDA and NIH are co-sponsoring a scientific workshop on dystrophin this month (see below for details). It would be great if you or a designate from EMA could attend the forum. Please let Mary Gross or myself know if this is possible. Thank you.

Best regards,

Ashutosh Rao, Ph.D.
FDA/CDER

From: Gross, Mary
Sent: Friday, February 27, 2015 11:34 AM
To: Flanigan, Kevin; Louise.Rudino-Klapac@nationwidechildrens.org; jervasti@umn.edu; Jeff Chamberlain; David.Rimm@Yale.edu; Pat Furlong; Morris Glenn (THE ROBERT JONES AND AGNES HUNT ORTHOPAEDIC HOSPITAL NHS FOUNDATION TRUST); c.beekman@prosensa.nl; Sahenk, Zarife; YHathout@childrensnational.org; ehoffman@childrensnational.org; wagnerk@kennedykrieger.org; lsweeney@mail.med.upenn.edu; Rabi_Tawil@urmc.rochester.edu; Sardone, Valentina; John Porter; Afrodite Loubakos
Cc: Nuckolls, Glen H (NIH); Rao, Ashutosh; Moscicki, Richard; Leptak, Christopher; Farkas, Ronald; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Kaiser, James; Rogers, Hobart; Ienzi, Georgiann; Xu, Lei (CBER); Mansfield, Elizabeth; Jenkins, John K; Loewke, Sally A; Tezak, Zivana; Woodcock, Janet; Boyce, Amanda T (NIH); Kaufmann, Petra (NIH); pmcinnis@mail.nih.gov; Austin, Christopher P (NIH)
Subject: Notice of Scientific Workshop on March 20; Dystrophin Methodologies

Hi everyone: FDA and NIH are co-sponsoring the scientific workshop entitled “Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data” that will be held on March 20 in Silver Spring MD. Please see the draft agenda and the meeting web link that will be updated with the FR notice shortly. The meeting page link will automatically update with other pertinent information, like the final agenda, once it becomes available. Anyone who isn't a speaker should register through the mailbox if you plan to attend the meeting. I will register the speakers for this event.

Attendees may participate either in person or view by webcast. There is no fee to attend the public workshop, but space is limited, and registration for in person attendance will be on a first-come, first-served basis. Email registrations should be sent to Dystrophin_Workshop@fda.hhs.gov by March 17, 2015.

Please share this information with any colleagues who might be interested in attending this meeting as pre-registration is required.

Thank you!

<http://www.fda.gov/Drugs/NewsEvents/ucm432429.htm>

Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data
March 20th 2015
Scientific Workshop

Scope of the meeting: Recent advances in drug development for Duchenne Muscular Dystrophy (DMD) present an opportunity for the development and validation of robust methods for the objective, reliable, and quantitative measurement of dystrophin and related muscle proteins. This workshop, cosponsored by the Food and Drug Administration and the National Institutes of Health was convened in order to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development.

Agenda

- 7:30 am Registration
- 8:30 am Opening Remarks
Christopher P. Austin, MD, Director, National Center for Advancing Translational Sciences, National Institutes of Health (NIH)
- 8:45 am Richard A. Moscicki, MD, Deputy Center Director for Science Operations, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)
- 8:55 am Dystrophin: Convening the Conversation - Pat Furlong, President, Parent Project Muscular Dystrophy
- 9:10 am Background and Meeting Objectives Related to Analytical Challenges and Opportunities with Dystrophin Methodologies - Ashutosh Rao, PhD, Division of Biotechnology Research and Review, Office of Biotechnology Products, CDER, FDA
- Session I: The Dystrophin Gene and Protein - Glen Nuckolls, PhD, Executive Secretary, Muscular Dystrophy Coordinating Committee, Program Officer, Neurogenetics Cluster, National Institute of Neurological Disorders and Stroke, NIH and Ashutosh Rao, PhD - Moderators
- This session will provide a background on current understanding of the dystrophin gene and its various products and associated proteins as they relate to protein quantification methodologies and assays of dystrophin function in DMD and BMD.
- 9:30 am Dystrophin Quantitation Using Full-Length Recombinant Protein as Standard - James M. Ervasti, PhD, Paul and Sheila Wellstone Muscular Dystrophy Center, University of Minnesota, Minneapolis, MN

9:45 am Expression of Exogenous Dystrophin, Isoforms, Splice Products and Synthetic Constructs - Jeff Chamberlain, PhD, Departments of Neurology, Medicine and Biochemistry, University of Washington, Seattle, WA

10:00 am Break

Session II: Dystrophin Quantification Methodologies - Glen Nuckolls, PhD, Ron Farkas, MD, PhD, Division of Neurology Products, Office of Drug Evaluation 1, CDER, FDA - Moderators

This session will focus on identifying key technologies, their limitations including detection and quantification sensitivities, linearity, reproducibility, and identified development and validation needs/hurdles for each method. Published and unpublished data using each method on human normal and disease samples will be discussed. Image and other data analysis, as well as statistical methods will also be discussed.

10:15 am Antibody Probes for Dystrophin Protein Detection - Glenn E. Morris, D.Phil., Wolfson Centre for Inherited Neuromuscular Disease, RJAH Orthopaedic Hospital and Keele University, Oswestry, UK

Immunohistochemistry/fluorescence and Image Analysis

10:30 am Detailed Methodology of Dystrophin Quantification – Valentina Sardone, PhD, Institute of Child Health, University College, London

10:45 am Changes and Variability in Dystrophin Detection: Immunofluorescence, Antibody Staining and Imaging Methodologies - Chantal AC Beekman, Prosensa, Leiden, Netherlands

11:00 am Methodology for Quantification of Dystrophin Positive Muscle Fibers Using Widefield Fluorescence Microscope – Zarife Sahenk, MD, PhD, The Research Institute at Nationwide Children’s Hospital, Columbus, OH

11:10 am Assessment of Mean Fluorescence Signal Intensity of Muscle Fibers Expressing Dystrophin - Louise R. Rodino-Klapac, PhD, The Research Institute at Nationwide Children’s Hospital, Columbus, OH

11:20 am A Comprehensive Approach to Quantifiable and Meaningful Dystrophin Measurements in Clinical Trials – Peter Sazani, PhD, Executive Director, Medical Affairs, Sarepta Therapeutics

11:35 am Defining Standards for Dystrophin Quantification in DMD Muscle Biopsies - John Babiak, PhD, Senior Vice President, Drug Discovery Technologies, PTC Therapeutics, Inc

11:50 am Quantitative In-Situ Measurement of Biomolecules for Companion Diagnostics - David Rimm, MD, PhD, Yale University School of Medicine, New Haven, CT

12:05 pm Panel Discussion - Dystrophin Quantification by Histological Methods

12:45 pm Lunch

Session II continued – Glen Nuckolls, PhD, Ashutosh Rao, PhD - Moderators

1:15 pm Dystrophin Quantification in Clinical Trials - Sebahattin Cirak, Dr. Med., Dipl Chem, Institut für Humangenetik, Klinik und Poliklinik für Kinder- und Jugendmedizin, Zentrum für Molekulare Medizin

1:30 pm Quantification by Western Blotting: Challenges and Correlations - Kevin Flanigan, MD, Center for Gene Therapy, The Research Institute at Nationwide Children's Hospital, Columbus, OH, Professor of Pediatrics and Neurology, Ohio State University

1:45 pm Targeted Quantification of Dystrophin by Mass Spectrometry and Comparison to Antibody Based Assays - Yetrib Hathout, PhD, Center for Genetic Medicine, Children's National Medical Center, Washington, DC

2:00 pm Variable Dystrophin Content within Myofibers, between Myofibers, and between Regions of Muscles: Determining the Level of Dystrophin that makes a Clinical Impact in BMD and Manifesting Carriers of DMD - Eric Hoffman, MD, Center for Genetic Medicine, Children's National Medical Center, Washington, DC

2:15 pm Panel Discussion - Dystrophin Quantification from Tissue Extracts

Session III: Muscle Biopsies and Sample Handling Glen Nuckolls, PhD, Ron Farkas, MD - Moderators

This session will focus on muscle biopsy collection procedures (open and needle), anatomical site selection, guided versus non-guided biopsy, experiences with muscle biopsy handling and processing, and reference tissue banks.

2:45 pm Methods of Muscle Sampling - Rabi Tawil, MD, Professor of Neurology, University of Rochester Medical Center, Rochester, NY

3:00 pm Open Versus Needle Muscle Biopsy - Kathryn Wagner, MD, PhD, Center for Genetic Muscle Disorders, Kennedy Krieger Institute, Baltimore, MD

3:15 pm MRI/MRS Assessment of the Status of Skeletal Muscle in DMD Patients - Lee Sweeney, PhD, William Maul Measey Professor of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA

3:30 pm Break

Session IV Facilitated Panel Discussion

3:45 pm John Porter, PhD, Chief Executive Officer, Parent Project Muscular Dystrophy and Richard A. Moscicki, MD - Moderators
Panelists: Jeff Chamberlain, Kevin Flanigan, MD, Eric Hoffman, MD, Katherine Wagner, MD, Lee Sweeney, PhD

1. What is the current status of assay validation and methodology for quantification of dystrophin in the context of drug development? What are the key opportunities and knowledge gaps in the field?
2. What are the necessary next steps to advance the precision and reproducibility of technology to acquire, measure, and analyze the proteins that are associated with Duchenne muscular dystrophy?
3. What are the Action Items from this workshop that will continue to advance robust methods for the objective, reliable, and quantitative measurement of dystrophin and dystrophin-related muscle proteins?

5:15 pm Closing Remarks
Ellis Unger, MD, FDA

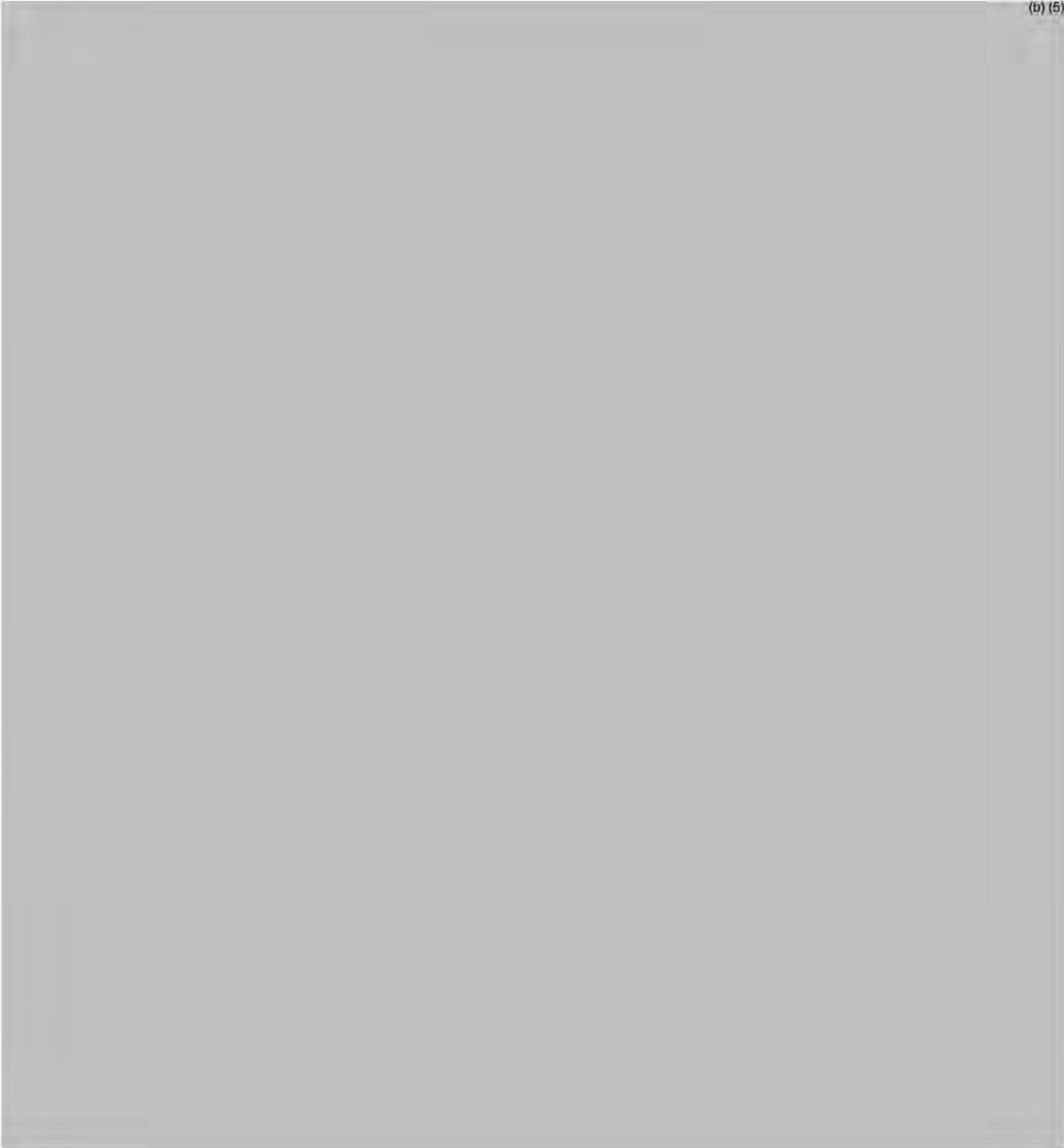
5:30 pm Adjournment

FDA-NIH Dystrophin Methodology Workshop
Location FDA White Oak Campus
Date March 20th 2015
(TENTATIVE AGENDA)

(b) (5)



(b) (5)



From: [Gross, Mary](#)
To: [Flanigan, Kevin](#); jsc5@uw.edu; [Wagner, Kathryn](#); [John Porter](#); [Lee Sweeney](#); [Moscicki, Richard](#)
Cc: ehoffman@childrensnational.org; [Stout, Christa](#)
Subject: RE: Scheduling a Call to Discuss Panel 4 - March 20 Dystrophin Meeting - Response needed
Date: Wednesday, March 18, 2015 11:13:02 AM

Hi – we will not be holding this call today @ 430 and will try to set something up to discuss panel 4 at the meeting on March 20. Thanks.

Mary

From: [Flanigan, Kevin](mailto:Kevin.Flanigan@nationwidechildrens.org) [mailto:Kevin.Flanigan@nationwidechildrens.org]
Sent: Tuesday, March 17, 2015 8:04 PM
To: [Gross, Mary](#); jsc5@uw.edu; [Wagner, Kathryn](#); [John Porter](#)
Subject: RE: Scheduling a Call to Discuss Panel 4 - March 20 Dystrophin Meeting - Response needed

Mary,

I am traveling Wednesday and will be unable to make the call.

Kevin

From: [Gross, Mary](mailto:Mary.Gross@fda.hhs.gov) [mailto:Mary.Gross@fda.hhs.gov]
Sent: Monday, March 16, 2015 5:29 PM
To: jsc5@uw.edu; [Wagner, Kathryn](#); [Flanigan, Kevin](#); [John Porter](#)
Subject: Scheduling a Call to Discuss Panel 4 - March 20 Dystrophin Meeting - Response needed

Hi – a call was held today at 4:30 (eastern standard time) to discuss your participation on Panel 4 as discussants or moderator at the Dystrophin scientific workshop on March 20. It appears that there must have been a miscommunication about the call because I thought you were available to participate on today's call. I'd like to reschedule the call if there is time available. Would you check your calendars and let me know if you are available from 4:30 pm – 5:00 pm (eastern standard time) on Wednesday, March 18? Thanks.

Mary

From: [Gross, Mary](#)
Sent: Tuesday, March 10, 2015 10:20 AM
To: jsc5@uw.edu; [Wagner, Kathryn](#); lsweeney@mail.med.upenn.edu; ehoffman@childrensnational.org; [Flanigan, Kevin](#); [John Porter](#); [Moscicki, Richard](#)
Cc: [Nuckolls, Glen H \(NIH\)](#); [Rao, Ashutosh](#); [Leptak, Christopher](#); [Farkas, Ronald](#); [Ienzi, Georgiann](#)
Subject: Request to be discussants on Panel 4 - March 20 Dystrophin Meeting - Response needed

Hi – you are participating as speakers during the March 20 scientific workshop on Dystrophin methodologies. As the last panel, we are holding an interactive discussion to wrap up the day with specific questions and feedback from the

audience. You have been nominated to participate as part of this panel. We'd like to do a call on March 16 at 4:30 (eastern standard time) to discuss this role. I'm also attaching the draft agenda so you can review this session. Would you let me know if this time works out for you?

Thanks so much!

TCON number 877 704 7717; PC (b) (4)

<< File: Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx >>

From: [Gross, Mary](#)
To: [Mosicki, Richard](#); [John Porter](#)
Cc: [Rao, Ashutosh](#)
Subject: Moderator duties for Panel 4 Dystrophin Meeting
Date: Tuesday, March 17, 2015 10:37:57 AM

Hi – we tried to hold a call yesterday @ 4:30 pm with panel 4 panelists and only one made it to the call. I've tried to reschedule for Wednesday but so far have only heard from one (Sweeney) who said he'll have to leave a meeting to make the call. Do you want to try and do a call or send something in writing to these proposed panelists about panel 4? Dr. Chamberlain will need to leave by 4:30 so won't be on the panel for the full time.

Thanks.

Mary

From: [Kweder, Sandra L](#)
To: [Rao, Ashutosh](#)
Cc: [Moscicki, Richard](#)
Subject: RE: Notice of Scientific Workshop on March 20; Dystrophin Methodologies
Date: Tuesday, March 17, 2015 12:32:43 PM

Hi Ash,

I definitely will. I let them know about it around a month ago, so they have it on their radar screen. Now that we have more details I will send a reminder.

Sandy

From: Rao, Ashutosh
Sent: Tuesday, March 17, 2015 4:20 PM
To: Kweder, Sandra L
Cc: Moscicki, Richard
Subject: FW: Notice of Scientific Workshop on March 20; Dystrophin Methodologies

Dear Sandy,

Rich Moscicki suggested that I forward this dystrophin workshop email to you to see if others from EMA might be interested in attending. The latest version of the agenda is attached. I got an out-of-office response from Sabine Haubenreisser.

Thanks

Best regards,

Ash

Ashutosh Rao, Ph.D.

CDER/OPQ/OBP

<< File: Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx >>

From: Rao, Ashutosh
Sent: Monday, March 02, 2015 3:38 PM
To: Haubenreisser, Sabine *
Cc: Gross, Mary; Farkas, Ronald; Bastings, Eric
Subject: FW: Notice of Scientific Workshop on March 20; Dystrophin Methodologies

Dear Dr. Haubenreisser,

The FDA and NIH are co-sponsoring a scientific workshop on dystrophin this month (see below for details). It would be great if you or a designate from EMA could attend the forum. Please

let Mary Gross or myself know if this is possible. Thank you.

Best regards,

Ashutosh Rao, Ph.D.

FDA/CDER

From: Gross, Mary

Sent: Friday, February 27, 2015 11:34 AM

To: Flanigan, Kevin; Louise.Rudino-Klapac@nationwidechildrens.org; jervasti@umn.edu; Jeff Chamberlain; David.Rimm@Yale.edu; Pat Furlong; Morris Glenn (THE ROBERT JONES AND AGNES HUNT ORTHOPAEDIC HOSPITAL NHS FOUNDATION TRUST); c.beekman@prosensa.nl; Sahenk, Zarife; YHathout@childrensnational.org; ehoffman@childrensnational.org; wagnerk@kennedykrieger.org; lsweeney@mail.med.upenn.edu; Rabi_Tawil@urmc.rochester.edu; Sardone, Valentina; John Porter; Afrodite Loubakos

Cc: Nuckolls, Glen H (NIH); Rao, Ashutosh; Moscicki, Richard; Leptak, Christopher; Farkas, Ronald; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Kaiser, James; Rogers, Hobart; Ienzi, Georgiann; Xu, Lei (CBER); Mansfield, Elizabeth; Jenkins, John K; Loewke, Sally A; Tezak, Zivana; Woodcock, Janet; Boyce, Amanda T (NIH); Kaufmann, Petra (NIH); pmcinnes@mail.nih.gov; Austin, Christopher P (NIH)

Subject: Notice of Scientific Workshop on March 20; Dystrophin Methodologies

Hi everyone: FDA and NIH are co-sponsoring the scientific workshop entitled "Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data" that will be held on March 20 in Silver Spring MD. Please see the draft agenda and the meeting web link that will be updated with the FR notice shortly. The meeting page link will **automatically** update with other pertinent information, like the final agenda, once it becomes available. Anyone who isn't a speaker should register through the mailbox if you plan to attend the meeting. I will register the speakers for this event.

Attendees may participate either in person or view by webcast. There is no fee to attend the public workshop, but space is limited, and registration for in person attendance will be on a first-come, first-served basis. Email registrations should be sent to Dystrophin_Workshop@fda.hhs.gov by March 17, 2015.

Please share this information with any colleagues who might be interested in attending this meeting as pre-registration is required.

Thank you!

<< File: FDA-NIH Dystrophin Workshop abbreviated.pdf >>

<http://www.fda.gov/Drugs/NewsEvents/ucm432429.htm>

From: Gross, Mary
To: Rao, Ashutosh; YHathout@childrensnational.org; Louise.Rodino-Klapac@nationwidechildrens.org; Austin, Christopher P (NIH); 'jervasti@umn.edu'; 'jsc5@uw.edu'; 'David.Rimm@Yale.edu'; '(b) (6)'; 'c.beekman@prosenza.nl'; 'zarife.sahenk@nationwidechildrens.org'; 'ehoffman@childrensnational.org'; 'lsweeney@mail.med.upenn.edu'; 'Rabi_Tawil@urmc.rochester.edu'; 'wagnerk@kennedykrieger.org'; Sardone, Valentina; 'psazani@sarepta.com'; Pat Furlong; Sebahattin Cirak; Babiak, John; Flanigan, Kevin
Cc: Nuckolls, Glen H (NIH); John Porter; Farkas, Ronald; Ienzi, Georgiann; Reid, Kelli W (NIH); Jackie Gibson at NCATS; Quartey, Elizabeth O (NIH); Leptak, Christopher; Unger, Ellis; Moscicki, Richard
Subject: RE: Reminder- dystrophin workshop slides
Date: Tuesday, March 17, 2015 7:59:49 AM

Hi everyone – if you reduce your number of slides, please send the new set to me by noon Wednesday, March 18 at the latest.

Would you mark them slides #2 with your name so there is no confusion with mixing them up with your first set of slides. Thanks so much for your cooperation and we are looking forward to seeing you Friday.

Mary

From: Rao, Ashutosh
Sent: Monday, March 16, 2015 6:25 PM
To: YHathout@childrensnational.org; Louise.Rodino-Klapac@nationwidechildrens.org; Austin, Christopher P (NIH); 'jervasti@umn.edu'; 'jsc5@uw.edu'; 'David.Rimm@Yale.edu'; '(b) (6)'; 'c.beekman@prosenza.nl'; 'zarife.sahenk@nationwidechildrens.org'; 'ehoffman@childrensnational.org'; 'lsweeney@mail.med.upenn.edu'; 'Rabi_Tawil@urmc.rochester.edu'; 'wagnerk@kennedykrieger.org'; Sardone, Valentina; 'psazani@sarepta.com'; Pat Furlong; Sebahattin Cirak; Babiak, John; Flanigan, Kevin
Cc: Gross, Mary; Nuckolls, Glen H (NIH); John Porter; Farkas, Ronald; Ienzi, Georgiann; Reid, Kelli W (NIH); Jackie Gibson at NCATS; Quartey, Elizabeth O (NIH); Leptak, Christopher; Unger, Ellis; Moscicki, Richard
Subject: Reminder- dystrophin workshop slides

Dear Speakers,

Thank you for agreeing to participate in this workshop. It may be worth reminding everyone that each individual speaker is allowed no more than 15 minutes (including questions) and it wouldn't be practical to try and present more than 12-15 slides. Please be courteous to the other speakers and limit your presentation to fewer than 15 slides. There will be a separate Q&A/discussion time at the end of each of the session. Please send your presentation or revised version with fewer than 15 slides to Mary Gross at the earliest possible. As Mary mentioned in her email, it will not be a possible to bring your talk on your own electronic device during the workshop.

We look forward to your participation.

Best regards,

Ashutosh Rao and Glen Nuckolls

From: Rao, Ashutosh
To: YHathout@childrensnational.org; Louise.Rodino-Klapac@nationwidechildrens.org; Austin, Christopher P (NIH); "jervasti@umn.edu"; "jsc5@uw.edu"; "David.Rimm@Yale.edu"; "(b) (6)"; "c.beekman@prosensa.nl"; "zarife.sahenk@nationwidechildrens.org"; "ehoffman@childrensnational.org"; "lsweeney@mail.med.upenn.edu"; "Rabi_Tawil@urmc.rochester.edu"; "wagnerk@kennedykrieger.org"; Sardone, Valentina; "psazani@sarepta.com"; Pat Furlong; Sebahattin Cirak; Babiak, John; Flanigan, Kevin
Cc: Gross, Mary; Nuckolls, Glen H (NIH); John Porter; Farkas, Ronald; Tenzi, Georgiann; Reid, Kelli W (NIH); Jackie Gibson at NCATS; Quartey, Elizabeth O (NIH); Leptak, Christopher; Unger, Ellis; Moscicki, Richard
Subject: Reminder- dystrophin workshop slides
Date: Monday, March 16, 2015 6:25:17 PM

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We look forward to your participation.

Best regards,

Ashutosh Rao and Glen Nuckolls

From: [Gross, Mary](#)
To: [Moscicki, Richard](#); [Nuckolls, Glen H \(NIH\)](#); [Rao, Ashutosh](#); [Farkas, Ronald](#); [Leptak, Christopher](#)
Cc: [Gross, Mary](#)
Subject: Final call for Dystrophin agenda comments - please send me any comments by tomorrow, March 17. I'd like to finalize and post to meeting page tomorrow.
Date: Monday, March 16, 2015 6:00:59 PM
Attachments: [Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx](#)

Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data
March 20th 2015
Scientific Workshop

Scope of the meeting: Recent advances in drug development for Duchenne Muscular Dystrophy (DMD) present an opportunity for the development and validation of robust methods for the objective, reliable, and quantitative measurement of dystrophin and related muscle proteins. This workshop, cosponsored by the Food and Drug Administration and the National Institutes of Health was convened in order to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development.

Agenda

- 7:30 am Registration
- 8:30 am Opening Remarks
Christopher P. Austin, MD, Director, National Center for Advancing Translational Sciences, National Institutes of Health (NIH)
- 8:45 am Richard A. Moscicki, MD, Deputy Center Director for Science Operations, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)
- 8:55 am Dystrophin: Convening the Conversation - Pat Furlong, President, Parent Project Muscular Dystrophy
- 9:10 am Background and Meeting Objectives Related to Analytical Challenges and Opportunities with Dystrophin Methodologies - Ashutosh Rao, PhD, Division of Biotechnology Research and Review, Office of Biotechnology Products, CDER, FDA
- Session I: The Dystrophin Gene and Protein - Glen Nuckolls, PhD, Executive Secretary, Muscular Dystrophy Coordinating Committee, Program Officer, Neurogenetics Cluster, National Institute of Neurological Disorders and Stroke, NIH and Ashutosh Rao, PhD - Moderators
- This session will provide a background on current understanding of the dystrophin gene and its various products and associated proteins as they relate to protein quantification methodologies and assays of dystrophin function in DMD and BMD.
- 9:30 am Dystrophin Quantitation Using Full-Length Recombinant Protein as Standard - James M. Ervasti, PhD, Paul and Sheila Wellstone Muscular Dystrophy Center, University of Minnesota, Minneapolis, MN

9:45 am Expression of Exogenous Dystrophin, Isoforms, Splice Products and Synthetic Constructs - Jeff Chamberlain, PhD, Departments of Neurology, Medicine and Biochemistry, University of Washington, Seattle, WA

10:00 am Break

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This session will focus on identifying key technologies, their limitations including detection and quantification sensitivities, linearity, reproducibility, and identified development and validation needs/hurdles for each method. Published and unpublished data using each method on human normal and disease samples will be discussed. Image and other data analysis, as well as statistical methods will also be discussed.

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Immunohistochemistry/fluorescence and Image Analysis

10:30 am Detailed Methodology of Dystrophin Quantification – Valentina Sardone, PhD, Institute of Child Health, University College, London

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11:20 am A Comprehensive Approach to Quantifiable and Meaningful Dystrophin Measurements in Clinical Trials – Peter Sazani, PhD, Executive Director, Medical Affairs, Sarepta Therapeutics

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- 11:50 am Quantitative In-Situ Measurement of Biomolecules for Companion Diagnostics - David Rimm, MD, PhD, Yale University School of Medicine, New Haven, CT
- 12:05 pm Panel Discussion - Dystrophin Quantification by Histological Methods
- 12:45 pm Lunch
- Session II continued – Glen Nuckolls, PhD, Ashutosh Rao, PhD - Moderators
- 1:15 pm Dystrophin Quantification in Clinical Trials - Sebahattin Cirak, Dr. Med., Dipl Chem, Institut für Humangenetik, Klinik und Poliklinik für Kinder- und Jugendmedizin, Zentrum für Molekulare Medizin
- 1:30 pm Quantification by Western Blotting: Challenges and Correlations - Kevin Flanigan, MD, Center for Gene Therapy, The Research Institute at Nationwide Children's Hospital, Columbus, OH, Professor of Pediatrics and Neurology, Ohio State University
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- 3:30 pm Break

Session IV Facilitated Panel Discussion

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Panelists: Jeff Chamberlain, Kevin Flanigan, MD, Eric Hoffman, MD, Katherine Wagner, MD, Lee Sweeney, PhD

1. What is the current status of assay validation and methodology for quantification of dystrophin in the context of drug development? What are the key opportunities and knowledge gaps in the field?
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5:15 pm Closing Remarks
Ellis Unger, MD, FDA

5:30 pm Adjournment

From: [Gross, Mary](#)
To: [Austin, Christopher P \(NIH\); "jsc5@uw.edu"; "lsweeney@mail.med.upenn.edu"; Rao, Ashutosh; Moscicki, Richard; "wagnerk@kennedykrieger.org"; Flanagan, Kevin; Pat@parentprojectmd.org](#)
Cc: [Leptak, Christopher; Nuckolls, Glen H \(NIH\); Tenzi, Georgiann](#)
Subject: Slide Reminder for Dystrophin Meeting - due no later than COB tomorrow
Date: Monday, March 16, 2015 3:52:12 PM
Importance: High

Hi everyone – Please note that slides are due for the Dystrophin Methodologies scientific workshop by no later than COB tomorrow. When you submit your slides in power point, please remember that formal remarks should not exceed 12 – 15 minutes in length. If you do not plan on using slides, please let me know. Thank you.

Mary

From: [Gross, Mary](#)
To: [Goodman, Roberta](#)
Cc: [Moscicki, Richard](#)
Subject: Here is the latest Dystrophin Agenda - also attached in calendar update.
Date: Monday, March 16, 2015 2:43:36 PM
Attachments: [Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx](#)

Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data
March 20th 2015
Scientific Workshop

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9:45 am Expression of Exogenous Dystrophin, Isoforms, Splice Products and Synthetic Constructs - Jeff Chamberlain, PhD, Departments of Neurology, Medicine and Biochemistry, University of Washington, Seattle, WA

10:00 am Break

Session II: Dystrophin Quantification Methodologies - Glen Nuckolls, PhD, Ron Farkas, MD, PhD, Division of Neurology Products, Office of Drug Evaluation 1, CDER, FDA - Moderators

This session will focus on identifying key technologies, their limitations including detection and quantification sensitivities, linearity, reproducibility, and identified development and validation needs/hurdles for each method. Published and unpublished data using each method on human normal and disease samples will be discussed. Image and other data analysis, as well as statistical methods will also be discussed.

10:15 am Antibody Probes for Dystrophin Protein Detection - Glenn E. Morris, D.Phil., Wolfson Centre for Inherited Neuromuscular Disease, RJA Orthopaedic Hospital and Keele University, Oswestry, UK

Immunohistochemistry/fluorescence and Image Analysis

10:30 am Detailed Methodology of Dystrophin Quantification – Valentina Sardone, PhD, Institute of Child Health, University College, London

10:45 am Changes and Variability in Dystrophin Detection: Immunofluorescence, Antibody Staining and Imaging Methodologies - Chantal AC Beekman, Prosensa, Leiden, Netherlands

11:00 am Methodology for Quantification of Dystrophin Positive Muscle Fibers Using Widefield Fluorescence Microscope – Zarife Sahenk, MD, PhD, The Research Institute at Nationwide Children’s Hospital, Columbus, OH

11:10 am Assessment of Mean Fluorescence Signal Intensity of Muscle Fibers Expressing Dystrophin - Louise R. Rodino-Klapac, PhD, The Research Institute at Nationwide Children’s Hospital, Columbus, OH

11:20 am A Comprehensive Approach to Quantifiable and Meaningful Dystrophin Measurements in Clinical Trials – Peter Sazani, PhD, Executive Director, Medical Affairs, Sarepta Therapeutics

11:35 am Defining Standards for Dystrophin Quantification in DMD Muscle Biopsies - John Babiak, PhD, Senior Vice President, Drug Discovery Technologies, PTC Therapeutics, Inc

- 11:50 am Quantitative In-Situ Measurement of Biomolecules for Companion Diagnostics - David Rimm, MD, PhD, Yale University School of Medicine, New Haven, CT
- 12:05 pm Panel Discussion - Dystrophin Quantification by Histological Methods
- 12:45 pm Lunch
- Session II continued – Glen Nuckolls, PhD, Ashutosh Rao, PhD - Moderators
- 1:15 pm Dystrophin Quantification in Clinical Trials - Sebahattin Cirak, Dr. Med., Dipl Chem, Institut für Humangenetik, Klinik und Poliklinik für Kinder- und Jugendmedizin, Zentrum für Molekulare Medizin
- 1:30 pm Quantification by Western Blotting: Challenges and Correlations - Kevin Flanigan, MD, Center for Gene Therapy, The Research Institute at Nationwide Children's Hospital, Columbus, OH, Professor of Pediatrics and Neurology, Ohio State University
- 1:45 pm Targeted Quantification of Dystrophin by Mass Spectrometry and Comparison to Antibody Based Assays - Yetrib Hathout, PhD, Center for Genetic Medicine, Children's National Medical Center, Washington, DC
- 2:00 pm Variable Dystrophin Content within Myofibers, between Myofibers, and between Regions of Muscles: Determining the Level of Dystrophin that makes a Clinical Impact in BMD and Manifesting Carriers of DMD - Eric Hoffman, MD, Center for Genetic Medicine, Children's National Medical Center, Washington, DC
- 2:15 pm Panel Discussion - Dystrophin Quantification from Tissue Extracts
- Session III: Muscle Biopsies and Sample Handling Glen Nuckolls, PhD, Ron Farkas, MD - Moderators
- This session will focus on muscle biopsy collection procedures (open and needle), anatomical site selection, guided versus non-guided biopsy, experiences with muscle biopsy handling and processing, and reference tissue banks.
- 2:45 pm Methods of Muscle Sampling - Rabi Tawil, MD, Professor of Neurology, University of Rochester Medical Center, Rochester, NY
- 3:00 pm Open Versus Needle Muscle Biopsy - Kathryn Wagner, MD, PhD, Center for Genetic Muscle Disorders, Kennedy Krieger Institute, Baltimore, MD
- 3:15 pm MRI/MRS Assessment of the Status of Skeletal Muscle in DMD Patients - Lee Sweeney, PhD, William Maul Measey Professor of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA
- 3:30 pm Break

Session IV Facilitated Panel Discussion

3:45 pm John Porter, PhD, Chief Executive Officer, Parent Project Muscular Dystrophy and Richard A. Moscicki, MD - Moderators
Panelists: Jeff Chamberlain, Kevin Flanigan, MD, Eric Hoffman, MD, Katherine Wagner, MD, Lee Sweeney, PhD

1. What is the current status of assay validation and methodology for quantification of dystrophin in the context of drug development? What are the key opportunities and knowledge gaps in the field?
2. What are the necessary next steps to advance the precision and reproducibility of technology to acquire, measure, and analyze the proteins that are associated with Duchenne muscular dystrophy?
3. What are the Action Items from this workshop that will continue to advance robust methods for the objective, reliable, and quantitative measurement of dystrophin and dystrophin-related muscle proteins?

5:15 pm Closing Remarks
Ellis Unger, MD, FDA

5:30 pm Adjournment

From: Gross, Mary
To: YHathout@childrensnational.org; Louise.Rodino-Klapac@nationwidechildrens.org; Austin, Christopher P (NIH); 'jervasti@umn.edu'; 'jsc5@uw.edu'; 'David.Rimm@Yale.edu'; (b) (6); 'c.beekman@prosensa.nl'; 'zarife.sahenk@nationwidechildrens.org'; 'ehoffman@childrensnational.org'; 'lsweeney@mail.med.upenn.edu'; 'Rabi_Tawil@urmc.rochester.edu'; Rao, Ashutosh; Moscicki, Richard; Unger, Ellis; 'wagnerk@kennedykrieger.org'; Sardone, Valentina; 'psazani@sarepta.com'; Pat Furlong; Sebahattin Cirak; Babiak, John; Flanigan, Kevin
Cc: Nuckolls, Glen H (NIH); John Porter; Farkas, Ronald; Tenzi, Georgiann; Reid, Kelli W (NIH); Jackie Gibson at NCATS; Quartey, Elizabeth O (NIH); Leptak, Christopher
Subject: Dystrophin Meeting Update - Slide Reminder by March 13
Date: Thursday, March 12, 2015 9:52:37 AM
Attachments: Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx
Importance: High

Dear Speakers and Moderators - The scientific workshop on Dystrophin Methodologies is coming up next Friday, March 20. This is a reminder that slides are due tomorrow, March 13. I am including the latest version of the meeting agenda. I think you will notice that it is completely packed with presentations and discussion time without much wiggle room for delays. Please keep your formal remarks to no longer than 12 - 15 minutes so we can keep the program on schedule. If you haven't returned your financial disclosure form, would you also send that back to me by March 13?

We will need to preload the slides prior to the meeting and no thumb drives with changes or personal computers for purposes of pulling up presentations will be permitted in the White Oak facility the day of the meeting.

Thank you very much for participating! We are looking forward to seeing you on March 20.

Mary

From: Gross, Mary
Sent: Monday, March 09, 2015 4:36 PM
To: 'YHathout@childrensnational.org'; 'Louise.Rodino-Klapac@nationwidechildrens.org'
Subject: FW: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)

From: Gross, Mary
Sent: Monday, March 09, 2015 4:03 PM
To: Austin, Christopher P (NIH); 'jervasti@umn.edu'; 'jsc5@uw.edu'; 'David.Rimm@Yale.edu'; (b) (6); 'c.beekman@prosensa.nl'; 'Louise.Rudino-Klapac@nationwidechildrens.org'; 'zarife.sahenk@nationwidechildrens.org'; 'YHathout@childrensnational.org'; 'ehoffman@childrensnational.org'; 'lsweeney@mail.med.upenn.edu'; 'Rabi_Tawil@urmc.rochester.edu'; Nuckolls, Glen H (NIH); Rao, Ashutosh; Moscicki, Richard; Farkas, Ronald; 'Sardone, Valentina'; 'Flanigan, Kevin'; Unger, Ellis; 'Sebahattin Cirak'; 'Babiak, John'; Pat Furlong; 'John Porter'; 'wagnerk@kennedykrieger.org'; 'psazani@sarepta.com'
Cc: Leptak, Christopher; Tenzi, Georgiann
Subject: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)

Dear Speakers and Moderators - Please see the next version of the draft agenda for the March 20, 2015 scientific workshop entitled "Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data". As you will see, the agenda is extremely full. We have added a couple of speakers so we need to ask speakers to limit remarks to between 12 and 15 minutes. There is time built in on the agenda after panels 2 and 3 for discussion.

Would you mind reviewing this agenda once more and correct any inaccuracies or anything you want changed at this time and return to me no later than March 11. And please remember that slides are due no later than Friday, March 13.

Please do not share this agenda as it hasn't been formally released.

Thanks so much and we look forward to seeing you on March 20 at FDA's White Oak Campus in Silver Spring, MD.

<< File: Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx
>>

From: [Leptak, Christopher](#)
To: [Rao, Ashutosh](#); [Gross, Mary](#)
Cc: [Moscicki, Richard](#)
Subject: Dystrophin Workshop
Date: Wednesday, March 11, 2015 6:12:52 PM

Ash and Mary,

I have two colleagues who can assist with tasks (advancing slides, etc.) on the day of the workshop.

Chris

From: [Leptak, Christopher](#)
To: [Nuckolls, Glen H \(NIH\)](#)
Cc: [Rao, Ashutosh](#); [Moscicki, Richard](#); [Gross, Mary](#); [Quartey, Elizabeth O \(NIH\)](#)
Subject: RE: support for speaker travel for FDA/NIH workshop on dystrophin
Date: Wednesday, March 11, 2015 6:11:11 PM

Glen... please see below.. Can you confirm that NINDS has arranged for Lee Sweeney's travel?

From: Gross, Mary
Sent: Wednesday, March 11, 2015 6:09 PM
To: Leptak, Christopher
Cc: Rao, Ashutosh; Moscicki, Richard; Nuckolls, Glen H (NIH); Quartey, Elizabeth O (NIH)
Subject: RE: support for speaker travel for FDA/NIH workshop on dystrophin

Hi – I didn't get confirmation that his travel has been completed. Thanks.

Mary

From: Leptak, Christopher
Sent: Wednesday, March 11, 2015 5:57 PM
To: Gross, Mary
Cc: Rao, Ashutosh; Moscicki, Richard; Nuckolls, Glen H (NIH)
Subject: FW: support for speaker travel for FDA/NIH workshop on dystrophin

Hi Mary,

I just saw your email RE travel for Lee Sweeney. He was assigned to NINDS back in late Jan.

Chris

From: Nuckolls, Glen (NIH/NINDS) [E] [<mailto:nuckollg@ninds.nih.gov>]
Sent: Wednesday, January 28, 2015 2:28 PM
To: McInnes, Pamela (NIH/NCATS) [E]; Reid, Kelli W (NIH); Lam, Christine (NIH); Freaner, Deb K (NIH); Free, Susan B (NIH); Kaufmann, Petra (NIH)
Cc: Leptak, Christopher
Subject: support for speaker travel for FDA/NIH workshop on dystrophin

Attached is a list of speakers for the FDA/NIH dystrophin workshop that the ICs will need to travel. I revised the list that Chris sent yesterday to move one speaker (Kathryn Wagner only 35mi from Baltimore) from the NINDS to the NCATS list to match the expected 2 for NCATS and 3 for NINDS.

One wrinkle with this plan. I've learned that NIH professional services contracts should include an honorarium, but FDA cannot provide an honorarium to the people that they travel. So there may be this inconsistency between the people that are supported by NIH vs FDA. Let's, at least, be consistent among the ICs; I recommend a \$200 honorarium for each of our speakers. We should also decide about non-reimbursed local travel speakers (Eric Hoffman, Yetrib Hathout) whether they should get honoraria also.

The NIH ICs will also need a copy of the Conference Approval Request Form that the FDA has prepared for this meeting. Chris Leptak can provide this.

Glen

From: McInnes, Pamela (NIH/NCATS) [E]
Sent: Wednesday, January 21, 2015 11:19 AM
To: Nuckolls, Glen (NIH/NINDS) [E]
Cc: Reid, Kelli (NIH/NIAMS) [E]; Lam, Christine (NIH/NINDS) [E]; Freaner, Deborah (NIH/NINDS) [E]; Free, Susan (NIH/NINDS) [E]; Kaufmann, Petra (NIH/NCATS) [E]
Subject: RE: NCATS AO contact for FDA/NIH Dystrophin Workshop

Please work with me directly.

From: Free, Susan (NIH/NINDS) [E]
Sent: Wednesday, January 21, 2015 10:44 AM
To: Nuckolls, Glen (NIH/NINDS) [E]; McInnes, Pamela (NIH/NCATS) [E]; Kaufmann, Petra (NIH/NCATS) [E]
Cc: Reid, Kelli (NIH/NIAMS) [E]; Lam, Christine (NIH/NINDS) [E]; Freaner, Deborah (NIH/NINDS) [E]
Subject: RE: NCATS AO contact for FDA/NIH Dystrophin Workshop

Hi Glen,

I've already been in contact and am working with the FDA for the NINDS contribution. We are preparing an InterAgency Agreement. Each IC will prepare their own.

I hope this is helpful.

Susan Free
NINDS Budget Analyst
Bldg. 31, Rm. 8A34
301-435-7725

From: Nuckolls, Glen (NIH/NINDS) [E]
Sent: Wednesday, January 21, 2015 10:40 AM
To: McInnes, Pamela (NIH/NCATS) [E]; Kaufmann, Petra (NIH/NCATS) [E]
Cc: Reid, Kelli (NIH/NIAMS) [E]; Lam, Christine (NIH/NINDS) [E]; Free, Susan (NIH/NINDS) [E]; Freaner, Deborah (NIH/NINDS) [E]
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Pamela or Petra,
Can you provide the contact of someone in your admin office who is involved in the cofunding for this FDA/NIH workshop on dystrophin quantification? I'd like to set up a call to coordinate efforts among the AOs/budget people at the three ICs so that the support is consistent and streamlined. Thanks

Best regards,
Glen

Glen Nuckolls, Ph.D.

Program Officer, Neurogenetics Cluster
National Institute of Neurological Disorders and Stroke (NINDS)
National Institutes of Health (NIH)
6001 Executive Blvd.
Bethesda, MD 20892
glen.nuckolls@nih.gov
301-496-5876

From: [Gross, Mary](#)
To: [Leptak, Christopher](#)
Cc: [Rao, Ashutosh](#); [Moscicki, Richard](#); [Nuckolls, Glen H \(NIH\)](#); [Quartey, Elizabeth O \(NIH\)](#)
Subject: RE: support for speaker travel for FDA/NIH workshop on dystrophin
Date: Wednesday, March 11, 2015 6:09:02 PM
Attachments: [IC traveler assignments 1 27.docx](#)

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Sent: Wednesday, March 11, 2015 5:57 PM
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Cc: Reid, Kelli (NIH/NIAMS) [E]; Lam, Christine (NIH/NINDS) [E]; Freaner, Deborah (NIH/NINDS) [E]; Free, Susan (NIH/NINDS) [E]; Kaufmann, Petra (NIH/NCATS) [E]
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Best regards,
Glen

Glen Nuckolls, Ph.D.
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Professor

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NIAMS

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James M. Ervasti, Professor

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Distinguished Scholar and Research Director

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Louise R. Rodino-Klapac, Ph.D

Principal Investigator

Center for Gene Therapy

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Kevin Flanagan Kevin.Flanigan@nationwidechildrens.org

Kevin M. Flanagan, MD

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NCATS

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Fax: 020 7905 2832

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FDA

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Director, Yale Pathology Tissue Services
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fax 203-737-5089
[http://www.tissuearray.org/\[tissuearray.org\]](http://www.tissuearray.org/[tissuearray.org])
[http://www.yalepath.org/faculty.lasso?id=RimmDL\[yalepath.org\]](http://www.yalepath.org/faculty.lasso?id=RimmDL[yalepath.org])
David.Rimm@Yale.edu

Rabi Tawil Rabi_Tawil@urmc.rochester.edu
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School of Medicine and Dentistry
601 Elmwood Ave, Box 673
Rochester, NY 14642
Office: (585) 275-2559
Fax: (585) 273-1255

From: Rao, Ashutosh
To: Unger, Ellis
Cc: Moscicki, Richard; Temple, Robert; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Kaiser, James; Rogers, Hobart; Leptak, Christopher
Subject: RE: Draft dystrophin workshop slides
Date: Wednesday, March 11, 2015 3:51:04 PM

Hi Ellis,

Thanks for the suggestions. They have been incorporated into the script.

Best,
Ash

From: Unger, Ellis
Sent: Wednesday, March 11, 2015 2:29 PM
To: Rao, Ashutosh
Cc: Moscicki, Richard; Temple, Robert; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Kaiser, James; Rogers, Hobart; Leptak, Christopher
Subject: RE: Draft dystrophin workshop slides

Ash,

They look good. A few suggestions...

On slide 9, I think you want to stress specificity (or lack thereof) of the antibodies, which is what those papers are about. It's the old adage – garbage in; garbage out. Lack of specificity is not in your script, and no one will be able to read the print in the papers, obviously.

I think that slide 12 makes a few important points about IHC. First, immunostaining is a good method for localization of protein in tissue sections. Here, for example, there's no question that the protein of interest is located at the periphery of the myocytes. And immunostaining is good for categorizing cells as positive or negative, when differences between + and - are obvious. Here, for example, we'd have no trouble identifying the revertant fibers.

But immunostaining is not well suited or validated for the "gray area" between obviously positive and negative. I think you can see the difficulty in categorizing the non-revertant fibers as definitively positive or negative. The myocytes don't stain strongly, they don't stain uniformly, and technical factors are likely to be critical in determining the intensity of the staining.

Slide 13 – this slide is talking about assays that discriminate positive from negative – which gets into matters of sensitivity and specificity. If you're trying to use immunostaining to quantify a protein on a continuous scale, that is all the more difficult.

Ellis

From: Rao, Ashutosh

Sent: Wednesday, March 11, 2015 1:49 PM

To: Moscicki, Richard; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Kaiser, James; Rogers, Hobart; Leptak, Christopher

Subject: Draft dystrophin workshop slides

Hi all,

Please find attached my draft slides for the dystrophin workshop on the 20th. Please provide your input to me by next Tuesday the 17th.

Talking points or detailed scripts for what I could say for each slide are included in the notes section of each slide. There is a lot more to say on each topic but I've tried my best to prioritize relevant points from previous discussions that can be delivered in 15 minutes and keeping in mind the diversity of this audience. You can send comments and suggested talking points by email or we can set up time to talk, whichever works best for you. I will try to give this group a practice talk on the 18th during the last planning meeting after incorporating feedback.

Thanks very much.

Ash

From: [Ienzi, Georgiann](#)
To: [Gross, Mary](#); [Rao, Ashutosh](#); [Leptak, Christopher](#); [Nuckolls, Glen H \(NIH\)](#); [Moscicki, Richard](#)
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting
Date: Tuesday, March 10, 2015 12:25:34 PM

Hi,

Transportation (Strings Tour) has been arranged to take Drs. Tawil (flight at 10:00PM), Ervasti (flight at 7:16PM) and Rimm (6:25PM per his request) together to BWI. Dr. Rimm needs to leave by 4:30PM... according to the driver. Dr. Rimm and Tawil can drive together and leave at 5:15pm.

Thanks,

Georgiann

From: Gross, Mary
Sent: Tuesday, March 10, 2015 11:06 AM
To: Rao, Ashutosh; Leptak, Christopher; Nuckolls, Glen H (NIH); Moscicki, Richard
Cc: Ienzi, Georgiann
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

He could probably only stay for the panel discussion for 45 minutes but we didn't do his travel - NIH did. He may have opted for that time to get him home at a decent hour. Perhaps adding Ervasti to the panel too? - Georgi - what time does his flight leave?

From: Rao, Ashutosh
Sent: Tuesday, March 10, 2015 10:54 AM
To: Gross, Mary; Leptak, Christopher; Nuckolls, Glen H (NIH); Moscicki, Richard
Cc: Ienzi, Georgiann
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

Hi Mary,

The panel discussion ends at 5.15, I don't think that will work with his flight. Can we offer him a later flight?

Ash

From: Gross, Mary
Sent: Tuesday, March 10, 2015 9:50 AM
To: Rao, Ashutosh; Leptak, Christopher; Nuckolls, Glen H (NIH); Moscicki, Richard
Cc: Ienzi, Georgiann
Subject: FW: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

Hi - he is on our last panel and his flight leaves at 6:45 on Friday - FYI.

From: Quartey, Elizabeth (NIH/NINDS) [E] [<mailto:quarteyel@od.nih.gov>]
Sent: Tuesday, March 10, 2015 9:47 AM
To: Gross, Mary
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

He depart from Washington at 6:45PM on March 20th . Please let me know if you have questions.

From: Gross, Mary (FDA/CDER)
Sent: Tuesday, March 10, 2015 9:33 AM
To: Quartey, Elizabeth (NIH/NINDS) [E]
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

Hi – I meant when does he leave Washington to go home? Thanks. -- mary

From: Quartey, Elizabeth (NIH/NINDS) [E] [<mailto:quarteyel@od.nih.gov>]
Sent: Tuesday, March 10, 2015 9:27 AM
To: Gross, Mary
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

You welcome! He depart Seattle, Washington at 8:20 AM on March 19th and gets into Washington at 4:14PM.

From: Gross, Mary (FDA/CDER)
Sent: Tuesday, March 10, 2015 7:49 AM
To: Quartey, Elizabeth (NIH/NINDS) [E]
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

Thanks Liz – What is Jeff Chamberlain's departure time? He's on our last panel. - Mary

From: Quartey, Elizabeth (NIH/NINDS) [E] [<mailto:quarteyel@od.nih.gov>]
Sent: Monday, March 09, 2015 5:57 PM
To: Gross, Mary; Reid, Kelli W (NIH); Reid, Kelli W (NIH)
Cc: Nuckolls, Glen H (NIH); Ienzi, Georgiann
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

Hi Mary,

I left you a voicemail message this morning in reference to your email but have not heard back from you.

Travel arrangements was made for Drs. Zarife Sahenk and Jeff Chamberlain, has been completed and ticketed itinerary has been forwarded to both participants. Travelers did call the hotel and made their reservations as well. Please let me know if you want me to forward their ticketed itinerary to you for your information. Also, I will prepare their vouchers for reimbursement for hotel, taxi, and others receipts after the meeting on March 20th.

Let me know if you have questions.

From: Gross, Mary (FDA/CDER)
Sent: Friday, March 06, 2015 1:49 PM
To: Reid, Kelli (NIH/NIAMS) [E]; Reid, Kelli (NIH/NIAMS) [E]; Quartey, Elizabeth (NIH/NINDS) [E]
Cc: Nuckolls, Glen (NIH/NINDS) [E]; Ienzi, Georgiann (FDA/CDER)
Subject: FW: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

Hi – NIH and FDA are sharing responsibilities for traveling in and providing per diem for approximately 20 speakers who have been invited to speak at the Dystrophin Methodologies meeting being held at the FDA White Oak Campus on March 20. Your names have been identified as responsible for arranging travel on behalf of NIH. I'm the project manager for the meeting from FDA. Georgiann Ienzi is managing the travel process on behalf of FDA assigned speakers.

Would each of you send me your list of speakers that includes hotel information, per diem practices (eg, do they need to save their receipts) and the flight arrival and departure times? I'd like to have a master list of speakers with itinerary information with us the day of the meeting. Would you also send your phone numbers with the information?

Thanks!

Mary

From: Nuckolls, Glen (NIH/NINDS) [E] [<mailto:nuckollg@ninds.nih.gov>]
Sent: Friday, March 06, 2015 11:51 AM
To: Gross, Mary; Ienzi, Georgiann; Rao, Ashutosh
Cc: Leptak, Christopher
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

Liz Quartey for NINDS (quarteyel@mail.nih.gov)
Jackie Gibson at NCATS (jgibson@mail.nih.gov)
Kelli Reid at NIAMS (reidkw@mail.nih.gov)

From: [Gross, Mary](#)
To: [Unger, Ellis](#); [Moscicki, Richard](#)
Cc: [Rao, Ashutosh](#); [Farkas, Ronald](#); [Leptak, Christopher](#); [Ienzi, Georgiann](#)
Subject: RE: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)
Date: Tuesday, March 10, 2015 11:34:55 AM

There will be long lines – There is also likely a meeting going on in rooms b and c. I'm going to ask them to open the back side of the kiosk for the speakers only so they can get their lunches a little quicker.

From: Unger, Ellis
Sent: Tuesday, March 10, 2015 11:20 AM
To: Gross, Mary; Moscicki, Richard
Cc: Rao, Ashutosh; Farkas, Ronald; Leptak, Christopher; Ienzi, Georgiann
Subject: RE: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)

We'll just need to direct people to be efficient in getting their lunches. Presumably, they can carry their lunches back to their chairs, in which case there won't be a problem because people can continue to eat at the beginning of the PM session.

From: Gross, Mary
Sent: Tuesday, March 10, 2015 8:06 AM
To: Unger, Ellis; Moscicki, Richard
Cc: Rao, Ashutosh; Farkas, Ronald; Leptak, Christopher; Ienzi, Georgiann
Subject: RE: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)

Hi -- Yes -- We'll need to use the timer light and moderators will need to tell speakers when they are close to their time being up. I'll be tapping the moderators on the shoulder if anyone runs too long. We have to stick to the agenda as far as our snack and lunch time too because the kiosk opens and closes based on the agenda. Finally, I'm concerned about getting our speakers fed within the ½ hour allotted for lunch. There are quite a few patients and patient advocates in the audience. How do they usually behave? I presume someone will give them a little shout out in opening remarks?

Thanks.

Mary

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Sent: Monday, March 09, 2015 5:22 PM
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Cc: Rao, Ashutosh; Farkas, Ronald; Leptak, Christopher; Ienzi, Georgiann
Subject: RE: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)

OK. I'm happy to do that (as long as I can make a 10 PM flight out of BWI...).

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Sent: Monday, March 09, 2015 5:18 PM
To: Unger, Ellis; Gross, Mary
Cc: Rao, Ashutosh; Farkas, Ronald; Leptak, Christopher; Ienzi, Georgiann
Subject: RE: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)

On reflection, I am ok with chris austen and I having 5-10 minutes each and Ash 15-20 minutes. Ellis it would be grand if you could state what you heard in the day, your take aways, and id action items. Rich.

From: Unger, Ellis
Sent: Monday, March 09, 2015 5:15 PM
To: Gross, Mary
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Leptak, Christopher; Ienzi, Georgiann
Subject: RE: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)

All,

This is an incredibly ambitious agenda! I'm concerned about the number of talks, especially because many of the speakers and panelists are going to have a tendency to go over their time. We'll need to keep on top of the agenda!

In the interest of building in more time to talk about the science, I've been given 15 minutes at the very end to speak (5:15 – 5:30 PM). I'm not sure if I'm supposed to say simply "thank you for coming, you've been great" or whether the sense is that I should try to give an actual summary of lessons learned. But under the circumstances, it doesn't seem worthwhile to try to recapitulate the day's proceedings. So I suggest that I limit my closing remarks to 5 minutes or so, and simply congratulate everyone and say "thanks" - - if people are OK with that.

Similarly, in the morning there are 3 speakers scheduled to give opening remarks for 45 minutes (8:30 to 9:15), and that seems excessive to me. I think it would be advantageous to shorten that segment a bit, with the permission of the 3 speakers.

Also, at the top of page 1, below the title and date of the workshop, it would be good to write the workshop location.

Ellis

From: Gross, Mary
Sent: Monday, March 09, 2015 4:03 PM
To: Austin, Christopher P (NIH); jervasti@umn.edu; jsc5@uw.edu; David.Rimm@Yale.edu;

(b) (5) c.beekman@prosensa.nl; Louise.Rudino-Klapac@nationwidechildrens.org; zarife.sahenk@nationwidechildrens.org; YHathaout@childrensnational.org; ehoffman@childrensnational.org; lsweeney@mail.med.upenn.edu; Rabi_Tawil@urmc.rochester.edu; Nuckolls, Glen H (NIH); Rao, Ashutosh; Moscicki, Richard; Farkas, Ronald; Sardone, Valentina; Flanigan, Kevin; Unger, Ellis; Sebahattin Cirak; Babiak, John; Pat Furlong; John Porter; wagnerk@kennedykrieger.org; psazani@sarepta.com

Cc: Leptak, Christopher; Ienzi, Georgiann

Subject: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)

Dear Speakers and Moderators – Please see the next version of the draft agenda for the March 20, 2015 scientific workshop entitled “Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data”. As you will see, the agenda is extremely full. We have added a couple of speakers so we need to ask speakers to limit remarks to between 12 and 15 minutes. There is time built in on the agenda after panels 2 and 3 for discussion.

Would you mind reviewing this agenda once more and correct any inaccuracies or anything you want changed at this time and return to me no later than March 11. And please remember that slides are due no later than Friday, March 13.

Please do not share this agenda as it hasn't been formally released.

Thanks so much and we look forward to seeing you on March 20 at FDA's White Oak Campus in Silver Spring, MD.

<< File: Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx

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From: [Gross, Mary](#)
To: [jsc5@uw.edu](#); [Wagner, Kathryn](#); [lsweeney@mail.med.upenn.edu](#); [ehoffman@childrensnational.org](#); [Flanigan, Kevin](#); [John Porter](#); [Mosicki, Richard](#)
Cc: [Nuckolls, Glen H \(NIH\)](#); [Rao, Ashutosh](#); [Leptak, Christopher](#); [Farkas, Ronald](#); [Ienzi, Georgiann](#)
Subject: Request to be discussants on Panel 4 - March 20 Dystrophin Meeting - Response needed
Date: Tuesday, March 10, 2015 10:20:26 AM
Attachments: [Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx](#)

Hi - you are participating as speakers during the March 20 scientific workshop on Dystrophin methodologies. As the last panel, we are holding an interactive discussion to wrap up the day with specific questions and feedback from the audience. You have been nominated to participate as part of this panel. We'd like to do a call on March 16 at 4:30 (eastern standard time) to discuss this role. I'm also attaching the draft agenda so you can review this session. Would you let me know if this time works out for you?

Thanks so much!

TCON number 877 704 7717; PC (b) (4)

Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data
March 20th 2015
Scientific Workshop

Scope of the meeting: Recent advances in drug development for Duchenne Muscular Dystrophy (DMD) present an opportunity for the development and validation of robust methods for the objective, reliable, and quantitative measurement of dystrophin and related muscle proteins. This workshop, cosponsored by the Food and Drug Administration and the National Institutes of Health was convened in order to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development.

Agenda

- 7:30 am Registration
- 8:30 am Opening Remarks
Christopher P. Austin, M.D., Director, National Center for Advancing
Translational Sciences, National Institutes of Health (NIH)
- 8:45 am Richard A. Moscicki, M.D., Deputy Center Director for Science Operations,
Center for Drug Evaluation and Research (CDER), Food and Drug
Administration (FDA)
- 9:00 am Dystrophin: Convening the Conversation - Patricia Furlong, President, Parent
Project Muscular Dystrophy
- 9:15 am Background and Meeting Objectives Related to Analytical Challenges and
Opportunities with Dystrophin Methodologies - Ashutosh Rao, PhD, Senior
Investigator, Division of Biotechnology Research and Review, Office of
Biotechnology Products, CDER, FDA
- Session I: The Dystrophin Gene and Protein - Glen Nuckolls, PhD, Executive Secretary,
Muscular Dystrophy Coordinating Committee, Program Officer, Neurogenetics
Cluster, National Institute of Neurological Disorders and Stroke, NIH and
Ashutosh Rao, PhD - Moderators
- This session will provide a background on current understanding of the
 dystrophin gene and its various products and associated proteins as they relate to
 protein quantification methodologies and assays of dystrophin function in DMD
 and BMD.
- 9:30 am Dystrophin Quantitation Using Full-Length Recombinant Protein as Standard -
James M. Ervasti, Paul and Sheila Wellstone Muscular Dystrophy Center,
University of Minnesota, Minneapolis, MN

- 9:45 am Expression of Exogenous Dystrophin, Isoforms, Splice Products and Synthetic Constructs - Jeff Chamberlain, Departments of Neurology, Medicine and Biochemistry, University of Washington, Seattle, WA
- 10:00 am Break
- Session II: Dystrophin Quantification Methodologies - Glen Nuckolls, PhD, Ron Farkas, MD, PhD, Clinical Team Leader, Division of Neurology products, Office of Drug Evaluation 1, CDER, FDA - Moderators
- This session will focus on identifying key technologies, their limitations including detection and quantification sensitivities, linearity, reproducibility, and identified development and validation needs/hurdles for each method. Published and unpublished data using each method on human normal and disease samples will be discussed. Image and other data analysis, as well as statistical methods will also be discussed.
- 10:15 am Antibody Probes for Dystrophin Protein Detection - Glenn E. Morris, D.Phil., Professor of Biochemistry, Wolfson Centre for Inherited Neuromuscular Disease, RJA Orthopaedic Hospital and Keele University, Oswestry, UK
- Immunohistochemistry/fluorescence and Image Analysis
- 10:30 am Detailed Methodology of Dystrophin Quantification – Valentina Sardone, London, UK (title, credentials)?
- 10:45 am Changes and Variability in Dystrophin Detection: Immunofluorescence, Antibody Staining and Imaging Methodologies - Chantal AC Beekman, Prosensa, Leiden, Netherlands, Afrodite Lourakis, Prosensa, Leiden, Netherlands (looking for 1 name)
- 11:00 am Methodology for Quantification of Dystrophin using Widefield Fluorescence Microscope – Zarife Sahenk, MD, PhD, Professor, Director of Clinical and Experimental Neuromuscular Laboratories, The Research Institute at Nationwide Children’s Hospital, Columbus, OH
- 11:10 am Assessment of Mean Fluorescence Signal Intensity of Muscle Fibers Expressing Dystrophin - Louise R. Rodino-Klapac, Principal Investigator, The Research Institute at Nationwide Children’s Hospital, Columbus, OH
- 11:20 am A Comprehensive Approach to Quantifiable and Meaningful Dystrophin Measurements in Clinical Trials – Peter Sazani, PhD, Executive Director, Medical Affairs, Sarepta Therapeutics
- 11:35 am Defining Standards for Dystrophin Quantification in DMD Muscle Biopsies - John Babiak, PhD, Senior Vice President, Drug Discovery Technologies, PTC Therapeutics, Inc

11:50 am Quantitative In-Situ Measurement of Biomolecules for Companion Diagnostics - David Rimm, MD, PhD, Yale University School of Medicine, New Haven, CT

12:05 pm Panel Discussion - Dystrophin Quantification by Histological Methods

12:45 pm Lunch

Session II continued – Glen Nuckolls, PhD, Ashutosh Rao, PhD - Moderators

1:15 pm Dystrophin Quantification in Clinical Trials - Sebahattin Cirak

1:30 pm Western Blotting - Kevin Flanigan The Research Institute at Nationwide Children's Hospital, Columbus, OH (need title)

1:45 pm Targeted Quantification of Dystrophin by Mass Spectrometry and Comparison to Antibody Based Assays - Yetrib Hathout, PhD, Center for Genetic Medicine, Children's National Medical Center, Washington, DC

2:00 pm Variable Dystrophin Content within Myofibers, between Myofibers, and between Regions of Muscles: Determining the Level of Dystrophin that makes a Clinical Impact in BMD and Manifesting Carriers of DMD - Eric Hoffman, MD, Center for Genetic Medicine, Children's National Medical Center, Washington, DC

2:15 pm Panel Discussion - Dystrophin Quantification from Tissue Extracts

Session III: Muscle Biopsies and Sample Handling (Moderators: Glen Nuckolls, PhD, Ron Farkas, MD)

This session will focus on muscle biopsy collection procedures (open and needle), anatomical site selection, guided versus non-guided biopsy, experiences with muscle biopsy handling and processing, and reference tissue banks.

2:45 pm Methods of Muscle Sampling - Rabi Tawil, MD, Professor of Neurology, University of Rochester Medical Center, Rochester, NY

3:00 pm Open versus needle muscle biopsy - Kathryn Wagner, MD, PhD, Center for Genetic Muscle Disorders, Kennedy Krieger Institute, Baltimore, MD

3:15 pm MRI/MRS Assessment of the Status of Skeletal Muscle in DMD Patients - Lee Sweeney, PhD, William Maul Measey Professor of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA

3:30 pm Break

Session IV Facilitated Panel Discussion

3:45 pm John Porter, PhD, Chief Executive Officer, Parent Project Muscular Dystrophy and Richard A. Moscicki, MD - Moderators

Panelists: Jeff Chamberlain, Kevin Flanigan, MD, Eric Hoffman, MD, Katherine Wagner, MD, Lee Sweeney, PhD

1. What is the current status of assay validation and methodology for quantification of dystrophin in the context of drug development? What are the key opportunities and knowledge gaps in the field?
2. What are the necessary next steps to advance the precision and reproducibility of technology to acquire, measure, and analyze the proteins that are associated with Duchenne muscular dystrophy?
3. What are the Action Items from this workshop that will continue to advance robust methods for the objective, reliable, and quantitative measurement of dystrophin and dystrophin-related muscle proteins?

5:15 pm Closing Remarks
 Ellis Unger, MD, FDA

5:30 pm Adjournment

From: [Gross, Mary](#)
To: [Rao, Ashutosh](#); [Leptak, Christopher](#); [Nuckolls, Glen H \(NIH\)](#); [Moscicki, Richard](#)
Cc: [Ienzi, Georgiann](#)
Subject: FW: Managing Speaker Travel, hotel etc. - Dystrophin Meeting
Date: Tuesday, March 10, 2015 9:50:00 AM

Hi – he is on our last panel and his flight leaves at 6:45 on Friday – FYI.

From: Quartey, Elizabeth (NIH/NINDS) [E] [<mailto:quarteyel@od.nih.gov>]
Sent: Tuesday, March 10, 2015 9:47 AM
To: Gross, Mary
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

He depart from Washington at 6:45PM on March 20th . Please let me know if you have questions.

From: Gross, Mary (FDA/CDER)
Sent: Tuesday, March 10, 2015 9:33 AM
To: Quartey, Elizabeth (NIH/NINDS) [E]
Subject: RE: Managing Speaker Travel, hotel etc. - Dystrophin Meeting

Hi – I meant when does he leave Washington to go home? Thanks. -- mary

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To: [Unger, Ellis](#); [Moscicki, Richard](#)
Cc: [Rao, Ashutosh](#); [Farkas, Ronald](#); [Leptak, Christopher](#); [Ienzi, Georgiann](#)
Subject: RE: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)
Date: Tuesday, March 10, 2015 8:43:50 AM

It's probably a good idea to encourage people to write questions on index cards that are collected and can be used for the discussion part of this meeting and using the microphone from the floor sparingly. Something to think about.

Mary

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Sent: Tuesday, March 10, 2015 8:06 AM
To: Unger, Ellis; Moscicki, Richard
Cc: Rao, Ashutosh; Farkas, Ronald; Leptak, Christopher; Ienzi, Georgiann
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All,

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To: Austin, Christopher P (NIH); jervasti@umn.edu; jsc5@uw.edu; David.Rimm@Yale.edu; [\(b\) \(6\); c.beekman@prosensa.nl](mailto:(b) (6); c.beekman@prosensa.nl); Louise.Rudino-Klapac@nationwidechildrens.org; zarife.sahenk@nationwidechildrens.org; YHathaout@childrensnational.org; ehoffman@childrensnational.org; lsweeney@mail.med.upenn.edu; Rabi_Tawil@urmc.rochester.edu; Nuckolls, Glen H (NIH); Rao, Ashutosh; Moscicki, Richard; Farkas, Ronald; Sardone, Valentina; Flanigan, Kevin; Unger, Ellis; Sebahattin Cirak; Babiak, John; Pat Furlong; John Porter; wagnerk@kennedykrieger.org; psazani@sarepta.com
Cc: Leptak, Christopher; Ienzi, Georgiann
Subject: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11

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To: Austin, Christopher P (NIH); jervasti@umn.edu; jsc5@uw.edu; David.Rimm@Yale.edu; (b) (6)
c.beekman@prosensa.nl; Louise.Rudino-Klapac@nationwidechildrens.org;
zarife.sahenk@nationwidechildrens.org; YHathaout@childrensnational.org; ehoffman@childrensnational.org;
Isweeney@mail.med.upenn.edu; Rabi.Tawil@urmc.rochester.edu; Nuckolls, Glen H (NIH); Rao, Ashutosh;
Moscicki, Richard; Farkas, Ronald; Sardone, Valentina; Flanigan, Kevin; Unger, Ellis; Sebahattin Cirak; Babiak,
John; Pat Furlong; John Porter; wagnerk@kennedykrieger.org; psazani@sarepta.com
Cc: Lentak, Christopher; Tenzi, Georgiann
Subject: Refined Agenda for March 20 FDA and NIH Dystrophin Meeting - for comment (due by noon Wednesday, March 11)
Date: Monday, March 09, 2015 4:02:52 PM
Attachments: Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx

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Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data
March 20th 2015
Scientific Workshop

Scope of the meeting: Recent advances in drug development for Duchenne Muscular Dystrophy (DMD) present an opportunity for the development and validation of robust methods for the objective, reliable, and quantitative measurement of dystrophin and related muscle proteins. This workshop, cosponsored by the Food and Drug Administration and the National Institutes of Health was convened in order to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development.

Agenda

- 7:30 am Registration
- 8:30 am Opening Remarks
Christopher P. Austin, M.D., Director, National Center for Advancing Translational Sciences, National Institutes of Health (NIH)
- 8:45 am Richard A. Moscicki, M.D., Deputy Center Director for Science Operations, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)
- 9:00 am Dystrophin: Convening the Conversation - Patricia Furlong, President, Parent Project Muscular Dystrophy
- 9:15 am Background and Meeting Objectives Related to Analytical Challenges and Opportunities with Dystrophin Methodologies - Ashutosh Rao, PhD, Senior Investigator, Division of Biotechnology Research and Review, Office of Biotechnology Products, CDER, FDA
- Session I: The Dystrophin Gene and Protein - Glen Nuckolls, PhD, Executive Secretary, Muscular Dystrophy Coordinating Committee, Program Officer, Neurogenetics Cluster, National Institute of Neurological Disorders and Stroke, NIH and Ashutosh Rao, PhD - Moderators
- This session will provide a background on current understanding of the dystrophin gene and its various products and associated proteins as they relate to protein quantification methodologies and assays of dystrophin function in DMD and BMD.
- 9:30 am Dystrophin Quantitation Using Full-Length Recombinant Protein as Standard - James M. Ervasti, Paul and Sheila Wellstone Muscular Dystrophy Center, University of Minnesota, Minneapolis, MN

- 9:45 am Expression of Exogenous Dystrophin, Isoforms, Splice Products and Synthetic Constructs - Jeff Chamberlain, Departments of Neurology, Medicine and Biochemistry, University of Washington, Seattle, WA
- 10:00 am Break
- Session II: Dystrophin Quantification Methodologies - Glen Nuckolls, PhD, Ron Farkas, MD, PhD, Clinical Team Leader, Division of Neurology products, Office of Drug Evaluation 1, CDER, FDA - Moderators
- This session will focus on identifying key technologies, their limitations including detection and quantification sensitivities, linearity, reproducibility, and identified development and validation needs/hurdles for each method. Published and unpublished data using each method on human normal and disease samples will be discussed. Image and other data analysis, as well as statistical methods will also be discussed.
- 10:15 am Antibody Probes for Dystrophin Protein Detection - Glenn E. Morris, D.Phil., Professor of Biochemistry, Wolfson Centre for Inherited Neuromuscular Disease, RJA Orthopaedic Hospital and Keele University, Oswestry, UK
- Immunohistochemistry/fluorescence and Image Analysis
- 10:30 am Detailed Methodology of Dystrophin Quantification – Valentina Sardone, London, UK (title, credentials)?
- 10:45 am Changes and Variability in Dystrophin Detection: Immunofluorescence, Antibody Staining and Imaging Methodologies - Chantal AC Beekman, Prosensa, Leiden, Netherlands, Afrodite Lourakis, Prosensa, Leiden, Netherlands (looking for 1 name)
- 11:00 am Methodology for Quantification of Dystrophin using Widefield Fluorescence Microscope – Zarife Sahenk, MD, PhD, Professor, Director of Clinical and Experimental Neuromuscular Laboratories, The Research Institute at Nationwide Children’s Hospital, Columbus, OH
- 11:10 am Assessment of Mean Fluorescence Signal Intensity of Muscle Fibers Expressing Dystrophin - Louise R. Rodino-Klapac, Principal Investigator, The Research Institute at Nationwide Children’s Hospital, Columbus, OH
- 11:20 am A Comprehensive Approach to Quantifiable and Meaningful Dystrophin Measurements in Clinical Trials – Peter Sazani, PhD, Executive Director, Medical Affairs, Sarepta Therapeutics
- 11:35 am Defining Standards for Dystrophin Quantification in DMD Muscle Biopsies - John Babiak, PhD, Senior Vice President, Drug Discovery Technologies, PTC Therapeutics, Inc

- 11:50 am Quantitative In-Situ Measurement of Biomolecules for Companion Diagnostics - David Rimm, MD, PhD, Yale University School of Medicine, New Haven, CT
- 12:05 pm Panel Discussion - Dystrophin Quantification by Histological Methods
- 12:45 pm Lunch
- Session II continued – Glen Nuckolls, PhD, Ashutosh Rao, PhD - Moderators
- 1:15 pm Dystrophin Quantification in Clinical Trials - Sebahattin Cirak
- 1:30 pm Western Blotting - Kevin Flanigan The Research Institute at Nationwide Children’s Hospital, Columbus, OH (need title)
- 1:45 pm Targeted Quantification of Dystrophin by Mass Spectrometry and Comparison to Antibody Based Assays - Yetrib Hathout, PhD, Center for Genetic Medicine, Children’s National Medical Center, Washington, DC
- 2:00 pm Variable Dystrophin Content within Myofibers, between Myofibers, and between Regions of Muscles: Determining the Level of Dystrophin that makes a Clinical Impact in BMD and Manifesting Carriers of DMD - Eric Hoffman, MD, Center for Genetic Medicine, Children’s National Medical Center, Washington, DC
- 2:15 pm Panel Discussion - Dystrophin Quantification from Tissue Extracts
- Session III: Muscle Biopsies and Sample Handling (Moderators: Glen Nuckolls, PhD, Ron Farkas, MD)
- This session will focus on muscle biopsy collection procedures (open and needle), anatomical site selection, guided versus non-guided biopsy, experiences with muscle biopsy handling and processing, and reference tissue banks.
- 2:45 pm Methods of Muscle Sampling - Rabi Tawil, MD, Professor of Neurology, University of Rochester Medical Center, Rochester, NY
- 3:00 pm Open versus needle muscle biopsy - Kathryn Wagner, MD, PhD, Center for Genetic Muscle Disorders, Kennedy Krieger Institute, Baltimore, MD
- 3:15 pm MRI/MRS Assessment of the Status of Skeletal Muscle in DMD Patients - Lee Sweeney, PhD, William Maul Measey Professor of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA
- 3:30 pm Break
- Session IV Facilitated Panel Discussion
- 3:45 pm John Porter, PhD, Chief Executive Officer, Parent Project Muscular Dystrophy and Richard A. Moscicki, MD - Moderators

Panelists: Jeff Chamberlain, Kevin Flanigan, MD, Eric Hoffman, MD, Katherine Wagner, MD, Lee Sweeney, PhD

1. What is the current status of assay validation and methodology for quantification of dystrophin in the context of drug development? What are the key opportunities and knowledge gaps in the field?
2. What are the necessary next steps to advance the precision and reproducibility of technology to acquire, measure, and analyze the proteins that are associated with Duchenne muscular dystrophy?
3. What are the Action Items from this workshop that will continue to advance robust methods for the objective, reliable, and quantitative measurement of dystrophin and dystrophin-related muscle proteins?

5:15 pm Closing Remarks
 Ellis Unger, MD, FDA

5:30 pm Adjournment

From: [Gross, Mary](#)
To: [Moscicki, Richard](#); [Rao, Ashutosh](#); [Leptak, Christopher](#); [Nuckolls, Glen H \(NIH\)](#)
Subject: Do you want a conference call with Panel 4 Discussants (dystrophin) scheduled? I don't believe they have been invited to participate on this panel yet.
Date: Friday, March 06, 2015 2:25:56 PM

From: [Parekh, Ameeta](#)
To: [Moscicki, Richard](#)
Cc: [Clingman, Chekesha](#); [Buckman-Garner, ShaAvhrée](#)
Subject: RE: Nice to meet & question.
Date: Sunday, March 05, 2017 7:36:47 PM

Hi Dr. Moscicki, thanks for forwarding. I will share this with Dr. Chekesha Clingman who leads the CPIM effort.

Ameeta

From: Moscicki, Richard <Richard.Moscicki@fda.hhs.gov>
Date: March 5, 2017 at 6:12:15 PM EST
To: 'UsinLife LLC' <atgc@usinlife.com>
Cc: Parekh, Ameeta <Ameeta.Parekh@fda.hhs.gov>
Subject: RE: Nice to meet & question.

Ameeta Parekh in OTS

From: UsinLife LLC [mailto:atgc@usinlife.com]
Sent: Thursday, March 02, 2017 1:54 PM
To: Moscicki, Richard
Subject: Nice to meet & question.

Hello Richard,

It was good to meet at the Jett Foundation luncheon and though we spoke briefly, enjoyed our conversation.

We spoke about [REDACTED] (b) (4)

[REDACTED] You had mentioned that I should reach out to "Critical Path Innovation". Can you please forward the email or let me know the best person to contact?

Thank you for the wonderful thought provoking talk and lively discussion!

Anil

Anil Tarachandani, PhD.

Founder, Usin'Life LLC

Tel: (347) 542 7466



www.usinlife.com

From: [Gross, Mary](#)
To: [Rao, Ashutosh](#); [Leptak, Christopher](#); [Nuckolls, Glen H \(NIH\)](#); [Moscicki, Richard](#); [Farkas, Ronald](#)
Subject: FW: Newest Dystrophin Agenda
Date: Thursday, March 05, 2015 1:14:24 PM
Attachments: [Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx](#)

Here is the revised agenda with speakers at 15 minute increments (except nationwide). If you have comments, please send them back to me. Thanks.

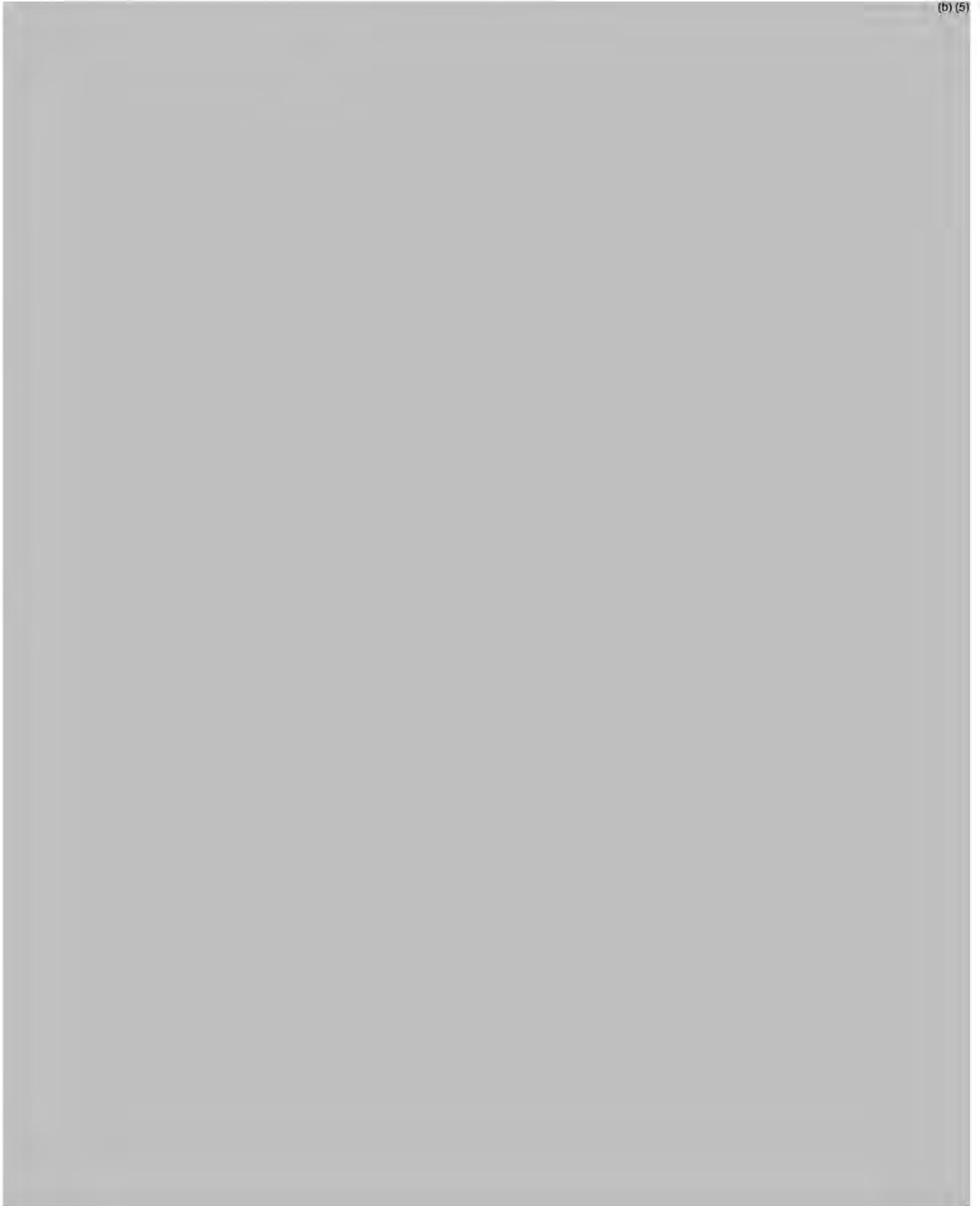
Mary

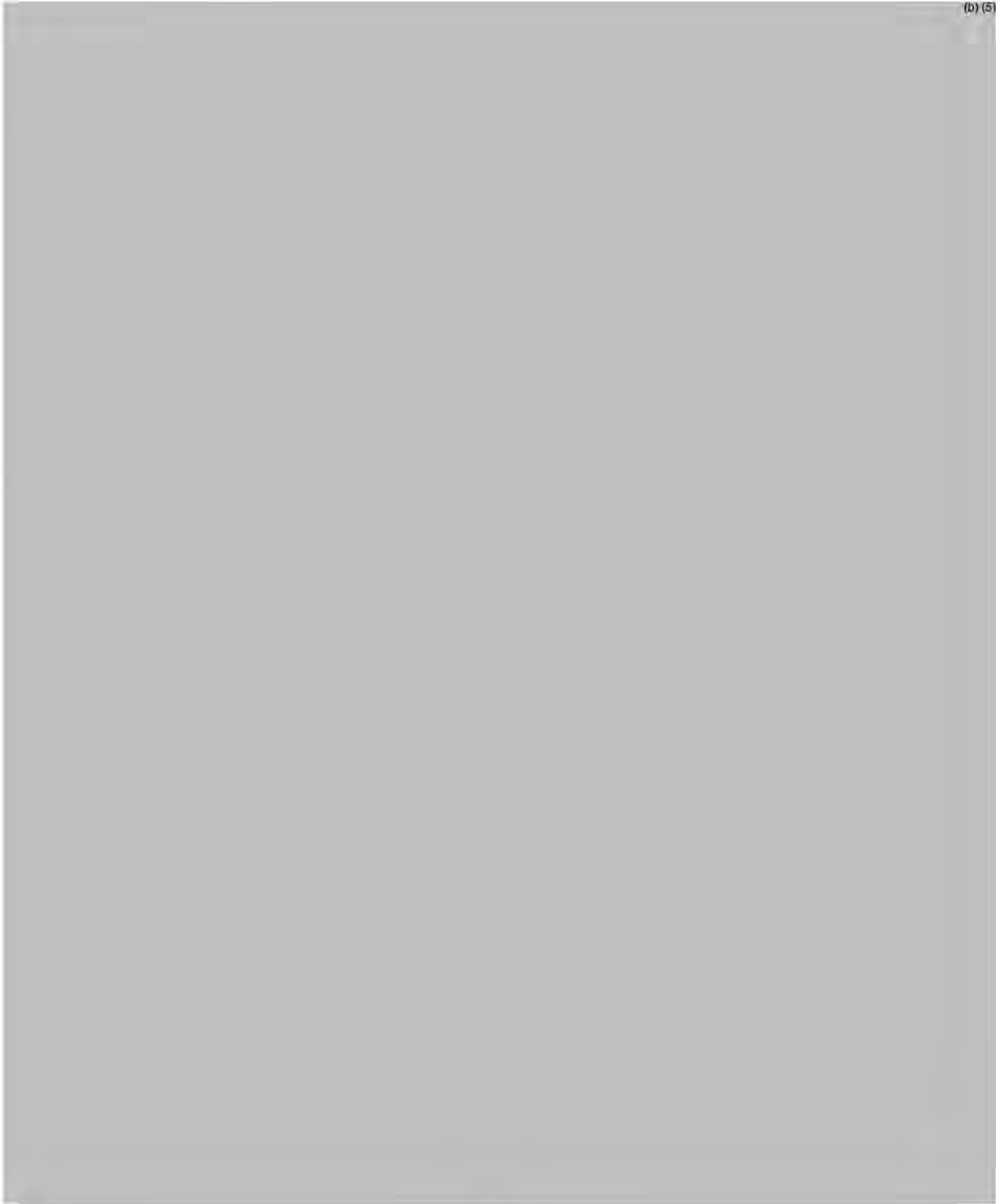
From: Gross, Mary
Sent: Wednesday, March 04, 2015 4:36 PM
To: Gross, Mary
Subject: FW: Newest Dystrophin Agenda

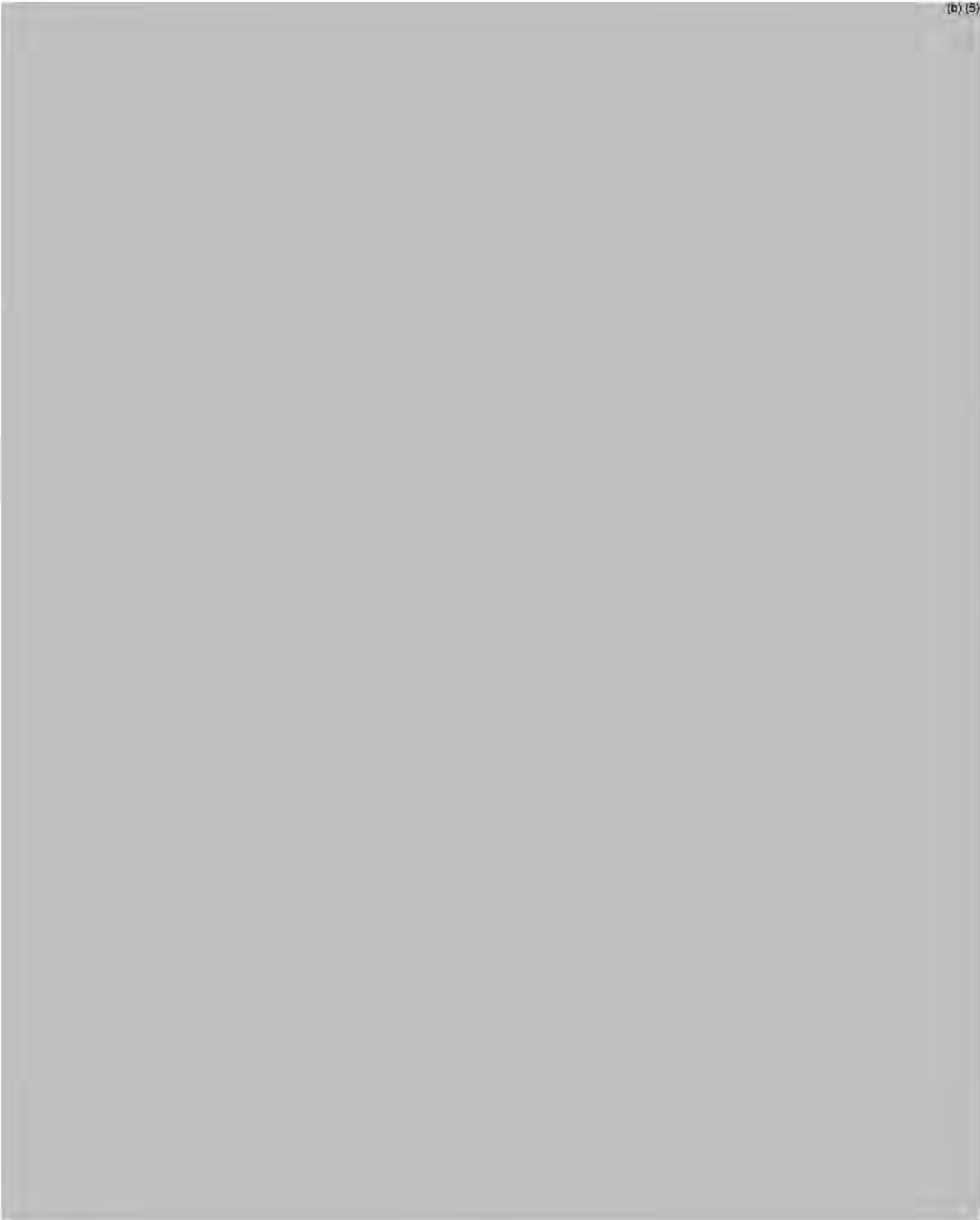
From: Gross, Mary
Sent: Tuesday, March 03, 2015 1:12 PM
To: Gross, Mary
Subject:

Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data
March 20th 2015

(b) (5)









From: [Gross, Mary](#)
To: [Rao, Ashutosh](#); [Leptak, Christopher](#); [Nuckolls, Glen H \(NIH\)](#); [Moscicki, Richard](#)
Subject: FW: Speaker for Dystrophin meeting
Date: Thursday, March 05, 2015 11:44:34 AM

FYI

From: Babiak, John [<mailto:jbabiak@ptcbio.com>]
Sent: Thursday, March 05, 2015 11:14 AM
To: Gross, Mary
Cc: Peltz, Stuart; Sniecinski, Megan
Subject: Speaker for Dystrophin meeting

Mary,

I will be speaking at the Dystrophin meeting on 20 March. Please add me to the list for information and updates.

Regards,

John

John Babiak, PhD
Senior Vice President, Drug Discovery Technologies
PTC Therapeutics, Inc
www.ptcbio.com

E-mail: jbabiak@ptcbio.com
Office: 908-912-9117
Cell: (b) (6)

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From: [Gross, Mary](#)
To: [Leptak, Christopher](#); [Moscicki, Richard](#); [Rao, Ashutosh](#); [Nuckolls, Glen H \(NIH\)](#); [Ienzi, Georgiann](#); [Boyce, Amanda T \(NIH\)](#); [Kaufmann, Petra \(NIH\)](#); [Farkas, Ronald](#); pmcinnes@mail.nih.gov
Subject: RE: Hold for Sarepta call on Dystrophin Workshop
Date: Thursday, March 05, 2015 7:34:01 AM

Agree - please call the toll free number at 8:30 am from home. -- thanks. Mary

-----Original Message-----

From: Leptak, Christopher

Sent: Thursday, March 05, 2015 6:51 AM

To: Gross, Mary; Moscicki, Richard; Rao, Ashutosh; Nuckolls, Glen H (NIH); Ienzi, Georgiann; Boyce, Amanda T (NIH); Kaufmann, Petra (NIH); Farkas, Ronald; pmcinnes@mail.nih.gov

Subject: Hold for Sarepta call on Dystrophin Workshop

All fed offices are closed, recommend we still have the call to be able to finalize speakers and agenda.

Chris

From: [Rao, Ashutosh](#)
To: [Moscicki, Richard](#)
Cc: [Leptak, Christopher](#); [Farkas, Ronald](#); [Gross, Mary](#)
Subject: RE: Dystrophin Workshop - Mar 20
Date: Monday, March 02, 2015 11:14:36 AM

Hi Mary,

Could you please help set up this call with Sarepta? Rich and I just discussed and we will propose to Sarepta that they work with their NCH partners to incorporate their viewpoints on the slides by NCH speakers. I am flexible between 12.30-3.30 today. Please include the usual suspects on the call and Rich, if it works for his schedule.

Thanks
Ash

From: Rao, Ashutosh
Sent: Monday, March 02, 2015 10:57 AM
To: Moscicki, Richard
Cc: Leptak, Christopher; Farkas, Ronald; Gross, Mary
Subject: RE: Dystrophin Workshop - Mar 20

Hi Rich,

Thanks. I can check with Mary about setting up a call with Sarepta to discuss having Ed Kaye or someone from technical side participate in the workshop. Would you like to be on that call?

Best,
Ash

From: Moscicki, Richard
Sent: Sunday, March 01, 2015 11:12 PM
To: Rao, Ashutosh
Subject: RE: Dystrophin Workshop - Mar 20

I think that's the best approach

From: Rao, Ashutosh
Sent: Friday, February 27, 2015 3:25 PM
To: Moscicki, Richard; Leptak, Christopher
Subject: RE: Dystrophin Workshop - Mar 20

Session II has 11 speakers in a less than 4 hour span that includes a working lunch, it's going to be very tough to manage with any more. Can we ask Sarepta to work with their NCH collaborators to work together on the slides? If you feel strongly about this, we can take away 5 minutes from my talk (down to 10 min) and 10 from the panel discussion (down to 65 mins) and make room for Ed Kaye. Please advise.

From: Moscicki, Richard
Sent: Friday, February 27, 2015 3:15 PM
To: Rao, Ashutosh; Leptak, Christopher

Subject: FW: Dystrophin Workshop - Mar 20

I know we thought we were including them by including Nationwide Children's but what do you think? Ed Kaye of Sarepta

From: Diane Berry [mailto:DBerry@Sarepta.com]
Sent: Friday, February 27, 2015 3:05 PM
To: Gross, Mary
Cc: Moscicki, Richard
Subject: Dystrophin Workshop - Mar 20

Hi Mary,

Thanks so much for sharing the tentative agenda with me yesterday. Before the agenda is finalized, I would like to ask the FDA to consider including Sarepta representation on the Session II panel "Dystrophin Quantification Methodologies." It is an exciting time for the Duchenne community with a lot of hope residing on several drugs in clinical trials. Three of those drugs are aimed at restoring dystrophin but we note that only 2 of the 3 companies sponsoring these studies have been given the opportunity to participate in the workshop discussion. We believe the addition of Sarepta would lead to a more scientifically balanced and productive discussion regarding the state of the art, strengths, limitations, and areas to improve upon. Sarepta has been at the forefront of working with dystrophin experts and the FDA on dystrophin methodologies and quantification over several years. We believe we have the most insight of any industry representative to contribute to advancing the field, informing direction of future analyses, and identifying areas for improvement.

We appreciate your consideration of this request. Please don't hesitate to reach out if you have any questions.

Kindest regards and very respectfully,

Diane

Diane L. Berry, Ph.D.

VP, Global Health Policy & Government Affairs

p617.274.4006 c (b) (6) f 617.945.1678

email dberry@sarepta.com

<image001.jpg>

215 First Street, Cambridge, MA 02142

From: Gross, Mary [mailto:Mary.Gross@fda.hhs.gov]
Sent: Thursday, February 26, 2015 11:26 AM
To: Diane Berry
Subject: RE: Dystrophin

FDA and NIH are holding a scientific workshop entitled "Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data" on March 20 in Silver Spring MD. Please see the draft agenda

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and the meeting web link that will be updated with the FR notice shortly. The meeting page link will automatically update with other pertinent information, like the final agenda, once it becomes available.

Attendees may participate either in person or by webcast. There is no fee to attend the public workshop, but attendees should register in advance. Space is limited, and registration for in person attendance will be on a first-come, first-served basis. Email registrations should be sent to Dystrophin_Workshop@fda.hhs.gov by March 17, 2015.

We hope you can join us on March 20 for this discussion. Thank you. - Mary

<http://www.fda.gov/Drugs/NewsEvents/ucm432429.htm>

From: Diane Berry [mailto:DBerry@Sarepta.com]
Sent: Thursday, February 26, 2015 11:22 AM
To: Gross, Mary
Subject: Dystrophin

Hi Mary,

I see there is workshop on dystrophin that was announced for March 20, however I didn't see a registration link. Does this email count as my registration or should I keep a look out for an update?

Thanks so much for the clarification.

Kindest regards,
Diane

Diane L. Berry, Ph.D.
VP, Global Health Policy & Government Affairs
p 617.274.4006 c (b) (6) f 617.945.1678
email dberry@sarepta.com



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From: [Leptak, Christopher](#)
To: [Moscicki, Richard](#); [Rao, Ashutosh](#)
Subject: RE: Dystrophin Workshop - Mar 20
Date: Friday, February 27, 2015 3:26:58 PM

I leave this up to Ash and Ron as they are the SMEs. We could respond that the academic collaborators with Sarepta are already speaking and hope that is well-received. Honestly, in less Serepta has something unique to offer that is not already covered, it's tough to justify just to add the "name". And honestly, any drug program will likely go to an AC so it's not like they will not be given an opportunity to choose their own people to make their pitch.

From: Moscicki, Richard
Sent: Friday, February 27, 2015 3:15 PM
To: Rao, Ashutosh; Leptak, Christopher
Subject: FW: Dystrophin Workshop - Mar 20

I know we thought we were including them by including Nationwide Children's but what do you think? Ed Kaye of Sarepta

From: Diane Berry [<mailto:DBerry@Sarepta.com>]
Sent: Friday, February 27, 2015 3:05 PM
To: Gross, Mary
Cc: Moscicki, Richard
Subject: Dystrophin Workshop - Mar 20

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Kindest regards and very respectfully,

Diane

Diane L. Berry, Ph.D.
VP, Global Health Policy & Government Affairs

p617.274.4006 c (b) (6) f 617.945.1678
email dberry@sarepta.com
<image001.jpg>
215 First Street, Cambridge, MA 02142

From: Gross, Mary [<mailto:Mary.Gross@fda.hhs.gov>]
Sent: Thursday, February 26, 2015 11:26 AM
To: Diane Berry
Subject: RE: Dystrophin

FDA and NIH are holding a scientific workshop entitled "Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data" on March 20 in Silver Spring MD. Please see the draft agenda and the meeting web link that will be updated with the FR notice shortly. The meeting page link will automatically update with other pertinent information, like the final agenda, once it becomes available.

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We hope you can join us on March 20 for this discussion. Thank you. - Mary

<http://www.fda.gov/Drugs/NewsEvents/ucm432429.htm>

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Sent: Thursday, February 26, 2015 11:22 AM
To: Gross, Mary
Subject: Dystrophin

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Thanks so much for the clarification.

Kindest regards,
Diane

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From: Gross, Mary
To: Flanigan, Kevin; Louise.Rudino-Klapac@nationwidechildrens.org; jervasti@umn.edu; Jeff Chamberlain; David.Rimm@Yale.edu; Pat Furlong; Morris Glenn (THE ROBERT JONES AND AGNES HUNT ORTHOPAEDIC HOSPITAL NHS FOUNDATION TRUST); c.beekman@prosensa.nl; Sahenk, Zarife; YHathout@childrensnational.org; ehoffman@childrensnational.org; wagnerk@kennedykrieger.org; lsweeney@mail.med.upenn.edu; Rabi Tawil@urmc.rochester.edu; Sardone, Valentina; John Porter; Afrodite Lourbakos
Cc: Nuckolls, Glen H (NIH); Rao, Ashutosh; Moscicki, Richard; Leptak, Christopher; Farkas, Ronald; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Kaiser, James; Rogers, Hobart; Tenzi, Georgiann; Xu, Lei (CBER); Mansfield, Elizabeth; Jenkins, John K; Loewke, Sally A; Tezak, Zivana; Woodcock, Janet; Boyce, Amanda T (NIH); Kaufmann, Petra (NIH); pmcinnes@mail.nih.gov; Austin, Christopher P (NIH)
Subject: Notice of Scientific Workshop on March 20; Dystrophin Methodologies
Date: Friday, February 27, 2015 11:33:42 AM
Attachments: FDA-NIH Dystrophin Workshop abbreviated.pdf

Hi everyone: FDA and NIH are co-sponsoring the scientific workshop entitled "Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data" that will be held on March 20 in Silver Spring MD. Please see the draft agenda and the meeting web link that will be updated with the FR notice shortly. The meeting page link will automatically update with other pertinent information, like the final agenda, once it becomes available. Anyone who isn't a speaker should register through the mailbox if you plan to attend the meeting. I will register the speakers for this event.

Attendees may participate either in person or view by webcast. There is no fee to attend the public workshop, but space is limited, and registration for in person attendance will be on a first-come, first-served basis. Email registrations should be sent to Dystrophin_Workshop@fda.hhs.gov by March 17, 2015.

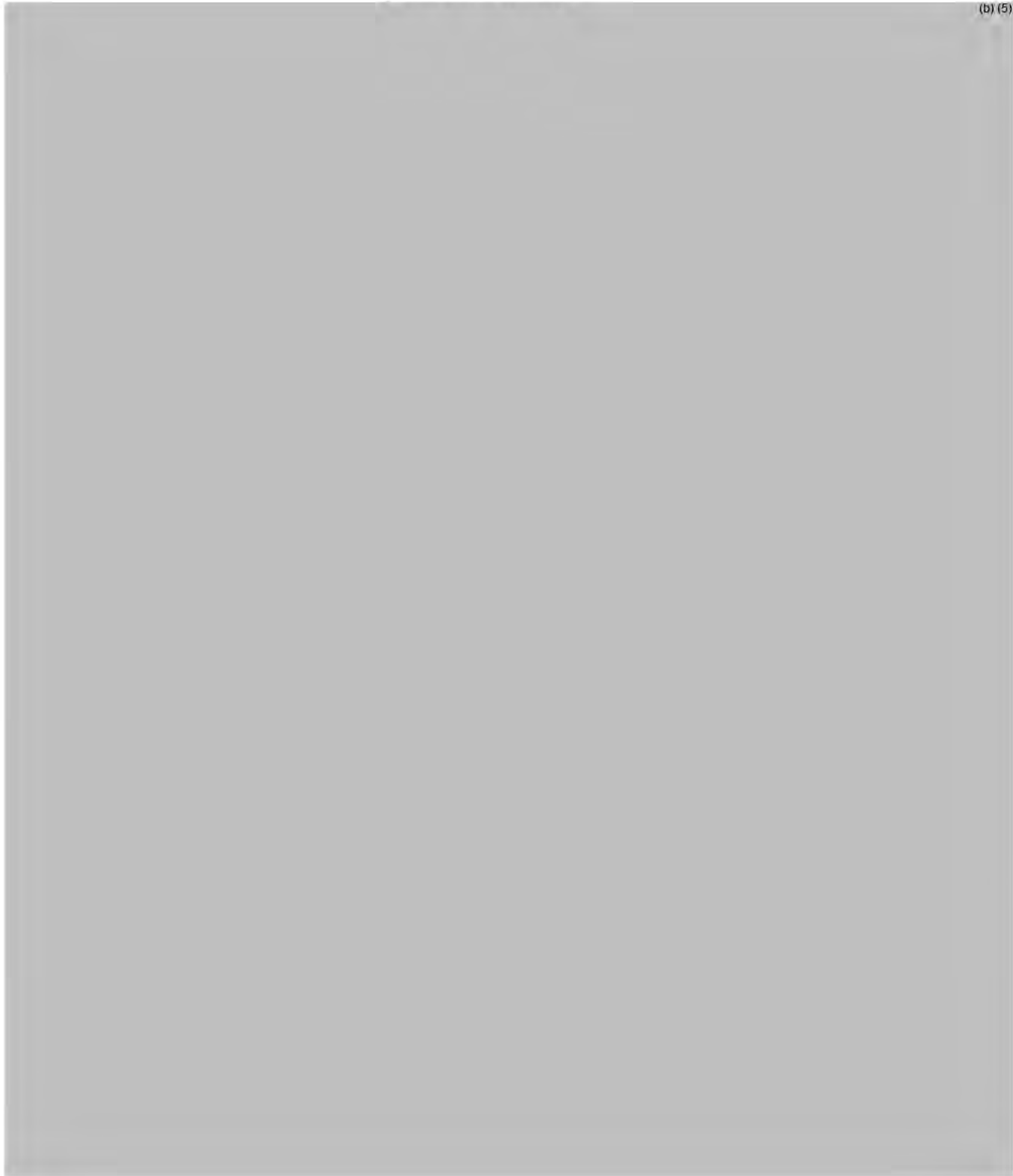
Please share this information with any colleagues who might be interested in attending this meeting as pre-registration is required.

Thank you!

<http://www.fda.gov/Drugs/NewsEvents/ucm432429.htm>

FDA-NIH Dystrophin Methodology Workshop
Location FDA White Oak Campus
Date March 20th 2015
(TENTATIVE AGENDA)

(b) (5)





From: Leptak, Christopher
To: (cc: Wei, Grant; Mary, Thomas; Kimberly K (ORP))
Cc: (CDER-ORP Requests: (Houck), (Figueroa), (Sawyer), (Sullivan), (Lombard), (Sullivan), (A...))
Subject: RE: Display & Publication Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data; Public Scientific Workshop
Date: Thursday, February 26, 2015 3:45:39 PM

Thanks to all for the efforts to make this happen. Gotta be one of the fastest FR Notice publications on record!

Best,
Chris

From: Lu, Wei
Sent: Thursday, February 26, 2015 3:44 PM
To: Leptak, Christopher; Gross, Mary; Thomas, Kimberly K (ORP)
Cc: CDER-ORP Requests
Subject: FYI: Display & Publication Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data; Public Scientific Workshop

Good afternoon,

Thanks to you all. See below:

The following documents are scheduled to display and publish as indicated in the table below.

Lead Center	FRDTS No.	Docket No.	Title	Category	Date Sent to OFR	Time Sent to OFR	Display Date	Display Time	Publication Date
CDER	2015-82*	FDA-2015-N-0001	Pediatric Neurocognitive Workshop; Advancing the Development of Pediatric Therapeutics Public Workshop	Notice	2/26/2015	1:36 p.m.	3/2/2015	8:45 a.m.	3/3/2015
CDER	2015-98*	FDA-2015-N-0430	Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data; Public Scientific Workshop: Request for Comments	Notice	2/26/2015	1:48 p.m.	3/2/2015	8:45 a.m.	3/3/2015

The Regulations Editorial Staff's E-room has been replaced by an FDA SharePoint Web site. The SharePoint site is now active. The URL for the site is <http://sharepoint.fda.gov/orgs/OC-FedRegister/FederalRegisterDocs/default.aspx>.

As a member of this email group, you have been automatically granted visitor access and you should have received a 'Welcome to SharePoint' email. If you did not receive this email, please contact Janet Nickerson at Janet.Nickerson@fda.hhs.gov or Jonathan Derr at Jonathan.Derr@fda.hhs.gov to request visitor access.

To view documents on display at Office of the Federal Register: <https://www.federalregister.gov/public-inspection>

To view published documents online at GPO: <http://www.gpoaccess.gov/fr/index.html>

*Digital Signature: FDA participates in a digital signature and electronic transmission program with the Office of the Federal Register (OFR). Federal Register documents may be digitally signed by authorized signers in FDA and transmitted electronically to the Office of the Federal Register. For information on the program, contact Joyce Strong (Joyce.Strong@FDA.HHS.GOV) or Lisa Granger (Lisa.Granger@FDA.HHS.GOV)

Best,
Wei

Wei Lu, RN, MS
CDER/DEP/DEO
Bldg 51, Room 6174
Office 301-795-3448
Fax 301-847-8753
Email: Wei.Lu@fda.hhs.gov

From: [Gross, Mary](#)
To: [Moscicki, Richard](#)
Subject: RE: Announcement of Government Workshop on Dystrophin Methodology - March 20, 2015
Date: Thursday, February 26, 2015 11:16:26 AM

Hi – we are working on finalizing the agenda now – We usually don't make the final agenda available until a few days before the meeting. But if we finish this early, we'll go ahead and make it available as soon as it's ready. - Mary

From: Moscicki, Richard
Sent: Thursday, February 26, 2015 10:51 AM
To: Gross, Mary
Subject: RE: Announcement of Government Workshop on Dystrophin Methodology - March 20, 2015

Mary, when will the agenda be made public?

From: Gross, Mary
Sent: Thursday, February 26, 2015 8:59 AM
To: Susan Behling (Susan.Behling@bms.com); Nhu Tran (Debi) (debi.tran@pfizer.com); Michael Jirousek Ph. D. (michaeljirousek@catabasis.com); Marc B. Blaustein (mblaustein@halotherapeutics.com); Larry Bell (l.bell@prosensa.nl); Kati Broderick (Broderick_Kathryn_E@lilly.com); Ann Tunstall, PhD (atunstall@scilucent.com); mlee@marathonpharma.com; Shamim Ruff; rbloch@umaryland.edu; ifogelman@lifetechresearch.com; richard@pacificlinkconsulting.com; cmmcdonald@ucdavis.edu; knagaraju@childrensnational.org; fischbek@ninds.nih.gov; bonnemanncg@mail.nih.gov; pclemens@pitt.edu; Justin_fallon@brown.edu; hstedman@mail.med.upenn.edu; dburkin@med.unr.edu; cmiceli@ucla.edu; duand@missouri.edu; m.matsuoka@po.nippon-shinyaku.co.jp; xxiao@email.unc.edu
Cc: Rao, Ashutosh; Leptak, Christopher; Moscicki, Richard; Nuckolls, Glen H (NIH); Ienzi, Georgiann
Subject: Announcement of Government Workshop on Dystrophin Methodology - March 20, 2015

FDA and NIH are holding a scientific workshop entitled "Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data" on March 20 in Silver Spring MD. Please see the draft agenda and the meeting web link that will be updated with the FR notice shortly. The meeting page link will automatically update with other pertinent information, like the final agenda, once it becomes available.

Attendees may participate either in person or by webcast. There is no fee to attend the public workshop, but attendees should register in advance. Space is limited, and registration for in person attendance will be on a first-come, first-served basis. Email registrations should be sent to Dystrophin_Workshop@fda.hhs.gov by March 17, 2015.

We hope you can join us on March 20 for this discussion. Thank you.

<< File: FDA-NIH Dystrophin Workshop abbreviated.pdf >>

<http://www.fda.gov/Drugs/NewsEvents/ucm432429.htm>

kind regards,
Sebahattin Cirak

Dr.med.Dipl.Chem. Sebahattin Cirak
Emmy Noether Arbeitsgruppenleiter
Facharzt für Kinderheilkunde und Jugendmedizin
<http://humangenetik.uk-koeln.de/Research/cirak-lab>

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Von: Rao, Ashutosh [Ashutosh.Rao@fda.hhs.gov]
Gesendet: Mittwoch, 25. Februar 2015 08:58
An: Cirak, Sebahattin
Cc: Nuckolls, Glen H (NIH)
Betreff: Invitation to Dystrophin workshop

Dear Dr. Cirak,

The FDA and NIH are jointly organizing a scientific workshop on the FDA campus to discuss opportunities and challenges with the methodologies for dystrophin quantification. As co-chairs of the workshop, Dr. Glen Nuckolls and I would like to request one of you to speak and participate at this workshop. A draft agenda is attached.

Specifically, we would like to hear of your cumulative experience with immunofluorescence and western blotting methods for dystrophin in patient samples as described in your Mol Ther Nucleic Acids (2014) and Lancet (2011) papers. We believe that scientists and drug developers in the field of DMD and at the FDA would benefit greatly from this technical discussion on the methodology and a frank assessment of the current state of methodologies.

Realizing that this is short notice, the workshop is scheduled for March 20th 2015 at the White Oak, Silver Spring, Maryland campus of the FDA. Could you please let us know at the earliest if you would be interested in speaking and participating? We can follow-up over a teleconference to discuss details.

Best regards,

Ashutosh Rao (FDA/CDER) and Glen Nuckolls (NIH/NIHNS)

Ashutosh Rao, Ph.D.

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Senior Drug Quality Reviewer
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From: [Gross, Mary](#)
To: [Rao, Ashutosh](#); [Nuckolls, Glen H \(NIH\)](#)
Cc: [Leptak, Christopher](#); [Farkas, Ronald](#); [Moscicki, Richard](#)
Subject: RE: Invitation to Dystrophin workshop
Date: Thursday, February 26, 2015 11:13:45 AM

Just to let you know, some patients or patient advocates (not sure which) registered for the meeting this morning.

From: Rao, Ashutosh
Sent: Thursday, February 26, 2015 9:40 AM
To: Gross, Mary; Nuckolls, Glen H (NIH)
Cc: Leptak, Christopher; Farkas, Ronald
Subject: Re: Invitation to Dystrophin workshop

Thanks. We can talk to Dr. Cirak and if he can join via Adobe Connect/phone.

From: Gross, Mary
Sent: Thursday, February 26, 2015 09:07 AM
To: Rao, Ashutosh; Nuckolls, Glen H (NIH)
Cc: Leptak, Christopher; Farkas, Ronald
Subject: RE: Invitation to Dystrophin workshop

ok

From: Rao, Ashutosh
Sent: Wednesday, February 25, 2015 3:41 PM
To: Gross, Mary; Nuckolls, Glen H (NIH)
Cc: Leptak, Christopher; Farkas, Ronald
Subject: FW: Invitation to Dystrophin workshop

Dear Mary,

Could you please help set up a tcon with Dr. Cirak? He is local so travel should not be a big issue. I hope I am not jinxing us by saying – this is the last speaker we need to accommodate!

Thanks
Ash

From: Cirak, Sebahattin [<mailto:scirak@childrensnational.org>]
Sent: Wednesday, February 25, 2015 3:33 PM
To: Rao, Ashutosh; Sebahattin.Cirak@uk-koeln.de
Subject: AW: Invitation to Dystrophin workshop

Dear Dr.Rao,

thanks for your invitation. I would be delighted to participate and to speak in this important workshop.

From: [Leptak, Christopher](#)
To: [Gross, Mary](#); [Lu, Wei](#); [Thomas, Kimberly K \(ORP\)](#)
Cc: [Moscicki, Richard](#); [Rao, Ashutosh](#)
Subject: RE: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients
Date: Tuesday, February 24, 2015 2:05:53 PM

Understood Mary. So that we do not break any "rules" (real or historically perceived), we should hold off on sharing the events page link with outsiders until the FR Notice posts. Agree?

From: Gross, Mary
Sent: Tuesday, February 24, 2015 2:02 PM
To: Leptak, Christopher; Lu, Wei; Thomas, Kimberly K (ORP)
Cc: Moscicki, Richard; Rao, Ashutosh
Subject: RE: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients

Hi Chris – I've been working with Kim and Wei. We are going to post something on the meetings and events page today (once the link is made live) and the FR notice should publish by Friday this week. I planned to send something once everything was ready to go.

Mary

From: Leptak, Christopher
Sent: Tuesday, February 24, 2015 2:00 PM
To: Lu, Wei; Thomas, Kimberly K (ORP)
Cc: Moscicki, Richard; Rao, Ashutosh; Gross, Mary
Subject: FW: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients
Importance: High

Hello Wei and Kim,

Following up on Mary's emails to see if you know when the FR Notice will post. If there is someone else we should email for this information, please share the names of the appropriate FR Notice POCs.

Much appreciated!

Chris

From: Lu, Wei
Sent: Thursday, February 19, 2015 12:22 PM
To: Leptak, Christopher; Thomas, Kimberly K (ORP)
Subject: Re: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients

Hi Chris,

I believe the FR will be announced as scheduled.

Thanks,

Wei

From: Leptak, Christopher
Sent: Thursday, February 19, 2015 11:57 AM
To: Lu, Wei; Thomas, Kimberly K (ORP)
Subject: RE: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients

Hello Wei and Kim,

Touching base to see if things are still on track for the FR Notice to publish early next week.

Thanks for the update,
Chris

From: Lu, Wei
Sent: Monday, February 09, 2015 11:46 AM
To: Moran, Kristy
Cc: JW Direct Reports & Deputies; Walsh, Sandy; CDER-EOS; Behr, Virginia L; Liscinsky, Morgan; Kremzner, Mary E; Chew, Catherine; Hong, Jaewon; Drug Safety Web; Peterson, Jayne E; Sherwood, Edward M; MedWatch Safety Alerts; Unger, Ellis; Locicero, Colleen L; Pahon, Eric; Thomas, Kimberly K (ORP); Moscicki, Richard; Rao, Ashutosh; Gross, Mary; Leptak, Christopher; CDER-ORP Requests
Subject: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients

Hi Kristy,

On or about February 23rd, 2015, FDA will publish a Federal Register notice announcing a public scientific workshop to discuss dystrophin protein quantification methodologies for human tissue. This workshop is being cosponsored by the National Institutes of Health (NIH). The purpose of the workshop is to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development. The intended audiences for this workshop are scientists and clinicians involved in acquiring, measuring, and analyzing proteins associated with Duchenne Muscular Dystrophy (DMD).

This announcement will be of interest to the pharmaceutical industry, scientists, and clinicians diagnosing and treating patients with DMD. FDA will not issue a press release..

Please find the information advisory attached.

*****PLEASE NOTE THAT THIS INFORMATION IS NOT RELEASABLE TO THE PUBLIC UNTIL THE ACTION TAKES PLACE*****

Thanks,
Wei

Wei Lu, RN, MS
CDER/OEP/DEO
Bldg 51, Room 6174

Office: 301-796-3448
Fax: 301-847-8753
Email: Wei.Lu@fda.hhs.gov

From: [Gross, Mary](#)
To: [John Porter](#)
Cc: [Pat Furlong](#); [Rao, Ashutosh](#); [Leptak, Christopher](#); [Moscicki, Richard](#)
Subject: RE: Replacement Questions for Dystrophin Methodology Workshop
Date: Tuesday, February 24, 2015 10:57:10 AM

Hi: here is the tcon number for the call on Friday, February 27 at 2:00 pm

877 704 7717; Passcode (b) (4)

Thanks - Mary

From: John Porter [<mailto:John@parentprojectmd.org>]
Sent: Tuesday, February 24, 2015 10:53 AM
To: Gross, Mary
Cc: Pat Furlong
Subject: Re: Replacement Questions for Dystrophin Methodology Workshop

Yes. Thanks.
John

Sent from my iPhone

On Feb 24, 2015, at 10:00 AM, Gross, Mary <Mary.Gross@fda.hhs.gov> wrote:

John - Can you do a call with Dr. Moscicki on Friday, February 27 from 2:00 – 2:30 to discuss the panel discussion? Thanks. – Mary

From: John Porter [<mailto:John@parentprojectmd.org>]
Sent: Tuesday, February 24, 2015 5:59 AM
To: Gross, Mary; Nuckolls, Glen H (NIH); Rao, Ashutosh
Cc: Pat Furlong
Subject: Replacement Questions for Dystrophin Methodology Workshop

Here is my replacement for the questions for the Dystrophin Methodology workshop panel discussion. We'll make sure that the panel covers the same turf that was intended by the original questions. Just want to stay neutral (non-directive) on the workshop outcomes, which will be determined by the participants and discussions that day. Thanks for including us in the agenda. Would be great if Richard Moscicki and I could get a time to talk prior to the workshop.

John

FDA-NIH Dystrophin Methodology Workshop Panel Discussion
Moderators: John Porter, PPMD and Richard Moscicki, FDA

1. What is the current status of assay validation and methodology for quantification of dystrophin in the context of drug development? What are the key opportunities and knowledge gaps in the field?
2. What are the necessary next steps to advance the precision and reproducibility of technology to acquire, measure, and analyze the proteins that are associated with Duchenne muscular dystrophy?
3. What are the Action Items from this workshop that will continue to advance robust methods for the objective, reliable, and quantitative measurement of dystrophin and dystrophin-related muscle proteins?

John D. Porter, Ph.D.
Chief Executive Officer
<image001.png>
Mobile: 202-440-3497
Email: john@parentprojectmd.org

National Headquarters:
401 Hackensack Avenue, 9th Floor
Hackensack, NJ 07601
Direct: 201.944.9985 **Fax:** 201.250.8435

ParentProjectMD.org | DuchenneConnect.org | RunForOurSons.org | CoachToCureMD.org

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From: Gross, Mary
To: Austin, Christopher P (NIH); jervasti@umn.edu; jsc5@uw.edu; David.Rimm@Yale.edu; (b) (6); c.beekman@prosensa.nl; Louise.Rudino-Klapac@nationwidechildrens.org; zanfe.sahenk@nationwidechildrens.org; YHathaojt@childrensnational.org; KevinFlanigan@nationwidechildrens.org; ehoffman@childrensnational.org; wagnerk@kennedykrieger.org; lsweeney@mail.med.upenn.edu; Rabi_Tawil@urmc.rochester.edu; Nuckolls, Glen H (NIH); Rao, Ashutosh; Moscicki, Richard; Sardone, Valentina; Pat Furlong; John Porter
Cc: Farkas, Ronald; Tenzi, Georgiann
Subject: Reminder about presentation titles, financial disclosure forms due date for Dystrophin Scientific Workshop - Due by February 23
Date: Friday, February 20, 2015 10:08:35 AM
Attachments: Draft Agenda FDA-NIH Dystrophin Workshop 2-19.docx
FDA1 (4).doc

Dear Speakers and or Moderators: This is a reminder that presentation titles, full name with titles etc. along with financial disclosure forms were due by February 18. Some of you have returned this information to me, but for those who haven't, would you respond by no later than February 23? I am including a draft agenda for purposes of providing information on these details. If you sent me the information for the agenda and it doesn't show here, please don't worry, I am waiting until everyone gets back to make the changes all at once. Please also remember that slides are due by March 13. If you have questions, please send me an email and one of us will respond to you.

The Agenda is still in draft form and has not been publicly released, so please don't share it with anyone at this time. Thanks once again for participating!

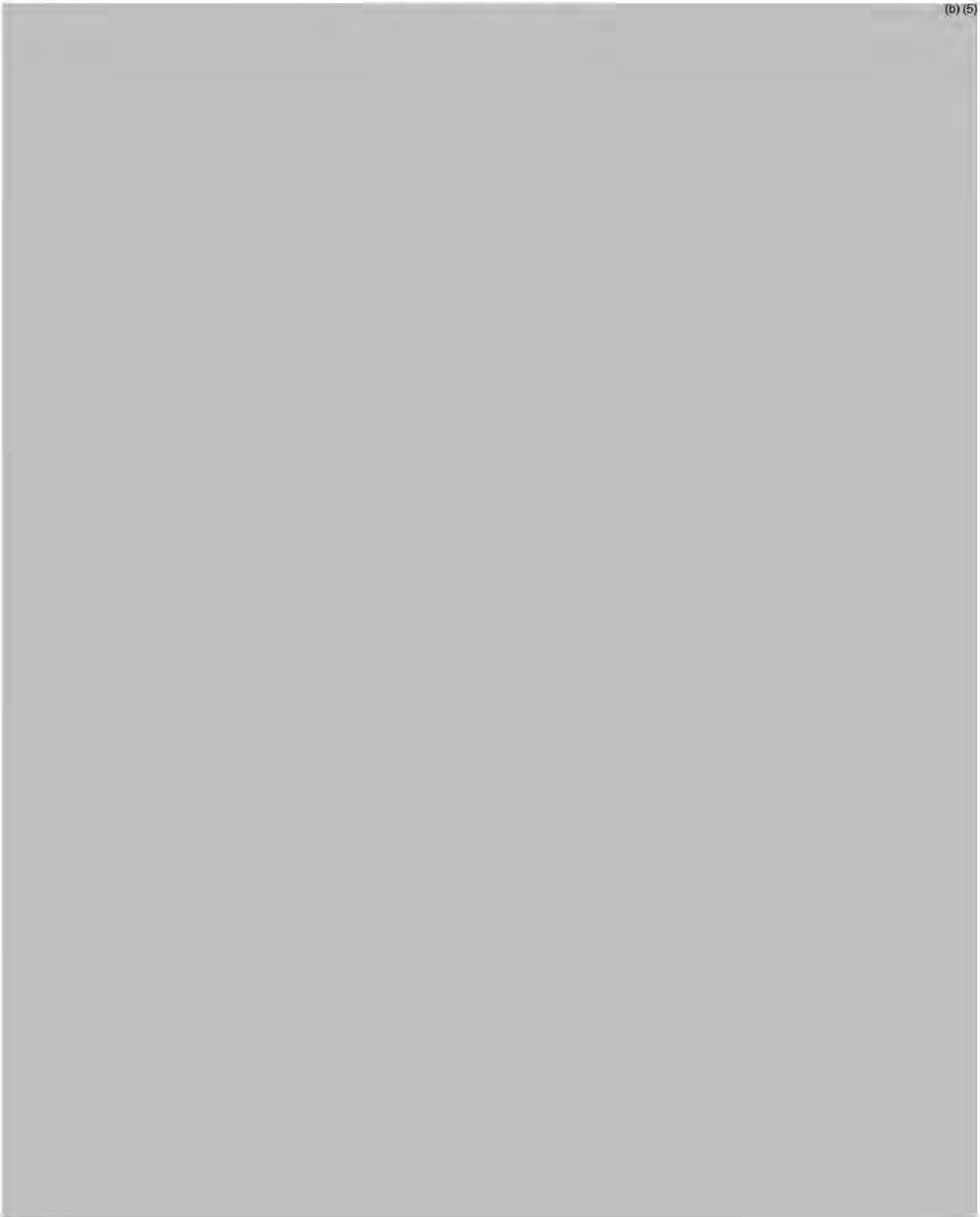
Mary

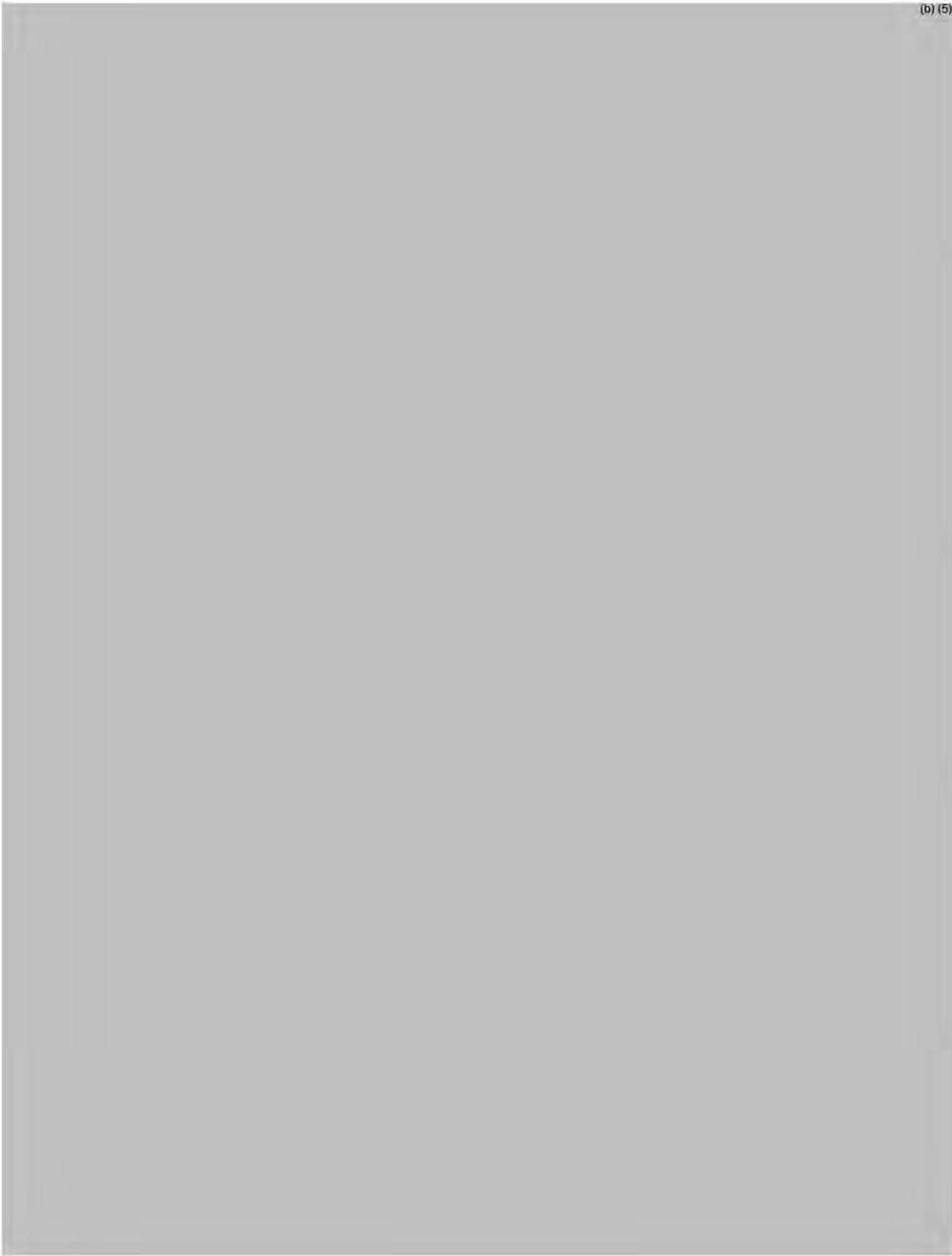
Dear Speakers, Panelists or Moderators - this note is in follow up to our recent telecons to help prepare for the March 20, 2015 scientific workshop on Dystrophin Methodologies. We are grateful that you will be able to join us and contribute your expertise to this important topic. I am attaching an updated draft agenda to this note and ask that you name your talk, and include other necessary information like full name, position title and credentials and return to me by February 18. The agenda for this meeting is very full and individual presentations will need to be limited to no more than 15 minutes in length. I have also attached a financial disclosure form. Would you complete this form and return to me before February 18.

We are asking for slides to be forwarded by March 13.

FDA-NIH Dystrophin Methodology Workshop
Location FDA White Oak Campus
Date March 20th 2015
DRAFT-DO NOT DISTRIBUTE

(b) (5)





From: [Rao, Ashutosh](#)
To: [Temple, Robert](#); [Unger, Ellis](#); [Dunn, Billy](#); [Moscicki, Richard](#)
Subject: Re: Commentary on Dystrophin
Date: Thursday, February 19, 2015 12:55:45 PM

The FR notice is on track for posting early next week. We should be able to have an agenda with the 2 new added speakers ready to share then. We speak to stu peltz and pat furlong on monday.

From: Temple, Robert
Sent: Thursday, February 19, 2015 05:19 PM
To: Rao, Ashutosh; Unger, Ellis; Dunn, Billy; Moscicki, Richard
Subject: RE: Commentary on Dystrophin

When does the agenda become available publicly. I guess we could send it to Christine when in is???

From: Rao, Ashutosh
Sent: Thursday, February 19, 2015 10:50 AM
To: Temple, Robert; Unger, Ellis; Dunn, Billy; Moscicki, Richard
Subject: Re: Commentary on Dystrophin

Hi Bob,

These 3 authors are not on the workshop agenda. However, Cirak used to be in the Muntoni lab, we did ask Muntoni and he recommended Valentina Sardone who is on the agenda. Two other speakers from Children's National are on the agenda (Hathout and Hoffman).

Ash

From: Temple, Robert
Sent: Thursday, February 19, 2015 03:57 PM
To: Unger, Ellis; Dunn, Billy; Moscicki, Richard; Rao, Ashutosh
Subject: FW: Commentary on Dystrophin

You probably all got this, but just in case.

From: Christine McSherry [<mailto:christine@jettfoundation.org>]
Sent: Thursday, February 19, 2015 8:06 AM
To: Temple, Robert
Subject: Commentary on Dystrophin

Bob,

Please read the below article. I would hope that the authors of this commentary - who are dystrophin experts, will be presenting at the upcoming dystrophin workshop.

Commentary

What Can We Learn From Clinical Trials of Exon Skipping for DMD?

OPEN

Qi-long Lu¹, Sebahattin Cirak² and Terence Partridge²

1. ¹Department of Neurology, McColl Lockwood Laboratory for Muscular Dystrophy Research, Carolinas Medical Center, Charlotte, North Carolina, USA

2. ²Center for Genetic Medicine, Children's National Medical Center, NW, Washington, DC, USA

Correspondence: Qi-long Lu, McColl Lockwood Laboratory for Muscular Dystrophy Research, Department of Neurology, Carolinas Medical Center, 1000 Blythe Blvd., Charlotte, North Carolina 28203, USA. E-mail: Qi.lu@Carolinashealthcare.org; Terence Partridge, Children's National Medical Center, 111 Michigan Ave, NW, Washington, DC 20010, USA. E-mail: TPartridge@childrensnational.org

On 20 September 2013, GlaxoSmithKline (GSK) and Prosensa announced that GSK's Phase III clinical trial (NCT01254019) of Drisapersen, an exon skipping drug for Duchenne muscular dystrophy (DMD), failed to meet the primary endpoint of a statistically significant improvement in the 6 Minute Walking Distance Test (6MWT) compared to placebo.¹ On 12 November 2013, Sarepta Therapeutics announced that the US Food and Drug Administration (FDA) has considered its application for accelerated approval of Eteplirsen as a DMD drug to be premature.² The news came as a great disappointment to the scientific community and more specifically to the families and foundations that had followed the trail of research articles and press announcements. Moreover, the clinical trial results and the FDA's view of the relationship between the dystrophin biomarker and functional endpoint of 6MWT in clinic will have a far reaching impact beyond exon skipping therapy in DMD.

Currently, the most promising therapies for DMD are arguably gene therapy and exon skipping, both aiming to restore the expression of dystrophin. For exon skipping, the general strategy of restoring expression of the mutated dystrophin gene by excluding frame-disrupting mutations was vindicated by early experiments in dystrophic animal models.^{3,4,5,6} This principle has been substantiated for DMD by clinical trials over the last 7 years with two chemistries, the 2'O-methyl phosphorothioate backbone (2OMePS, named PRO051/Drisapersen initiated by Prosensa/GSK) and the morpholino backbone (PMO, named Eteplirsen initiated by AVI Biopharma, now Sarepta Therapeutics).^{7,8,9,10} Both drugs target dystrophin exon 51 and both elicited the expected skipping of exon 51 and production of dystrophin protein following intramuscular injections.

In a subsequent open-label, dose-escalation systemic study, five weekly subcutaneous injections of Prosensa/GSK's PRO051 at 0.5, 2, 4, or 6 mg/kg induced skipping of exon 51 accompanied by low levels of dystrophin in 12 DMD boys. But, importantly, this data lacked pretreatment controls.¹⁰ This lack of pretreatment controls in combination with the use of the highly sensitive dystrophin antibody MANDYS106 led to reports of expansion of dystrophin positive fibre counts to up to 100%. The follow-up extension for 12-weeks at 6 mg/kg of the PRO051 reported stabilisation of motor function in the boys.¹⁰ However, the study included several boys below 7 years of age where natural history would predict improved motor function within the experimental period. A subsequent Phase IIb placebo-controlled 6 mg/kg/week study (NCT01153932) of Drisapersen on 53 DMD patients again reported a significant benefit in 6MWT in the treatment over the placebo group. Clinical benefits were maintained, but with reduced significance, after 48 weeks of treatment. However, no muscle biopsy results have yet been reported.¹¹ This was followed by the

phase III trial, with 186 patients, that failed to show statistically significant improvements in the primary outcome measure of the 6MWT. The difference in conclusion between the Phase III and earlier studies with the exact same treatment regime is therefore attributed almost solely to the high variability of the 6MWT endpoint measurement within the time-frame of the subject population and difference in sample sizes.

What have we learnt from the Prosensa/GSK trials? According to the comment from the FDA in response to Sarepta's application for Eteplirsen targeting the same dystrophin exon 51, the failure of the Drisapersen trial indicates a "*disconnect between increased expression of dystrophin and clinical efficacy.*" This criticism has serious implications far beyond exon skipping in DMD raising questions about our assessment of all experimental therapies that aim to restore or produce functional dystrophins in DMD, including gene replacement therapies that deliver a known functional gene product as a drug.

So, is there clear evidence indicating a disconnect between the levels of dystrophin expression and clinical efficacy? Fortunately, the answer is no. Results, both from animal models⁶ and clinical studies on Becker muscular dystrophy (BMD) patients, all point to a positive connection. Much of the confusion about levels of dystrophin expression come from over emphasizing assessment of dystrophin expression solely by immunohistochemistry (IHC) without pretreatment control biopsies for each patient and the use of highly sensitive antibody MANDYS106. Prosensa reported that up to 100% of fibers were dystrophin positive in the muscle samples of some Drisapersen-treated patients in its phase II study.¹⁰ IHC is critical to provide us with a rough estimate of the levels of protein expression, the proportion of cells expressing the protein, and especially patterns of distribution. However, one must be aware that judgment of positivity of dystrophin staining with IHC is highly subjective and especially troublesome in DMD samples due to many factors, including the degeneration-related background staining, and highly variable distribution of both revertant fibers (spontaneously expressing dystrophin) and antisense oligomer-induced dystrophin expression, all of which call for comparison with a pretreatment biopsy. Small areas of clustered revertant fibers, reaching a few dozen or more, could easily be misinterpreted to result from treatment. For these reasons, IHC, even though very valuable for assessing distribution and localization, should never be the sole source of evidence for levels of dystrophin expression and require confirmatory backup.

Currently, the most generally available and reliable assessment of dystrophin levels in muscles is by western blots although the data are still, arguably semiquantitative, and it is generally difficult to convincingly demonstrate levels of dystrophin below 10% of normal levels. However, dystrophin levels higher than 10% of normal level can be demonstrated without much difficulty in most laboratories as observed from western blots using tenfold dilutions of positive control protein.^{7,8,10} Unfortunately, data from western blots in the Drisapersen systemic trials showed only trace amounts of dystrophin in the treated muscle biopsy samples.¹⁰ In fact, the image presented in the publication shows no clear difference in signal intensity between the baseline samples and those from 2/7 weeks after treatment.¹⁰ The FDA also cited the failure of PTC Therapeutics's Ataluren trial as another example of the disconnect between levels of dystrophin and clinic outcomes. Ataluren has been selected to induce significant read-through of nonsense mutations of DMD gene, resulting in restoration of dystrophin expression in patients carrying such mutations. However, the screening assay method initially used to identify the specificity of PTC124 has been contradicted by more recent study.¹² Furthermore, studies to validate the effect of PTC124 in vitro did not demonstrate any significant read-through of nonsense mutations.¹³ More importantly, clinical trials of Ataluren have shown only the phase IIa results with little evidence of dystrophin restoration by IHC with a very subjective scoring method.¹⁴ Unfortunately, the phase IIb muscle biopsy results have not been presented and reported to the public. Therefore, the disappointing functional data from the Ataluren and Drisapersen trials are, in fact, entirely consistent with the failure of either agent to induce

production of significant amounts of dystrophin protein and do not support the notion of the “disconnect” proclaimed in the FDA report. The rationale of both exon-skipping and stop-codon read-through is that any benefit derives from production of significant amounts of dystrophin and the degree of efficacy should be related to the level of dystrophin. This has been clearly demonstrated in animal models of DMD.^{6,15} This conclusion is also consistent with the data from Sarepta’s clinical trials of the exon skipping drug Eteplirsen (formerly AVI-4658). The first open label, dose escalation (cohorts 1–6: 0.5, 1, 2, 4, 10, and 20 mg/kg bodyweight respectively), repeated intravenous administration study showed that Eteplirsen was well tolerated. There was a statistically significant dose-response as well as remarkable variability in dystrophin production in patient muscles. In the low dose cohorts 1–4, there was no increase in dystrophin expression, with the exception of one subject in cohort 3. However, 6 of 8 subjects in the two highest dose cohorts 5 and 6 showed an increase in dystrophin expression. Three patients, one in each of cohorts 3, 5, and 6, showed a substantial number of dystrophin-positive fibers, 21, 15, and 55%, respectively. Western blot analysis of these patients also showed an increase following treatment of protein levels from 2 to 18%, from 0.9 to 17% and from 0 to 7.7% of normal muscle values, respectively.⁸ This was followed by a placebo-controlled phase IIb trial using higher doses (30 and 50 mg/kg/week, each cohort had $n = 4$ subjects) of Eteplirsen.¹⁶ Ambulant boys were treated for 24 weeks and primary outcome was the percentage of increase in the number of dystrophin positive fibres in comparison to baseline biopsies. The secondary outcome was safety and the 6MWT. After another 24 weeks of open label extension, a final muscle biopsy was taken at 48 weeks. The results showed the number of dystrophin positive fibres up to 52 and 43% in the 30 and 50 mg/kg cohorts respectively.¹⁶ Overall, the Eteplirsen trials showed a clear trend of dose-dependent increase in dystrophin expression.

Clearly, one major difference between the two chemistries of exon skipping clinic trials is that Eteplirsen has been administered systemically at up to 50 mg/kg, more than eight times higher than Drisapersen. The limited dose of 6 mg/kg for Drisapersen was largely the result of kidney toxicity whereas no clear toxicity has so far been identified for Eteplirsen. Most preclinical studies have reported higher efficiency of exon skipping with the PMO chemistry than with equivalent amounts of reagent based on the 20MePS chemistry.^{4,5,6} It is therefore not surprising that the Eteplirsen trial reported detectable dystrophin by western blot. The Eteplirsen treated patients also showed a benefit of 67 m less decline in 6MWT over the placebo group.¹⁶ Stabilization of the motor function in DMD boys participating in Eteplirsen extension study has now being observed over 2 years. However one needs to be aware of the small sample sizes (only 12 subjects) and the bias associated with the open label nature of the extension study. Nevertheless, the levels of dystrophin were limited, clearly below 10% by western blot, and from only one sample (judged from the image presented in the publication) despite the high percentage of dystrophin positive fibers reported.¹⁶ This again illustrates the inflation of using IHC and number of dystrophin positive fibers as a marker of overall levels of dystrophin expression. One also needs to be aware that similar results of 6MWT stabilization have been reported from the Drisapersen open label extension studies and recently published natural history studies, although the interpretation is complex because of different age ranges and subpopulations.^{17,18} It therefore remains to be seen whether the reported levels of dystrophin under the current Eteplirsen treatment regime can be maintained. Upcoming placebo controlled phase III studies will be able to show if Eteplirsen can significantly delay the long-term disease progression.

There should be no doubt that dystrophin is critical for normal muscle functions, for its lack is the cause of DMD and BMD.¹⁹ One could argue that increase of any amount of dystrophin might benefit the dystrophic muscle. However, the presence of low amounts of dystrophin in these trials is associated with limited distribution of the dystrophin positive fibers. The small number of these fibers in dystrophic muscles is unlikely to provide widespread and measurable functional improvement to the general mass of muscle, a view supported by

studies in animal models.^{4,5,6} Therefore, therapy based on dystrophin restoration must ask the question: can the treatment produce sufficient amounts of dystrophin, measurable by both IHC and western blot, and sufficiently widely distributed, to effectively delay the disease progression? To answer this question, one would first ask how much dystrophin is required to have a significant impact on the disease outcome. Analyses of biopsies from BMD patients provide some insights. BMD is associated with natural occurring in-frame deletions from which reduced amounts of slightly shortened dystrophins are produced. The aim of exon skipping therapy in DMD patients is to mimic BMD by causing production of in-frame transcripts from the out-of-frame dystrophin gene. Published work on dystrophin levels in near-asymptomatic Becker patients suggests that this degree of amelioration can result from around 30% of normal dystrophin levels in western blots.²⁰ Dystrophinopathy patients of intermediate clinical severity have been associated with dystrophin levels of between 10 and 25% of normal levels²¹ while in-frame deletions in BMD patients with severe DMD phenotype have been associated with less than 10% dystrophin. From this data, it is reasonable to postulate that significant improvement in the disease phenotype by exon skipping will require expression of truncated dystrophin to at least 10% of normal levels with wide distribution. Such levels of dystrophin have not so far been convincingly demonstrated in any of the systemic trials of exon skipping and read-through treatments. Significantly higher levels of dystrophin are likely required to improve disease phenotype of individuals with diminished remaining muscle mass and higher variation in dystrophin distribution. This assumption does not exclude possible limited benefit to diseased muscle of lower levels of dystrophin, but the incidence of severe BMD patients with low levels of dystrophin indicates that this is unlikely.

With all the data available from animal model studies of exon skipping and adeno-associated virus gene therapy and clinic trials of exon skipping, we may conclude that dystrophin protein level, far from being dubious, is a fundamental biomarker to be taken into account when assessing experimental therapies that aim to produce and restore the expression of dystrophin in DMD. This principle is applicable to any therapy that aims to produce therapeutic protein.

We are still in the early stages of clinical trials for the exon skipping therapy. It is therefore critical to collect such data as accurately as possible, so that real guidance may be provided for later clinical trials targeting other exons or for gene replacement therapy. The efforts made by several large collaborative groups of physicians and scientists in the design and execution of these large clinical trials can't be appreciated enough as we have learnt invaluable lessons about the natural history of DMD, the practicability and utility of clinical trial procedures and outcome measures, and have created a sustainable clinical infrastructure for future clinical trials. The most important lesson learnt is that, clinical endpoints such as 6MWT are important for assessing the disease progression, but total dominance of this principle appears to have led to the misconception that clinical benefit can be achieved without the production of a therapeutic amount of relevant protein product.

Another valuable and important lesson from the two exon skipping trials is that the behaviour of a particular antisense chemistry in the mouse and dog models appears to provide a good guide to what it will do in human DMD. The relationship of dose per body weight to exon-skipping efficiency and dystrophin production with the PMO chemistry in animal models has been strongly paralleled in man. It reinforces the rationale for conducting initial investigations of the efficacy/toxicity window for a given chemistry in animals with a reasonable expectation that the general principles of dose and regime may be transferable to man.

In summary, detection of dystrophin is fundamental to exon-skipping therapy in DMD and it is important to gather reliable data relating levels of dystrophin expression to clinic outcome. This will provide guidance for later trials testing other antisense chemistries and targeting other exons as well as for gene replacement therapy. Preclinical studies in the

dystrophic mouse and dog have shown a dose dependent dystrophin induction and therapeutic effect on dystrophic muscles. In fact, clinical and biochemical outcome from the treatment regimes of the two different chemistries are strongly predicted from animal model studies. Data from the pivotal Ataluren and Drisapersen clinical trials of exon skipping have, so far demonstrated to our best knowledge too little dystrophin to justify the notion of a disconnection between the levels of dystrophin expression and clinical outcome measurement. The newly started Ataluren phase III trial (NCT01826487) might be able to determine clinical benefit to DMD patients, but unfortunately no muscle biopsies have been planned in this phase III study. Determination of dystrophin levels should rely more heavily on western blot, currently the most available method, with supporting data from IHC, although more reliable and accurate detection methods are currently being developed.²² Lastly, we would remind the FDA and ourselves that dystrophin is not a purely phenomenological biomarker for DMD; lack of dystrophin is the primary biochemical defect in DMD and denial of the importance of the principle of substantial dystrophin restoration in DMD would have future impact on all therapeutic investigations of inherited disorders.

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Making...TODAY COUNT - TO CHANGE TOMORROW

Christine McSherry, RN

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CELL: (781) 254-2669
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From: [Leptak, Christopher](#)
To: [Rao, Ashutosh](#); [Gross, Mary](#)
Cc: [Moscicki, Richard](#)
Subject: FW: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients
Date: Thursday, February 19, 2015 12:29:45 PM

FYI, the FR Notice posting for early next week remains on track.
Chris

From: Lu, Wei
Sent: Thursday, February 19, 2015 12:22 PM
To: Leptak, Christopher; Thomas, Kimberly K (ORP)
Subject: Re: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients

Hi Chris,

I believe the FR will be announced as scheduled.
Thanks,
Wei

From: Leptak, Christopher
Sent: Thursday, February 19, 2015 11:57 AM
To: Lu, Wei; Thomas, Kimberly K (ORP)
Subject: RE: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients

Hello Wei and Kim,

Touching base to see if things are still on track for the FR Notice to publish early next week.

Thanks for the update,
Chris

From: Lu, Wei
Sent: Monday, February 09, 2015 11:46 AM
To: Moran, Kristy
Cc: JW Direct Reports & Deputies; Walsh, Sandy; CDER-EOS; Behr, Virginia L; Liscinsky, Morgan; Kremzner, Mary E; Chew, Catherine; Hong, Jaewon; Drug Safety Web; Peterson, Jayne E; Sherwood, Edward M; MedWatch Safety Alerts; Unger, Ellis; Locicero, Colleen L; Pahon, Eric; Thomas, Kimberly K (ORP); Moscicki, Richard; Rao, Ashutosh; Gross, Mary; Leptak, Christopher; CDER-ORP Requests
Subject: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients

Hi Kristy,

On or about February 23rd, 2015, FDA will publish a Federal Register notice announcing a public scientific workshop to discuss dystrophin protein quantification methodologies for human tissue. This workshop is being cosponsored by the National Institutes of Health (NIH). The purpose of the workshop is to discuss currently available methodologies and to identify scientific knowledge gaps

and opportunities for improving dystrophin protein detection in the context of drug development. The intended audiences for this workshop are scientists and clinicians involved in acquiring, measuring, and analyzing proteins associated with Duchenne Muscular Dystrophy (DMD).

This announcement will be of interest to the pharmaceutical industry, scientists, and clinicians diagnosing and treating patients with DMD. FDA will not issue a press release..

Please find the information advisory attached.

*******PLEASE NOTE THAT THIS INFORMATION IS NOT RELEASABLE TO THE PUBLIC UNTIL THE ACTION TAKES PLACE*******

Thanks,
Wei

Wei Lu, RN, MS
CDER/OEP/DEO
Bldg 51, Room 6174
Office: 301-796-3448
Fax: 301-847-8753
Email: Wei.Lu@fda.hhs.gov

From: Gross, Mary
To: Austin, Christopher P (NIH); jervasti@umn.edu; jsc5@uw.edu; David.Rimm@Yale.edu; (b) (6); c.beekman@prosenza.nl; Louise.Rudino-Klapac@nationwidechildrens.org; zarife.sahenk@nationwidechildrens.org; YHathaout@childrensnational.org; KevinFlanigan@nationwidechildrens.org; ehoffman@childrensnational.org; wagnerk@kennedykrieger.org; lsweeney@mail.med.upenn.edu; Rabi.Tawil@urmc.rochester.edu; Sardone, Valentina; Nuckolls, Glen H (NIH); Rao, Ashutosh; Moscicki, Richard; Farkas, Ronald
Cc: Tenzi, Georgiann
Subject: FW: FDA-NIH Dystrophin Methodology Workshop - Responses due by February 18; Slides due March 13
Date: Friday, February 13, 2015 5:07:14 PM
Attachments: Draft Agenda FDA-NIH Dystrophin Workshop 2-12.docx
FDA1 (4).doc

Dear Speakers, Panelists or Moderators – this note is in follow up to our recent telecons to help prepare for the March 20, 2015 scientific workshop on Dystrophin Methodologies. We are grateful that you will be able to join us and contribute your expertise to this important topic. I am attaching an updated draft agenda to this note and ask that you name your talk, and include other necessary information like full name, position title and credentials and return to me by February 18. The agenda for this meeting is very full and individual presentations will need to be limited to no more than 15 minutes in length. I have also attached a financial disclosure form. Would you complete this form and return to me before February 18.

We are asking for slides to be forwarded by March 13. Meeting organizers will be reviewing speaker slides for any outstanding issues that might need follow up or include possible information overlap. Slides must be preloaded prior to the meeting and the conference center does not permit the use unapproved devices from outside sources (like thumb drives) into the facility the day of the meeting.

For those speakers who are receiving travel assistance, you should have been in contact with a representative from NIH or FDA about necessary paperwork. If you are receiving travel support from FDA and you have questions, please contact Georgiann.lenzi@fda.hhs.gov for additional information.

Once again, thank you very for agreeing to participate in the workshop! If you have questions, please let me know and we will respond as soon as possible. We look forward to seeing you on March 20, 2015. - Mary

From: Gross, Mary <Mary.Gross@fda.hhs.gov>

Sent: 21 January 2015 19:58

To: Austin, Christopher P (NIH); jervasti@umn.edu; jsc5@uw.edu; David.Rimm@Yale.edu;
(b) (6) [Sardone, Valentina](mailto:Sardone,Valentina); c.beekman@prosensa.nl; Louise.Rudino-Klapac@nationwidechildrens.org; zarife.sahenk@nationwidechildrens.org;
YHathaout@childrensnational.org; KevinFlanigan@nationwidechildrens.org;
ehoffman@childrensnational.org; Rabi-Tawil@urmc.rochester.edu; wagnerk@kennedykrieger.org;
lsweeney@mail.med.upenn.edu; sawchenko@salk.edu

Cc: Finnegan, Sean J (NIH); Rao, Ashutosh; Leptak, Christopher; Butler, Hope; lenzi, Georgiann; Moscicki, Richard; Farkas, Ronald

Subject: FDA-NIH Dystrophin Methodology Workshop

Dear Speakers/Panelists – This note seeks confirmation that you are available to participate in the scientific workshop on Dystrophin Methodology co-sponsored by NIH and FDA that will be held at the FDA White Oak campus, 10903 New Hampshire Avenue, Silver Spring, MD on March 20, 2015. The workshop discussion will focus on currently available dystrophin protein quantitative methodologies for human tissue samples. If you have not received an invitation or find you will not be able to participate in the public meeting, please let me know by January 23.

Some of you will be traveling long-distance and will be reimbursed for your expenses. Administrative contacts from either FDA or NIH will be back in touch with you shortly about the necessary paperwork needed for reimbursement purposes.

In addition, we plan to touch base with the speakers and schedule tcons according to panel to consider speaker presentations, panel discussions and respond to your logistical questions. I will be back in touch with scheduling details shortly.

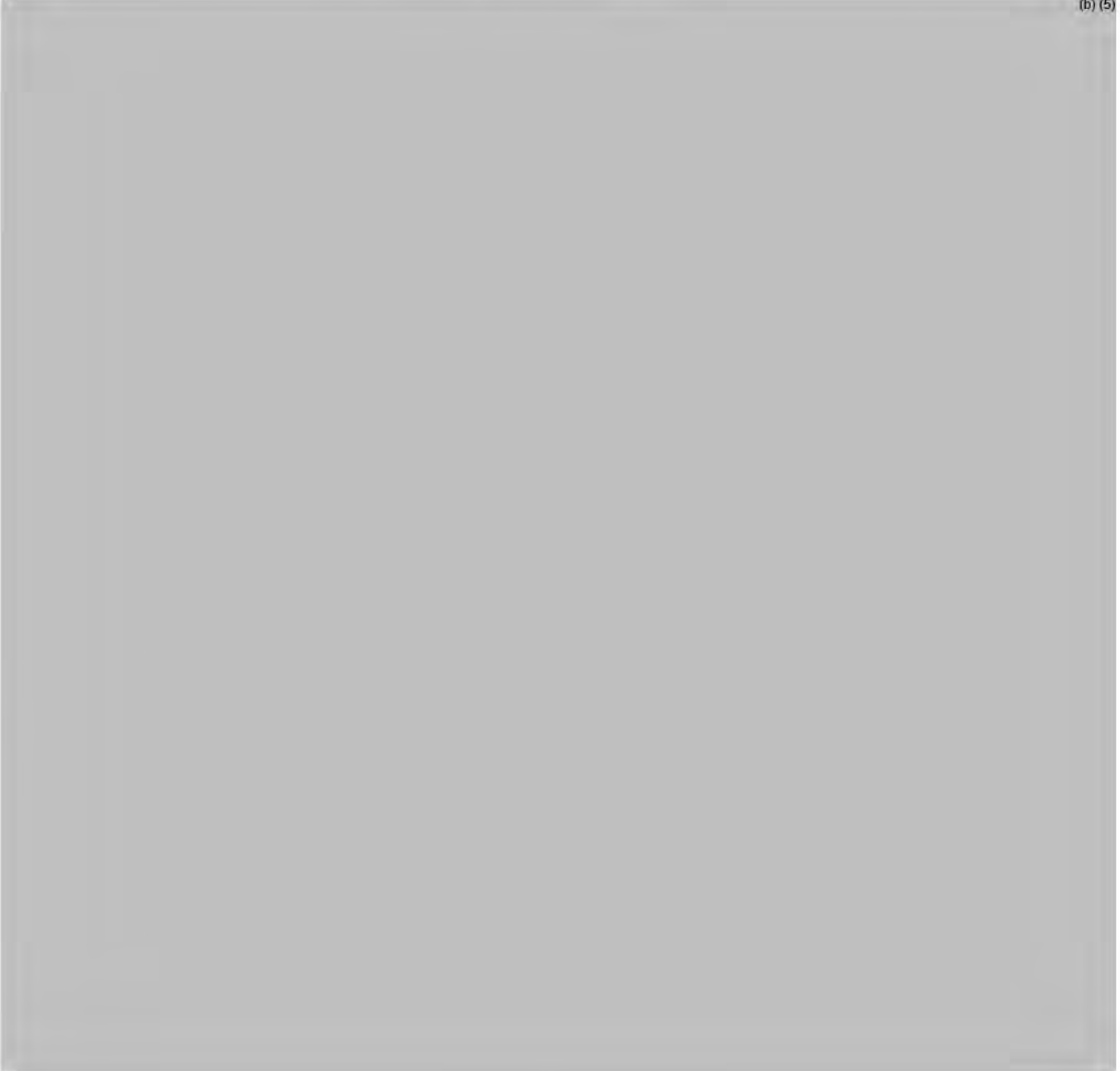
Thank you very much for agreeing to participate and we look forward to working with you on this important topic.

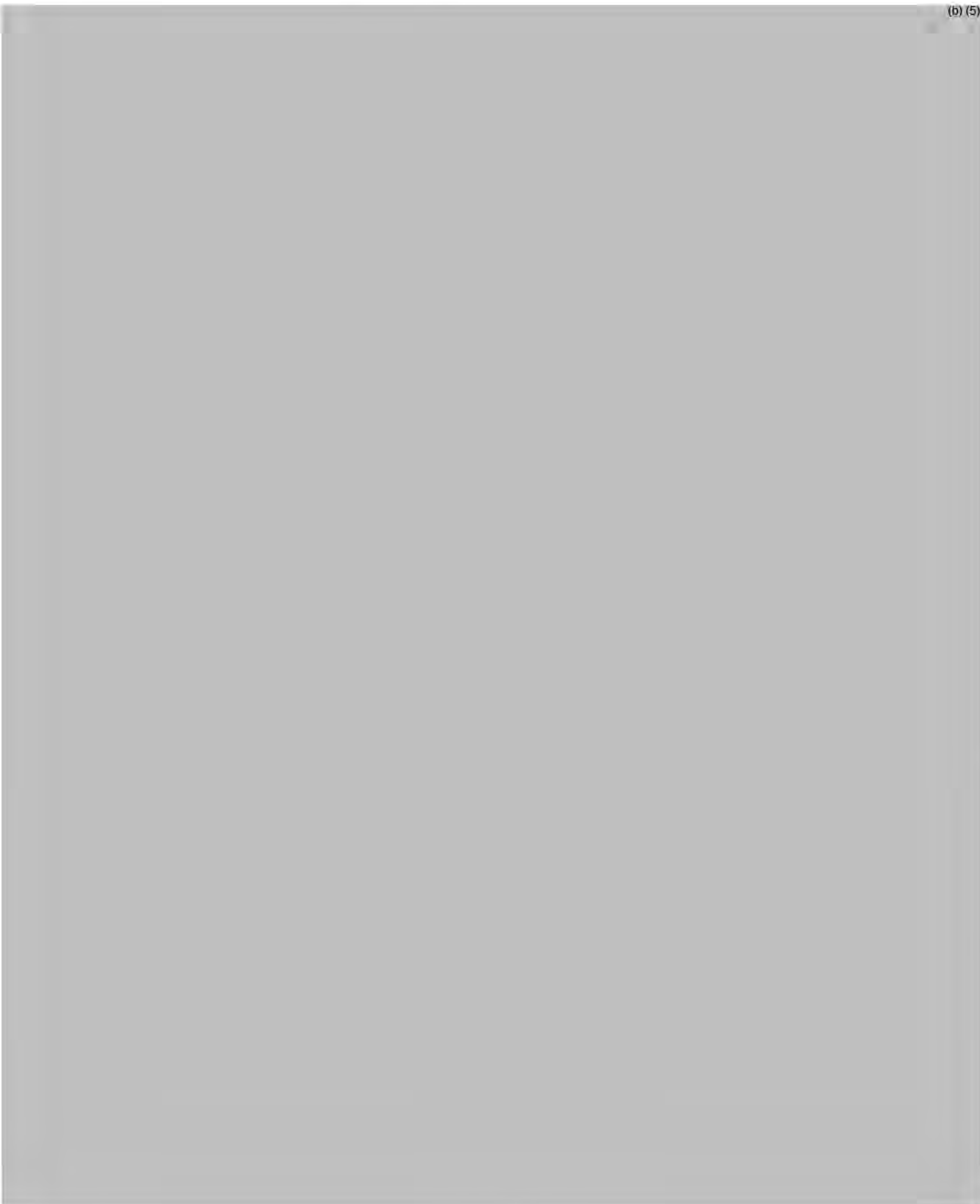
Mary

DRAFT AGENDA

FDA-NIH Dystrophin Methodology Workshop
Location FDA White Oak Campus
Date March 20th 2015
DRAFT-DO NOT DISTRIBUTE

(b) (5)







From: [Rao, Ashutosh](#)
To: [Moscicki, Richard](#); [Leptak, Christopher](#)
Subject: RE: White paper reviewing methodology for dystrophin measurement
Date: Thursday, February 12, 2015 5:39:34 PM

Hi Rich,

For our internal meeting planning group, most might be aware of the major publications but here is a short-list of "suggested reading". There could, of course, be several additions to this list.

Ash

1: Beekman C, Sipkens JA, Testerink J, Giannakopoulos S, Kreuger D, van Deutekom JC, Campion GV, de Kimpe SJ, Loubakos A. A sensitive, reproducible and objective immunofluorescence analysis method of dystrophin in individual fibers in samples from patients with duchenne muscular dystrophy. PLoS One. 2014 Sep 22;9(9):e107494. doi: 10.1371/journal.pone.0107494. eCollection 2014. PubMed PMID: 25244123; PubMed Central PMCID: PMC4171506.

2: Anthony K, Arechavala-Gomez V, Taylor LE, Vulin A, Kaminoh Y, Torelli S, Feng L, Janghra N, Bonne G, Beuvin M, Barresi R, Henderson M, Laval S, Loubakos A, Campion G, Straub V, Voit T, Sewry CA, Morgan JE, Flanigan KM, Muntoni F. Dystrophin quantification: Biological and translational research implications. Neurology. 2014 Nov 25;83(22):2062-9. doi: 10.1212/WNL.0000000000001025. Epub 2014 Oct 29. PubMed PMID: 25355828; PubMed Central PMCID: PMC4248450.

3: Mendell JR, Rodino-Klapac LR, Sahenk Z, Roush K, Bird L, Lowes LP, Alfano L, Gomez AM, Lewis S, Kota J, Malik V, Shontz K, Walker CM, Flanigan KM, Corridore M, Kean JR, Allen HD, Shilling C, Melia KR, Sazani P, Saoud JB, Kaye EM; Eteplirsen Study Group. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013 Nov;74(5):637-47. doi: 10.1002/ana.23982. Epub 2013 Sep 10. PubMed PMID: 23907995.

4: Chamberlain JS. Duchenne muscular dystrophy models show their age. Cell. 2010 Dec 23;143(7):1040-2. doi: 10.1016/j.cell.2010.12.005. PubMed PMID: 21183068; PubMed Central PMCID: PMC3038548.

5: Hathout Y, Marathi RL, Rayavarapu S, Zhang A, Brown KJ, Seol H, Gordish-Dressman H, Cirak S, Bello L, Nagaraju K, Partridge T, Hoffman EP, Takeda S, Mah JK, Henricson E, McDonald C. Discovery of serum protein biomarkers in the mdx mouse model and cross-species comparison to Duchenne muscular dystrophy patients. Hum Mol Genet. 2014 Dec 15;23(24):6458-69. doi: 10.1093/hmg/ddu366. Epub 2014 Jul 15. PubMed PMID: 25027324; PubMed Central PMCID: PMC4240201.

6: Brown KJ, Marathi R, Fiorillo AA, Ciccimaro EF, Sharma S, Rowlands DS, Rayavarapu S, Nagaraju K, Hoffman EP, Hathout Y. Accurate Quantitation of Dystrophin Protein in Human Skeletal Muscle Using Mass Spectrometry. *J Bioanal Biomed*. 2012 Dec 18;Suppl 7. pii: 001. PubMed PMID: 23646235; PubMed Central PMCID: PMC3642779.

7: Voit T, Topaloglu H, Straub V, Muntoni F, Deconinck N, Campion G, De Kimpe SJ, Eagle M, Guglieri M, Hood S, Liefaard L, Loubakos A, Morgan A, Nakielny J, Quarcoo N, Ricotti V, Rolfe K, Servais L, Wardell C, Wilson R, Wright P, Kraus JE. Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study. *Lancet Neurol*. 2014 Oct;13(10):987-96. doi: 10.1016/S1474-4422(14)70195-4. Epub 2014 Sep 7. PubMed PMID: 25209738.

8: Anthony K, Arechavala-Gomez V, Ricotti V, Torelli S, Feng L, Janghra N, Tasca G, Guglieri M, Barresi R, Armaroli A, Ferlini A, Bushby K, Straub V, Ricci E, Sewry C, Morgan J, Muntoni F. Biochemical characterization of patients with in-frame or out-of-frame DMD deletions pertinent to exon 44 or 45 skipping. *JAMA Neurol*. 2014 Jan;71(1):32-40. doi: 10.1001/jamaneurol.2013.4908. PubMed PMID: 24217213.

9: Arechavala-Gomez V, Feng L, Morgan JE, Muntoni F. Correspondence: Measuring dystrophin-faster is not necessarily better. *Nat Rev Neurol*. 2012 Aug;8(8):469. doi: 10.1038/nrneurol.2012.15-c1. Epub 2012 Jul 10. PubMed PMID: 22777248.

10: Aartsma-Rus A, Ferlini A, Vroom E. Biomarkers and surrogate endpoints in Duchenne: meeting report. *Neuromuscul Disord*. 2014 Aug;24(8):743-5. doi: 10.1016/j.nmd.2014.03.006. Epub 2014 May 28. PubMed PMID: 24951452.

11: van den Bergen JC, Wokke BH, Hulsker MA, Verschuuren JJ, Aartsma-Rus AM. Studying the role of dystrophin-associated proteins in influencing Becker muscular dystrophy disease severity. *Neuromuscul Disord*. 2015 Jan 14. pii: S0960-8966(15)00021-8. doi: 10.1016/j.nmd.2015.01.002. [Epub ahead of print] PubMed PMID: 25633150.

From: Moscicki, Richard

From: [Leptak, Christopher](#)
To: [Moscicki, Richard](#); [Rao, Ashutosh](#)
Subject: RE: White paper reviewing methodology for dystrophin measurement
Date: Thursday, February 12, 2015 2:35:24 PM

Hmmmm... do not recall seeing or hearing of a white paper on the topic. Is the author(s) from FDA do you recall? Ash likely will know more...

From: Moscicki, Richard
Sent: Thursday, February 12, 2015 2:31 PM
To: Leptak, Christopher; Rao, Ashutosh
Subject: White paper reviewing methodology for dystrophin measurement

I have in my file a white paper on measurement of dystrophin, it is very comprehensive but I can't remember the author and its not on the white paper, do either of you know? Is it something that should be distributed as a backgrounder for the meeting? Rich.

From: [Leptak, Christopher](#)
To: [Ehrlich, Diane T](#)
Cc: [Moscicki, Richard](#); [Ligon, Sharnell \(CDER\)](#); [Gross, Mary](#); [Rao, Ashutosh](#); [Loewke, Sally A](#)
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop
Date: Thursday, February 12, 2015 12:42:53 PM
Attachments: [FDA_NIH_MOU.PDF](#)

Hi Diane,

Attached is the signed MOU for archival purposes. FYI, the repeated scanning and signing of the document to collect the multiple signatures resulted in a less than pristine image. That said, I think we are good.

Thanks to you and Sharnell for the insights in closing this loop!

Best,
Chris

From: Ehrlich, Diane T
Sent: Tuesday, February 03, 2015 4:07 PM
To: Leptak, Christopher
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop

Chris,

The letter is signed by Dr. Woodcock and ready to be picked up. I'm located in Building 51, Room 6190.

Diane

From: Leptak, Christopher
Sent: Friday, January 30, 2015 2:08 PM
To: Ehrlich, Diane T; CDER EXSEC
Cc: Ligon, Sharnell (CDER); Moscicki, Richard; Rao, Ashutosh; Gross, Mary; Bechtel, Christine; Loewke, Sally A
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop

<< File: Final DMD Public Workshop Letter of Agreement 1.30.15.docx >>

Diane,

Now that the NIH cosponsorship negotiations are in the rearview mirror, I am circling back to close the loop on the Letter of Agreement (final attached) for the upcoming workshop. What is the best approach? Will you coordinate the NIH and Dr. Woodcock signatures?

Thanks again for your prior advice and assistance with this matter.

Best,
Chris

From: Ehrlich, Diane T
Sent: Tuesday, December 09, 2014 3:45 PM
To: Leptak, Christopher
Cc: Ligon, Sharnell (CDER); Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine; Loewke, Sally A

Subject: Letter of Agreement FW: MOU for Dystrophin Workshop

Chris,

Chris Bechtel asked me to follow-up on this. When you are ready, send me the letter of agreement and I will obtain Dr. Woodcock's signature. Please copy our group email box CDER EXSEC in all correspondence.

Documenting this process is a great idea. I will discuss the possibility of a MAPP with Office of Management.

Thanks,

Diane

Diane Ehrlich
Public Health Analyst
Office of Executive Programs
Division of Executive Operations
CDER
Food and Drug Administration
301-796-3452
diane.ehrlich@fda.hhs.gov

From: Leptak, Christopher
Sent: Friday, December 05, 2014 10:57 AM
To: Ligon, Sharnell (CDER)
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine; Loewke, Sally A
Subject: RE: MOU for Dystrophin Workshop

Understood Sharnell. That information is most welcome and helpful. I will rework MOU into the letter of agreement form.

As a lessons learned, is there a way to capture this process/information into an SOP or MAPP. Over the past two months, there are been lots of discussions between different parts of CDER and its only near the end that the path has become clear. Although we do not do that many inter-agency types of workshops, it would be helpful for the next person not to reinvent the proverbial wheel. Is there someone you can suggest that I might contact to see if documenting this information is feasible?

Thanks again for the perspective and assistance,
Chris

From: Ligon, Sharnell (CDER)
Sent: Friday, December 05, 2014 10:35 AM
To: Leptak, Christopher
Cc: Moseicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine
Subject: RE: MOU for Dystrophin Workshop

Hi Chris,

I actually connected with Mary Hitch in OHCA to get clarification. Since it appears there will be no transfer of funds between FDA and NIH, this should be a letter of agreement instead of an MOU. In this case, signatures do not have to be obtained by OCHA, OCC and Ethics. I have provided a sample letter of agreement that was used for similar public workshops sponsored by us. I am also copying Chris Bechtel on this email, as she is the one who

normally handles the signatures, since this is being endorsed by Dr. Woodcock. If you have any questions, please let me know.

Thanks

Sharnell

<< File: Sample Public Workshop-Fellow Letter of Agreement.doc >>

From: Leptak, Christopher
Sent: Friday, December 05, 2014 6:37 AM
To: Ligon, Sharnell (CDER)
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary
Subject: RE: MOU for Dystrophin Workshop

Hi Sharnell,

Based on my outreach, I was not aware that it had to be vetted through those groups. Before doing so, do you know if will have to revetted should the MOU be updated to include additional NIH signatories. I ask as, at present, only one of the three NIH groups is providing funding but the other two may do so upon formal evaluation later this month.

If it needs to be revetted, I will hold off until we have the final response from those two NIH groups and then update the MOU as needed before submission to OCC, etc.

Thanks for any input you can provide.

Best,
Chris

From: Ligon, Sharnell (CDER)
Sent: Thursday, December 04, 2014 2:56 PM
To: Leptak, Christopher
Subject: RE: MOU for Dystrophin Workshop

Dear Chris,

Can you please let me know if this MOU has been vetted and cleared in Office of Health and Constituent Affairs, OCC and Ethics?

Thanks

Sharnell

Sharnell M. Ligon
Executive Assistant to Dr. Janet Woodcock
Food and Drug Administration
Center for Drug Evaluation and Research
* sharnell.ligon@fda.hhs.gov
* Office: 301-796-5253
* Fax: 301-595-7910

From: Leptak, Christopher
Sent: Wednesday, December 03, 2014 1:22 PM
To: Woodcock, Janet

Cc: Moscicki, Richard; Ligon, Sharnell (CDER)
Subject: MOU for Dystrophin Workshop

Dr. Woodcock,

Attached is a signed MOU for the upcoming dystrophin workshop. NIH (NCATS) has agreed to be co-sponsors from a financial perspective and as such, have cosigned the agreement. There is a good chance that NIAMS and NINDS will also provide financial support but since their internal process will not be evaluated until later in the month, we did not want to delay our planning efforts in the meantime. If they should approve a financial commitment, we can amend the MOU with the additional signatures.

Of note, I confirmed with Debbie Lavine, CDER's Co-Sponsorship Liaison, that since this is an inter-agency engagement, we do not currently have a process/form (so MOU should be sufficient) and the other considerations of Co-sponsorship between federal and non-federal groups do not apply.

If you can sign and email back a PDF copy, I will forward to NIH to complete the loop.

Thanks for your consideration,
Chris

<< File: Dystrophin MOU Austin.pdf >>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD. 20993

This letter is offered to acknowledge an agreement between the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration, and the National Institutes of Health to collaborate and carryout a co-sponsored one-time public workshop on "Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data." The public workshop will be held on March 20, 2015, from 8:30 a.m. to 5:30 p.m. at the Federal Research Center at White Oak, 10903 New Hampshire Avenue, Silver Spring, Maryland.

The purpose of the workshop is to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development. The intended audiences for this workshop are scientists and clinicians involved in the acquisition, measurement, and analysis of proteins associated with Duchenne Muscular Dystrophy (DMD).

This is an internal government agreement between FDA and NIH and does not confer any rights or benefits to any person or Partner. FDA and NIH agree to co-sponsor a one-day public workshop on the topic listed above. FDA and NIH will also produce and distribute meeting related materials such as presentations, reference materials, meeting transcripts, and meeting summaries. The co-sponsored workshop will facilitate an ongoing dialogue among relevant parties on issues related to drug development and scientific research for DMD. The workshop will discuss dystrophin and other low-expression protein quantification methodologies for human tissue. Stakeholders, including industry sponsors, academia, FDA and NIH, will be engaged to address challenging issues related to detection technologies including limitations, detection sensitivities, linearity, and reproducibility. Muscle biopsy collection, sample handling, reference materials, and image analysis will also be discussed. FDA and NIH with the appointed Steering Committee will participate in planning the agenda and the selection of speakers and panelists.

FDA will provide the necessary administrative oversight for workshop planning and delivery including agenda development, support personnel, registration logistics, travel and subsistence for approximately six invited speakers and panelists, workshop materials production and transcription services. NIH will provide the necessary administrative oversight for workshop planning and delivery including agenda development, support personnel, and travel and subsistence for approximately eight invited speakers and panelists [National Center for Advancing Translational Sciences (NCATS) (2 speakers), National Institute of Neurological Disorders and Stroke (NINDS) (3 speakers up to \$3000), and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) (3 speakers up to \$3000)].

No fees will be charged to participants of the planned workshop.

All activities undertaken through this letter of agreement are subject to the availability of personnel and appropriations. This public workshop will not involve transfer of funds. Each agency will be accountable for their own expenditures for their own appropriations and level of agreed support and responsibilities implementing the workshop.

FDACDER0005853



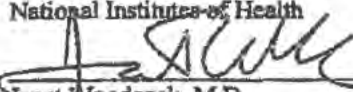
DEPARTMENT OF HEALTH & HUMAN SERVICES

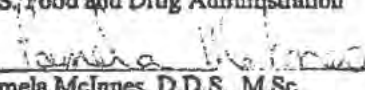
Public Health Service

Food and Drug Administration
Silver Spring, MD, 20993

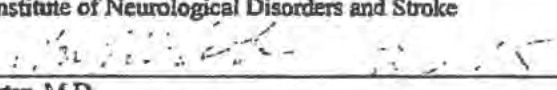
Agency Points of Contact: Chris Leptak (CDER/OND IO) and Ash Rao (CDER/OPS/OBP/DTP)
Food and Drug Administration
Center for Drug Evaluation and Research

Agency Points of Contact: Glen Nuckolls (NINDS), Amanda Boyce (NLAMS), and Petra Kaufmann (NCATS)
National Institutes of Health


Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration


Pamela McLane, D.D.S., M.Sc.
Deputy Director
National Institutes of Health
National Center for Advancing Translational Sciences


Walter Koroshetz, M.D.
Acting Director
National Institutes of Health
National Institute of Neurological Disorders and Stroke


Robert Carter, M.D.
Deputy Director
National Institutes of Health
National Institute of Arthritis and Musculoskeletal and Skin Diseases

FDACDER0005854

From: [Leptak, Christopher](#)
To: [Gross, Mary](#); [Rao, Ashutosh](#); [Moscicki, Richard](#)
Cc: [Ienzi, Georgiann](#)
Subject: RE: FDA public meeting transcriber request - Dystrophin
Date: Thursday, February 12, 2015 9:02:55 AM

From my point of view, we do not need the transcription since we will be generating a meeting summary (a few pages in length) that will be made public.

That's my two cents and open to whatever others think appropriate.
Chris

From: Gross, Mary
Sent: Thursday, February 12, 2015 7:59 AM
To: Rao, Ashutosh; Leptak, Christopher; Moscicki, Richard
Cc: Ienzi, Georgiann
Subject: FW: FDA public meeting transcriber request - Dystrophin

Hi - We said arranging for a transcriber was a go at the last steering committee meeting, but then understood from Chris that now we don't want it because NIH has sided with some in FDA, who think it's not necessary. Georgi arranged for the transcriber to come on March 20 and before we cancel, I'm double checking that you absolutely do not want a transcript of the meeting available. Would you let me know as soon as possible please? Thanks.

Mary

From: Ienzi, Georgiann
Sent: Monday, January 26, 2015 10:15 AM
To: amorjew@verizon.net
Subject: FDA public meeting transcriber request

Hi Janet,

CDER FDA is participating in a public meeting on March 20, 2015 on the FDA WO campus (Great Room). Are you available? If so, I will let the project manager know, so you can be sent the details. Hope to see you soon!

Thanks!

Georgiann

Georgiann Ienzi
Project Manager
CDER/OCD/IO
Drug Safety Oversight Board
301-796-3515
georgiann.ienzi@fda.hhs.gov

From: [Lu, Wei](#)
To: [Moran, Kristy](#)
Cc: [JW Direct Reports & Deputies](#); [Walsh, Sandy](#); [CDER-EOS](#); [Behr, Virginia L](#); [Liscinsky, Morgan](#); [Kremzner, Mary E](#); [Chew, Catherine](#); [Hong, Jaewon](#); [Drug Safety Web](#); [Peterson, Jayne E](#); [Sherwood, Edward M](#); [MedWatch Safety Alerts](#); [Unger, Ellis](#); [Locicero, Colleen L](#); [Pahon, Eric](#); [Thomas, Kimberly K \(ORP\)](#); [Moscicki, Richard](#); [Rao, Ashutosh](#); [Gross, Mary](#); [Leptak, Christopher](#); [CDER-ORP Requests](#)
Subject: Information Advisory: FRN of Public Scientific Workshop on Measuring Dystrophin in Dystrophinopathy Patients
Date: Monday, February 09, 2015 11:45:34 AM
Attachments: [IA announcing a public workshop on measuring dystrophin in dystrophinopathy patients CDER cleared.doc](#)

Hi Kristy,

On or about February 23rd, 2015, FDA will publish a Federal Register notice announcing a public scientific workshop to discuss dystrophin protein quantification methodologies for human tissue. This workshop is being cosponsored by the National Institutes of Health (NIH). The purpose of the workshop is to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development. The intended audiences for this workshop are scientists and clinicians involved in acquiring, measuring, and analyzing proteins associated with Duchenne Muscular Dystrophy (DMD).

This announcement will be of interest to the pharmaceutical industry, scientists, and clinicians diagnosing and treating patients with DMD. FDA will not issue a press release..

Please find the information advisory attached.

*****PLEASE NOTE THAT THIS INFORMATION IS NOT RELEASABLE TO THE PUBLIC UNTIL THE ACTION TAKES PLACE*****

Thanks,
Wei

Wei Lu, RN, MS
CDER/OEP/DEO
Bldg 51, Room 6174
Office: 301-796-3448
Fax: 301-847-8753
Email: Wei.Lu@fda.hhs.gov

Date: February 9, 2015

**INFORMATION ADVISORY
(CONFIDENTIAL)**

SUBJECT/LEAD COMPONENT: FDA to Issue Notice of Public Scientific Workshop to Discuss Dystrophin Protein Quantification Methodologies for Human Tissue

WHY THIS INFORMATION IS IMPORTANT FOR THE SECRETARY: On or about February 23rd, 2015, FDA will publish a Federal Register notice announcing a public scientific workshop to discuss dystrophin protein quantification methodologies for human tissue. This workshop is being cosponsored by the National Institutes of Health (NIH). The purpose of the workshop is to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development. The intended audiences for this workshop are scientists and clinicians involved in acquiring, measuring, and analyzing proteins associated with Duchenne Muscular Dystrophy (DMD).

This announcement will be of interest to the pharmaceutical industry, scientists, and clinicians diagnosing and treating patients with DMD. FDA will not issue a press release.

SUMMARY OF ISSUE, BACKGROUND, AND DEPARTMENT RESPONSE/ACTIONS:

- Dystrophinopathies result from genetic mutations in the dystrophin gene that decrease dystrophin protein levels and result in altered dystrophin function. These changes can lead to muscle degeneration and, in many patients, downstream pathologies including: inflammation and fibrosis that interfere with muscle regeneration, loss of movement, orthopedic complications, and ultimately respiratory and cardiac failure.
- The workshop will focus on: current methodologies being used in drug development and scientific research for DMD; and recent scientific advances that present opportunities for developing and validating robust methods for the objective, reliable, and quantitative measurement of DMD-associated proteins.
- The workshop will include overviews of current technologies used to detect dystrophin (including limitations, detection sensitivities, and reproducibility). A panel discussion will identify challenges of developing new detection methods. Muscle biopsy collection, sample handling, reference materials, and image analysis will also be discussed.
- The public hearing will be held on March 20, 2015 at FDA's White Oak Campus.

CONTACTS: Wei Lu, CDER/DEO, (301) 796-3448; Kristy Moran, FDA/OES, (301) 796-4678; Oliver Potts, OS/ES, (202) 401-4273.

The FRDTS number is 2015-98

Document history:

Prepared: WLu, DEO, 2/2/15

Edits: WLu, DEO, 2/4/15

Reviewed: ORP, 2/5/15

Edits: CLeptak, OND, 2/5/15

Edits: JBernstein, DEO, 2/5/15

Reviewed: MBClarke, OEP for CDER, 2/6/15

From: [Leptak, Christopher](#)
To: [Lu, Wei](#); [CDER-ORP Requests](#)
Cc: [Thomas, Kimberly K \(ORP\)](#); [Moscicki, Richard](#); [Rao, Asnutosn](#); [Gross, Mary](#)
Subject: RE: IA Drafting for FRN 2015-98 Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients
Date: Thursday, February 05, 2015 7:22:19 AM
Attachments: [Draft IA annuoucing a public workshop on DMD \(2\)CL.doc](#)

Hello Wei,

Thanks for the opportunity to review the draft IA for the dystrophin workshop. My edits are tracked in the attached document.

Best,
Chris

From: Lu, Wei
Sent: Wednesday, February 04, 2015 9:21 AM
To: CDER-ORP Requests
Cc: Leptak, Christopher; Thomas, Kimberly K (ORP)
Subject: FW: IA Drafting for FRN 2015-98 Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients
Importance: High

Good morning,

Please review the attached draft IA for FRN 2015-98 - Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients. Please provide comments back to me by COB Thursday, 2/5 if possible.

<< File: Draft IA annuoucing a public workshop on DMD.doc >>

Thanks,
Wei

Wei Lu, RN, MS
CDER/OEP/DEO
Bldg 51, Room 6174
Office: 301-796-3448
Fax: 301-847-8753
Email: Wei.Lu@fda.hhs.gov

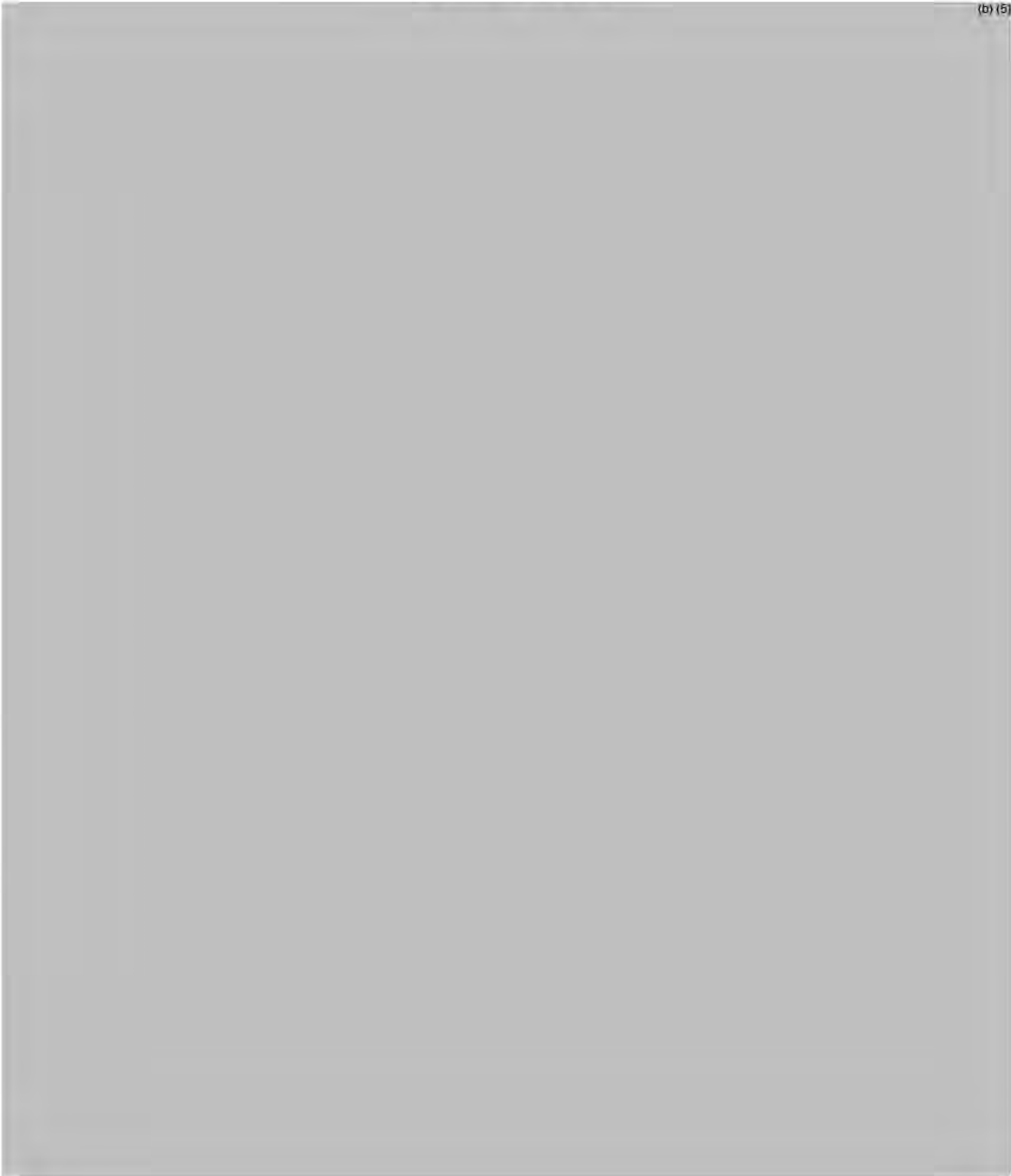
From: CDER-ORP Requests
Sent: Friday, January 30, 2015 1:04 PM
To: CDER EXSEC
Cc: Bechtel, Christine; Leptak, Christopher; CDER-ORP Requests
Subject: IA Drafting for FRN 2015-98 Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients
Importance: High

Hello,

Date: February 4, 2015

**INFORMATION ADVISORY
(CONFIDENTIAL)**

(b) (5)





From: [Leptak, Christopher](#)
To: [Thomas, Kimberly K \(ORP\)](#); [Lu, Wei](#); [CDER-ORP Requests](#)
Cc: [Moscicki, Richard](#); [Rao, Ashutosh](#); [Gross, Mary](#); [Loewke, Sally A](#)
Subject: RE: IA Drafting for FRN 2015-98 Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients
Date: Thursday, February 05, 2015 9:35:08 AM

Kim,

Thank you very much for your expeditious and efficient handling of this FR Notice.

Best,

Chris

From: Thomas, Kimberly K (ORP)
Sent: Thursday, February 05, 2015 9:30 AM
To: Leptak, Christopher; Lu, Wei; CDER-ORP Requests
Cc: Moscicki, Richard; Rao, Ashutosh; Gross, Mary
Subject: RE: IA Drafting for FRN 2015-98 Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients

Thanks,

Wei as a FYI the document was sent up this morning to RPMS. The request date for display is February 23 which means the target publish date is the day after. Christopher as soon as we get electronic sign off from the Office of Policy this can be announced on the Upcoming Meeting Page <http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm>

With regards,

Kim

~~~~~  
Kim K. Thomas, MS, PMP

Lead Regulatory Project Manager

FDA/CDER Office of Regulatory Policy

White Oak, Bldg 51 6220

10903 New Hampshire Ave

Silver Spring, MD 20903

Tel: 301.796.2357

[kimberly.k.thomas@fda.hhs.gov](mailto:kimberly.k.thomas@fda.hhs.gov)

---

**From:** Leptak, Christopher  
**Sent:** Thursday, February 05, 2015 7:22 AM  
**To:** Lu, Wei; CDER-ORP Requests  
**Cc:** Thomas, Kimberly K (ORP); Moscicki, Richard; Rao, Ashutosh; Gross, Mary  
**Subject:** RE: IA Drafting for FRN 2015-98 Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients

Hello Wei,

Thanks for the opportunity to review the draft IA for the dystrophin workshop. My edits are tracked in the attached document.

Best,

Chris

<< File: Draft IA annoucing a public workshop on DMD (2)CL.doc >>

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**From:** Lu, Wei  
**Sent:** Wednesday, February 04, 2015 9:21 AM  
**To:** CDER-ORP Requests  
**Cc:** Leptak, Christopher; Thomas, Kimberly K (ORP)  
**Subject:** FW: IA Drafting for FRN 2015-98 Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients  
**Importance:** High

Good morning,

Please review the attached draft IA for FRN 2015-98 - Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients. Please provide comments back to me by COB Thursday, 2/5 if possible.

<< File: Draft IA annoucing a public workshop on DMD.doc >>

Thanks,

Wei

---

Wei Lu, RN, MS

CDER/OEP/DEO

Bldg 51, Room 6174

**FDACDER0005863**

Office: 301-796-3448

Fax: 301-847-8753

Email: [Wei.Lu@fda.hhs.gov](mailto:Wei.Lu@fda.hhs.gov)

---

**From:** CDER-ORP Requests

**Sent:** Friday, January 30, 2015 1:04 PM

**To:** CDER EXSEC

**Cc:** Bechtel, Christine; Leptak, Christopher; CDER-ORP Requests

**Subject:** IA Drafting for FRN 2015-98 Public Workshop on Measuring Dystrophin in Dystrophinopathy Patients

**Importance:** High

Hello,

Please regard this email as a formal request for the drafting of an IA for the attached FR notice. Our goal is to send up to RPMS early next week. Upon completion, please send a copy of the draft to the CDER-ORP Requests mailbox.

The contact person is Christopher Leptak

The FRDTS number is 2015-98

<< File: Final Dystrophin Workshop FR Notice for clearance.docx >>

Thanks

With regards,

Kim

~~~~~  
Kim K. Thomas, MS, PMP

Lead Regulatory Project Manager

FDA/CDER Office of Regulatory Policy

White Oak, Bldg 51 6220

10903 New Hampshire Ave

Silver Spring, MD 20903

Tel: 301.796.2357

kimberly.k.thomas@fda.hhs.gov

From: [Leptak, Christopher](#)
To: [Gross, Mary](#); [Ienzi, Georgiann](#)
Cc: [Moscicki, Richard](#); [Rao, Ashutosh](#); [Boyce, Amanda T \(NIH\)](#)
Subject: FW: Dystrophin FR Notice
Date: Wednesday, February 04, 2015 1:46:07 PM
Attachments: [IC traveler assignments 1 27.docx](#)

Hi Mary and Georgiann,

In addition to the two previous speakers, please add the following person to our FDA list of sponsored speakers (now a total of three) who will need travel arrangements:

James Ervasti (requires travel from Florida) jervasti@umn.edu

James M. Ervasti, Professor

Department of Biochemistry, Molecular Biology & Biophysics

Distinguished Scholar and Research Director

Paul and Sheila Wellstone Muscular Dystrophy Center

University of Minnesota

6-155 Jackson Hall

321 Church Street SE

Minneapolis, MN 55455

<https://www.cbs.umn.edu/bmbb/contacts/james-m-ervasti>

Tel: 612-626-6517

Fax: 612-625-2163

Much appreciated,

Chris

From: Leptak, Christopher
Sent: Friday, January 30, 2015 11:50 AM
To: Gross, Mary
Cc: Ienzi, Georgiann; Rao, Ashutosh; Moscicki, Richard
Subject: RE: Dystrophin FR Notice

Hi Mary,

Here you go... Since a number of the speakers are local, we are only responsible for two speakers' travel. I previously asked for NIH to cover the one international speaker so that is off our plate.

Thanks

Chris

From: Gross, Mary
Sent: Friday, January 30, 2015 11:41 AM
To: Leptak, Christopher
Cc: Ienzi, Georgiann
Subject: RE: Dystrophin FR Notice

Hi Chris – I've included some language in the FR and have asked OCOMM to set up a webpage where we can post the FR, webcast info and agenda once it's ready. When I get this information back, I'll send it to you. I've asked for it back today.

Can you please send the names and addresses of the three travelers that FDA is responsible for so Georgi can get started putting them in Gov.trip. It's not an option for us to do international travel so another partner will need to be responsible for that assignment.

Thanks!

Mary

From: Leptak, Christopher
Sent: Friday, January 30, 2015 7:50 AM
To: Gross, Mary
Cc: Moscicki, Richard; Rao, Ashutosh
Subject: RE: Dystrophin FR Notice

Mary,

The FR Notice is ready for clearance except for your open elements. Do you have a timeline of when your last few pieces will be completed so that I can move it forward?

Thanks

Chris

From: Moscicki, Richard
Sent: Thursday, January 29, 2015 9:25 AM

To: Leptak, Christopher; Unger, Ellis; Dunn, Billy; Bastings, Eric; Gross, Mary
Cc: Rao, Ashutosh; Farkas, Ronald; Loewke, Sally A
Subject: RE: Dystrophin FR Notice

I have reviewed the proposed FR notice and have no additional comments, its fine with me.
Rich.

From: Leptak, Christopher
Sent: Thursday, January 29, 2015 6:59 AM
To: Moscicki, Richard; Unger, Ellis; Dunn, Billy; Bastings, Eric; Gross, Mary
Cc: Rao, Ashutosh; Farkas, Ronald; Loewke, Sally A
Subject: Dystrophin FR Notice
Importance: High

Hello,

I have updated the FR Notice based on input from FDA and NIH. The primary change was RE the transcript. NIH did not feel the need for a transcript (they too felt no one would read and it is not a standard practice for them). In lieu of a transcript, we agree to make a several page summary available to the public; that summary would be descriptive (not interpretive), drafted by FDA and NIH, and be at a high level.

If you can take a quick look for comments and Mary if you could address the missing information, I would like to get to ORP this week for clearance/publication. If I can assure ORP that Rich and OND have cleared this document, I think I can convince ORP that this simply needs to go to Dr. Woodcock for final endorsement.

Thanks

Chris

<< File: Dystrophin Workshop FR Notice 1.29.15.docx >>

NINDS

Jeff Chamberlain jsc5@uw.edu

Professor

Departments of Neurology, Medicine, and Biochemistry

McCaw Endowed Chair in Muscular Dystrophy

Director of the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center

University of Washington

HSB, Room K243

Seattle, Washington 98195-7720

Telephone: [206] 616-6645

Zarife Sahenk (Nationwide Children's) Zarife.Sahenk@NationwideChildrens.org

Zarife Sahenk, MD., PhD.

Professor, Pediatrics and Neurology

The Ohio State University

The Research Institute at Nationwide Children's Hospital

Neuromuscular Program

700 Children's Drive - Rm WA3024

Columbus, OH 43205

Ph: (614) 722-2202

Fax: (614) 355-5247

E-mail: Zarife.Sahenk@NationwideChildrens.org

Alt. E-mail: sahenk.1@osu.edu

Lee Sweeney lsweeney@mail.med.upenn.edu

William Maul Measey Professor in Physiology

University of Pennsylvania

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6085

Philadelphia, PA 19104-6085

Office: (215) 898-8727

Fax: (215) 573-2273

Email:

lsweeney@mail.med.upenn.edu

NIAMS

James Ervasti (requires travel from Florida) jervasti@umn.edu

James M. Ervasti, Professor

Department of Biochemistry, Molecular Biology & Biophysics

Distinguished Scholar and Research Director

Paul and Sheila Wellstone Muscular Dystrophy Center

University of Minnesota

6-155 Jackson Hall

321 Church Street SE

Minneapolis, MN 55455

<https://www.cbs.umn.edu/bmbb/contacts/james-m-ervasti>

Tel: 612-626-6517
Fax: 612-625-2163

Louise Rodino-Klapac (Nationwide Children's, does not expect travel assistance) Louise.Rodino-Klapac@nationwidechildrens.org
Louise R. Rodino-Klapac, Ph.D
Principal Investigator
Center for Gene Therapy
The Research Institute at Nationwide Children's Hospital
Assistant Professor-Department of Pediatrics
The Ohio State University
700 Children's Dr., Columbus OH 43205
Louise.Rodino-Klapac@nationwidechildrens.org

Kevin Flanagan Kevin.Flanigan@nationwidechildrens.org
Kevin M. Flanagan, MD
Principal Investigator
The Research Institute at Nationwide Children's Hospital
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Columbus, OH 43205
PH: (614) 722.5615
FX: (614) 722.3273

NCATS

Valentina Sardone (Muntoni Lab- UK) v.sardone@ucl.ac.uk
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Telephone: 020 7905 2111
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Kathryn Wagner MD PhD (Baltimore) wagnerk@kennedykrieger.org
Director, Center for Genetic Muscle Disorders
Kennedy Krieger Institute
801 N. Broadway
Baltimore, MD 21205
Phone: (443) 923-9525

FDA

David Rimm David.Rimm@Yale.edu
David L. Rimm M.D.-Ph.D.
Professor of Pathology and Medicine (Medical Oncology)

Director of Translational Pathology
Director, Yale Pathology Tissue Services
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New Haven, CT 06520-8023
ph 203-737-4204
fax 203-737-5089
[http://www.tissuearray.org/\[tissuearray.org\]](http://www.tissuearray.org/[tissuearray.org])
[http://www.yalepath.org/faculty.lasso?id=RimmDL\[yalepath.org\]](http://www.yalepath.org/faculty.lasso?id=RimmDL[yalepath.org])
David.Rimm@Yale.edu

Rabi Tawil Rabi_Tawil@urmc.rochester.edu
Rabi N. Tawil, M.D.
University of Rochester Medical Center
School of Medicine and Dentistry
601 Elmwood Ave, Box 673
Rochester, NY 14642
Office: (585) 275-2559
Fax: (585) 273-1255

From: Ehrlich, Diane T
To: Leptak, Christopher
Cc: Ligon, Sharnell (CDER); Moscicki, Richard; Rao, Ashutosh; Gross, Mary; Bechtel, Christine; Loewke, Sally A; CDER EXSEC
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop
Date: Monday, February 02, 2015 3:45:52 PM
Attachments: Final DMD Public Workshop Letter of Agreement 1.30.15.docx

Chris,

I will obtain Dr. Woodcock's signature on the Letter of Agreement, and let you know when it's ready to be picked up so that you can obtain the rest of the signatures from NIH. I assume that I need to remove the watermark which reads "SAMPLE" on this final version. Please confirm.

Diane

Diane Ehrlich
Public Health Analyst
Office of Executive Programs
Division of Executive Operations
CDER
Food and Drug Administration
301-796-3452
diane.ehrlich@fda.hhs.gov

From: Leptak, Christopher
Sent: Friday, January 30, 2015 2:08 PM
To: Ehrlich, Diane T; CDER EXSEC
Cc: Ligon, Sharnell (CDER); Moscicki, Richard; Rao, Ashutosh; Gross, Mary; Bechtel, Christine; Loewke, Sally A
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop

Diane,

Now that the NIH cosponsorship negotiations are in the rearview mirror, I am circling back to close the loop on the Letter of Agreement (final attached) for the upcoming workshop. What is the best approach? Will you coordinate the NIH and Dr. Woodcock signatures?

Thanks again for your prior advice and assistance with this matter.

Best,
Chris

From: Ehrlich, Diane T
Sent: Tuesday, December 09, 2014 3:45 PM
To: Leptak, Christopher
Cc: Ligon, Sharnell (CDER); Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine; Loewke, Sally A
Subject: Letter of Agreement FW: MOU for Dystrophin Workshop

Chris,

Chris Bechtel asked me to follow-up on this. When you are ready, send me the letter of agreement and I will obtain

Dr. Woodcock's signature. Please copy our group email box CDER EXSEC in all correspondence.

Documenting this process is a great idea. I will discuss the possibility of a MAPP with Office of Management.

Thanks,

Diane

Diane Ehrlich
Public Health Analyst
Office of Executive Programs
Division of Executive Operations
CDER
Food and Drug Administration
301-796-3452
diane.ehrlich@fda.hhs.gov

From: Leptak, Christopher
Sent: Friday, December 05, 2014 10:57 AM
To: Ligon, Sharnell (CDER)
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine; Loewke, Sally A
Subject: RE: MOU for Dystrophin Workshop

Understood Sharnell. That information is most welcome and helpful. I will rework MOU into the letter of agreement form.

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Thanks again for the perspective and assistance,
Chris

From: Ligon, Sharnell (CDER)
Sent: Friday, December 05, 2014 10:35 AM
To: Leptak, Christopher
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine
Subject: RE: MOU for Dystrophin Workshop

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Sharnell

<< File: Sample Public Workshop-Fellow Letter of Agreement.doc >>

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To: Leptak, Christopher
Subject: RE: MOU for Dystrophin Workshop

Dear Chris,

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Thanks

Sharnell

Sharnell M. Ligon
Executive Assistant to Dr. Janet Woodcock
Food and Drug Administration
Center for Drug Evaluation and Research
* sharnell.ligon@fda.hhs.gov
* Office: 301-796-5253
* Fax: 301-595-7910

From: Leptak, Christopher
Sent: Wednesday, December 03, 2014 1:22 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Ligon, Sharnell (CDER)
Subject: MOU for Dystrophin Workshop

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Agency Points of Contact: Chris Leptak (CDER/OND IO) and Ash Rao (CDER/OPS/OBP/DTP)
Food and Drug Administration
Center for Drug Evaluation and Research

Agency Points of Contact: Glen Nuckolls (NINDS), Amanda Boyce (NIAMS), and Petra Kaufmann (NCATS)
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Janet Woodcock, M.D.
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Acting Director
National Institutes of Health
National Institute of Neurological Disorders and Stroke

Robert Carter, M.D.
Deputy Director
National Institutes of Health
National Institute of Arthritis and Musculoskeletal and Skin Diseases

From: [Ehrlich, Diane T](#)
To: [Moscicki, Richard](#)
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop
Date: Tuesday, February 03, 2015 1:19:36 PM
Attachments: [Final DMD Public Workshop Letter of Agreement 1 30 15.docx](#)
Importance: High

Attached is the final letter of agreement for your review. Please let me know if you have any revisions/edits. Sharnell said if you're okay with it, we can just use the auto-pen machine to sign Dr. Woodcock's name.

Thanks,

Diane

From: Moscicki, Richard
Sent: Monday, February 02, 2015 4:09 PM
To: Ehrlich, Diane T; Leptak, Christopher
Cc: Ligon, Sharnell (CDER); Rao, Ashutosh; Gross, Mary; Bechtel, Christine; Loewke, Sally A; CDER EXSEC
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop

Fine to get Dr. Woodcock's signature but I would ask if I could sign in her place. We are trying to reduce the administrative burden and time on Dr. Woodcock. Rich.

From: Ehrlich, Diane T
Sent: Monday, February 02, 2015 3:46 PM
To: Leptak, Christopher
Cc: Ligon, Sharnell (CDER); Moscicki, Richard; Rao, Ashutosh; Gross, Mary; Bechtel, Christine; Loewke, Sally A; CDER EXSEC
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop

Chris,

I will obtain Dr. Woodcock's signature on the Letter of Agreement, and let you know when it's ready to be picked up so that you can obtain the rest of the signatures from NIH. I assume that I need to remove the watermark which reads "SAMPLE" on this final version. Please confirm.

Diane

Diane Ehrlich
Public Health Analyst
Office of Executive Programs
Division of Executive Operations
CDER
Food and Drug Administration
301-796-3452
diane.ehrlich@fda.hhs.gov

From: Leptak, Christopher
Sent: Friday, January 30, 2015 2:08 PM
To: Ehrlich, Diane T; CDER EXSEC
Cc: Ligon, Sharnell (CDER); Moscicki, Richard; Rao, Ashutosh; Gross, Mary; Bechtel, Christine; Loewke, Sally A
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop

<< File: Final DMD Public Workshop Letter of Agreement 1.30.15.docx >>

Diane,

Now that the NIH cosponsorship negotiations are in the rearview mirror, I am circling back to close the loop on the Letter of Agreement (final attached) for the upcoming workshop. What is the best approach? Will you coordinate the NIH and Dr. Woodcock signatures?

Thanks again for your prior advice and assistance with this matter.

Best,
Chris

From: Ehrlich, Diane T
Sent: Tuesday, December 09, 2014 3:45 PM
To: Leptak, Christopher
Cc: Ligon, Sharnell (CDER); Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine; Loewke, Sally A
Subject: Letter of Agreement FW: MOU for Dystrophin Workshop

Chris,

Chris Bechtel asked me to follow-up on this. When you are ready, send me the letter of agreement and I will obtain Dr. Woodcock's signature. Please copy our group email box CDER EXSEC in all correspondence.

Documenting this process is a great idea. I will discuss the possibility of a MAPP with Office of Management.

Thanks,

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Diane Ehrlich
Public Health Analyst
Office of Executive Programs
Division of Executive Operations
CDER
Food and Drug Administration
301-796-3452
diane.ehrlich@fda.hhs.gov

From: Leptak, Christopher
Sent: Friday, December 05, 2014 10:57 AM
To: Ligon, Sharnell (CDER)
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine; Loewke, Sally A
Subject: RE: MOU for Dystrophin Workshop

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agreement form.

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Dear Chris,

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Silver Spring, MD. 20993

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FDACDER0005883

From: [Leptak, Christopher](#)
To: [Ehrlich, Diane T](#); [CDER EXSEC](#)
Cc: [Ligon, Sharnell \(CDER\)](#); [Moscicki, Richard](#); [Rao, Ashutosh](#); [Gross, Mary](#); [Bechtel, Christine](#); [Loewke, Sally A](#)
Subject: RE: Letter of Agreement FW: MOU for Dystrophin Workshop
Date: Friday, January 30, 2015 2:07:35 PM
Attachments: [Final DMD Public Workshop Letter of Agreement 1.30.15.docx](#)

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FDACDER0005885

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Sharnell M. Ligon

Executive Assistant to Dr. Janet Woodcock

Food and Drug Administration

Center for Drug Evaluation and Research

✉ sharnell.ligon@fda.hhs.gov

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Public Health Service

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Deputy Director
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National Institute of Arthritis and Musculoskeletal and Skin Diseases

From: [Leptak, Christopher](#)
To: [Gross, Mary](#)
Cc: [Ienzi, Georgiann](#); [Rao, Ashutosh](#); [Moscicki, Richard](#)
Subject: RE: Dystrophin FR Notice
Date: Friday, January 30, 2015 11:49:50 AM
Attachments: [IC traveler assignments 1 27.docx](#)

Hi Mary,

Here you go... Since a number of the speakers are local, we are only responsible for two speakers' travel. I previously asked for NIH to cover the one international speaker so that is off our plate.

Thanks
Chris

From: Gross, Mary
Sent: Friday, January 30, 2015 11:41 AM
To: Leptak, Christopher
Cc: Ienzi, Georgiann
Subject: RE: Dystrophin FR Notice

Hi Chris - I've included some language in the FR and have asked OCOMM to set up a webpage where we can post the FR, webcast info and agenda once it's ready. When I get this information back, I'll send it to you. I've asked for it back today.

Can you please send the names and addresses of the three travelers that FDA is responsible for so Georgi can get started putting them in Gov.trip. It's not an option for us to do international travel so another partner will need to be responsible for that assignment. Thanks!

Mary

From: Leptak, Christopher
Sent: Friday, January 30, 2015 7:50 AM
To: Gross, Mary
Cc: Moscicki, Richard; Rao, Ashutosh
Subject: RE: Dystrophin FR Notice

Mary,

The FR Notice is ready for clearance except for your open elements. Do you have a timeline of when your last few pieces will be completed so that I can move it forward?

Thanks
Chris

From: Moscicki, Richard
Sent: Thursday, January 29, 2015 9:25 AM
To: Leptak, Christopher; Unger, Ellis; Dunn, Billy; Bastings, Eric; Gross, Mary

Cc: Rao, Ashutosh; Farkas, Ronald; Loewke, Sally A
Subject: RE: Dystrophin FR Notice

I have reviewed the proposed FR notice and have no additional comments, its fine with me. Rich.

From: Leptak, Christopher
Sent: Thursday, January 29, 2015 6:59 AM
To: Moscicki, Richard; Unger, Ellis; Dunn, Billy; Bastings, Eric; Gross, Mary
Cc: Rao, Ashutosh; Farkas, Ronald; Loewke, Sally A
Subject: Dystrophin FR Notice
Importance: High

Hello,

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Thanks
Chris

<< File: Dystrophin Workshop FR Notice 1.29.15.docx >>

NINDS

Jeff Chamberlain jsc5@uw.edu

Professor

Departments of Neurology, Medicine, and Biochemistry

McCaw Endowed Chair in Muscular Dystrophy

Director of the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center

University of Washington

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Telephone: [206] 616-6645

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NIAMS

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James M. Ervasti, Professor

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Distinguished Scholar and Research Director

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Principal Investigator

Center for Gene Therapy

The Research Institute at Nationwide Children's Hospital

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Louise.Rodino-Klapac@nationwidechildrens.org

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NCATS

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FDA

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David L. Rimm M.D.-Ph.D.

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New Haven, CT 06520-8023
ph 203-737-4204
fax 203-737-5089
[http://www.tissuearray.org/\[tissuearray.org\]](http://www.tissuearray.org/[tissuearray.org])
[http://www.yalepath.org/faculty.lasso?id=RimmDL\[yalepath.org\]](http://www.yalepath.org/faculty.lasso?id=RimmDL[yalepath.org])
David.Rimm@Yale.edu

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School of Medicine and Dentistry
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Rochester, NY 14642
Office: (585) 275-2559
Fax: (585) 273-1255

From: [Leptak, Christopher](#)
To: [Unger, Ellis](#); [Moscicki, Richard](#); [Dunn, Billy](#); [Bastings, Eric](#); [Gross, Mary](#)
Cc: [Rao, Ashutosh](#); [Farkas, Ronald](#); [Loewke, Sally A](#)
Subject: RE: Dystrophin FR Notice
Date: Thursday, January 29, 2015 12:41:44 PM

Changes made. Thanks Ellis

From: Unger, Ellis
Sent: Thursday, January 29, 2015 12:37 PM
To: Leptak, Christopher; Moscicki, Richard; Dunn, Billy; Bastings, Eric; Gross, Mary
Cc: Rao, Ashutosh; Farkas, Ronald; Loewke, Sally A
Subject: RE: Dystrophin FR Notice

A couple of comments:

1. In 3 places the announcement uses the word "hearing" instead of "workshop." If this is correct, I'm fine with it, but I wanted to draw your attention to it.
2. In the sentence below, I think the "or" should be "and":

"Dystrophinopathies result from genetic mutations in the dystrophin gene that decrease dystrophin protein expression levels ~~or~~ and result in altered dystrophin function."

Ellis

From: Leptak, Christopher
Sent: Thursday, January 29, 2015 6:59 AM
To: Moscicki, Richard; Unger, Ellis; Dunn, Billy; Bastings, Eric; Gross, Mary
Cc: Rao, Ashutosh; Farkas, Ronald; Loewke, Sally A
Subject: Dystrophin FR Notice
Importance: High

Hello,

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Thanks

Chris

<< File: Dystrophin Workshop FR Notice 1.29.15.docx >>

From: [Leptak, Christopher](#)
To: [Moscicki, Richard](#)
Subject: RE: Dystrophin FR Notice
Date: Thursday, January 29, 2015 9:25:52 AM

Rich,

Much appreciated.

Chris

From: Moscicki, Richard
Sent: Thursday, January 29, 2015 9:25 AM
To: Leptak, Christopher; Unger, Ellis; Dunn, Billy; Bastings, Eric; Gross, Mary
Cc: Rao, Ashutosh; Farkas, Ronald; Loewke, Sally A
Subject: RE: Dystrophin FR Notice

I have reviewed the proposed FR notice and have no additional comments, its fine with me.
Rich.

From: Leptak, Christopher
Sent: Thursday, January 29, 2015 6:59 AM
To: Moscicki, Richard; Unger, Ellis; Dunn, Billy; Bastings, Eric; Gross, Mary
Cc: Rao, Ashutosh; Farkas, Ronald; Loewke, Sally A
Subject: Dystrophin FR Notice
Importance: High

Hello,

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Thanks

Chris

<< File: Dystrophin Workshop FR Notice 1.29.15.docx >>

From: [Leptak, Christopher](#)
To: [Moscicki, Richard](#); [Unger, Ellis](#); [Dunn, Billy](#); [Bastings, Eric](#); [Gross, Mary](#)
Cc: [Rao, Ashutosh](#); [Farkas, Ronald](#); [Loewke, Sally A](#)
Subject: Dystrophin FR Notice
Date: Thursday, January 29, 2015 6:58:56 AM
Attachments: [Dystrophin Workshoo FR Notice 1.29.15.docx](#)
Importance: High

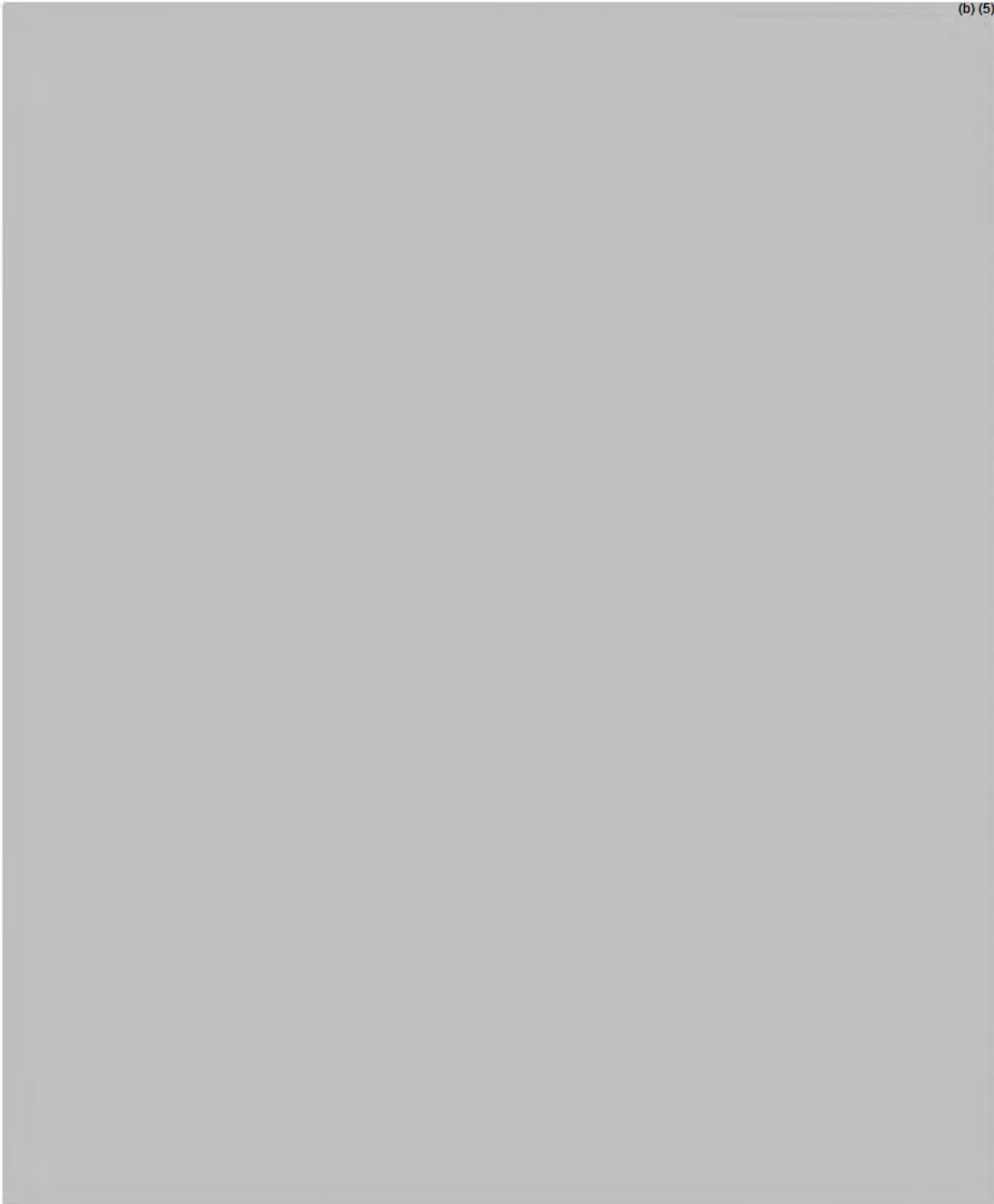
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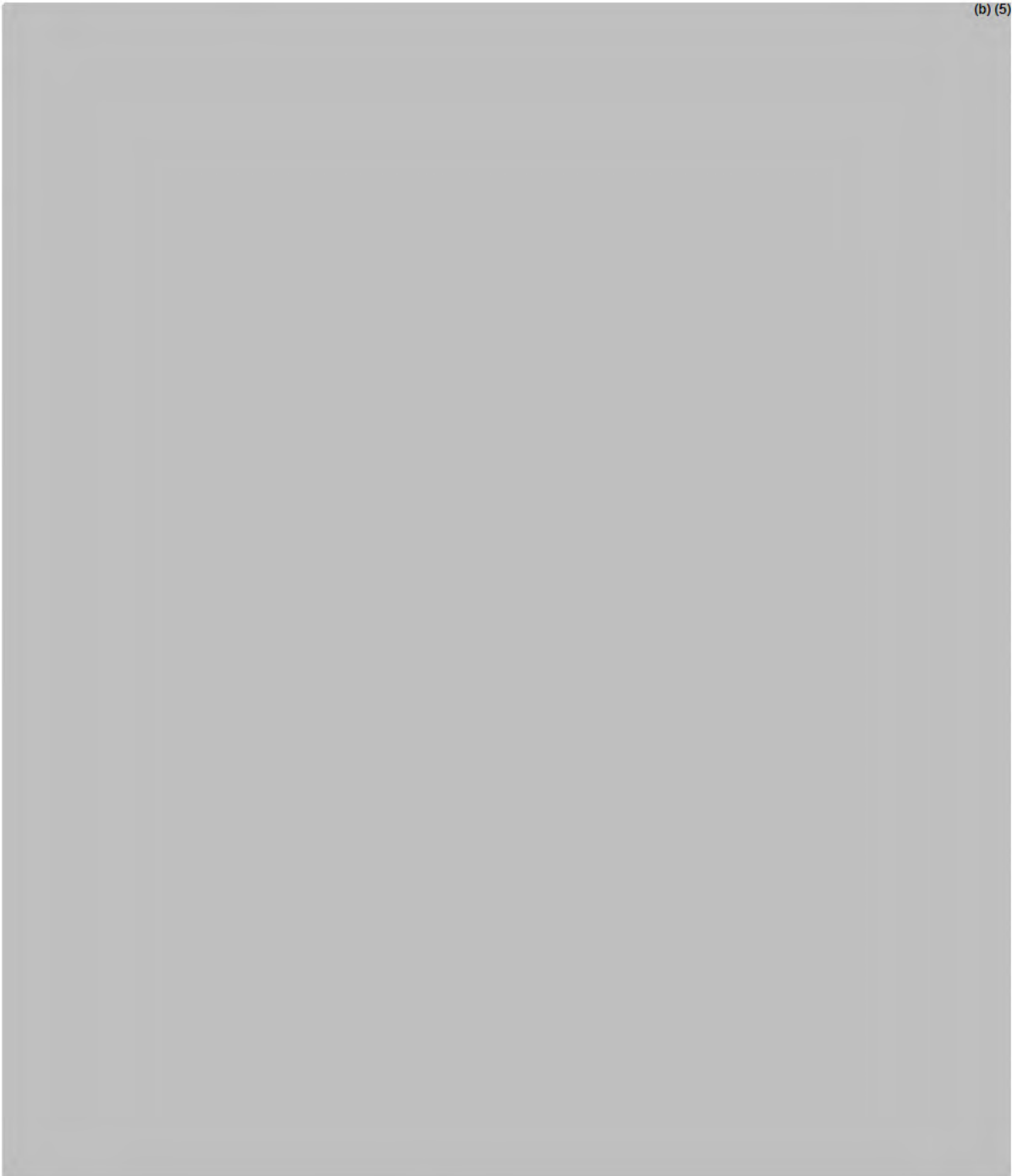
Thanks
Chris

(b) (5)





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(b) (5)

From: [Gross, Mary](#)
To: [Leptak, Christopher](#); [Moscicki, Richard](#); [Rao, Ashutosh](#)
Cc: [Ienzi, Georgiann](#); [Butler, Hope](#)
Subject: RE: Dystrophin
Date: Wednesday, January 28, 2015 1:02:42 PM

Ok. I guess our speakers lose out then. Obviously, we shouldn't mention honoraria during any of our calls with the speakers no matter who is traveling them in, once they are set up. And if any of them mention it, we just refer them back to NIH. I'm sure that the travel arrangements will be done differently as far as NIH and FDA go too.

Mary

From: Leptak, Christopher
Sent: Wednesday, January 28, 2015 12:55 PM
To: Gross, Mary; Moscicki, Richard; Rao, Ashutosh
Cc: Ienzi, Georgiann; Butler, Hope
Subject: RE: Dystrophin

Glen was very clear that it was a necessity on their part for the contract. It may be that each NIH silo does things a bit differently. Honestly, I was surprised that they still offer honoraria as it is rarely used anymore in professional settings.

From: Gross, Mary
Sent: Wednesday, January 28, 2015 12:53 PM
To: Leptak, Christopher; Moscicki, Richard; Rao, Ashutosh
Cc: Ienzi, Georgiann; Butler, Hope
Subject: RE: Dystrophin

I believe it's the only alternative since we don't offer honoraria here and we won't be picking up everyone's travel – can you double check to be sure that NIH has to offer honoraria. I've worked with NIH before on public meetings and haven't heard of it. I can't imagine why they would put an iron clad clause in their contract about offering honoraria. Thanks.

Mary

From: Leptak, Christopher
Sent: Wednesday, January 28, 2015 12:48 PM
To: Moscicki, Richard; Rao, Ashutosh; Gross, Mary
Subject: RE: Dystrophin

So given Hope's response, if we go ahead with the original plan of each group handling the travel assistance for its assigned speakers, there will be a \$200 honoraria going to NIH-sponsored folks that the FDA-sponsored folks will not receive. Are folks OK with that?

From: Butler, Hope
Sent: Wednesday, January 28, 2015 12:45 PM

To: Gross, Mary
Cc: Leptak, Christopher; Moscicki, Richard; Rao, Ashutosh
Subject: RE: Dystrophin

We don't offer honorariums for our speakers. NIH may want to check with the funding staff how to handle. The travel should be handled as discussed earlier---split among the three groups.

From: Gross, Mary
Sent: Wednesday, January 28, 2015 11:25 AM
To: Butler, Hope
Cc: Leptak, Christopher; Moscicki, Richard; Rao, Ashutosh
Subject: FW: Dystrophin

Hope – please see this note from Chris over the honoraria question. I don't think it's a good idea for NIH to provide honoraria and we don't give our speakers honoraria. Another not (at all) good option is for us to do all the travel and if we attach the IA, I believe we need ethics and OCC review, another bad option. Can you let us know about the option for providing honoraria to outside speakers from FDA's perspective.

Mary

From: Leptak, Christopher
Sent: Wednesday, January 28, 2015 11:02 AM
To: Gross, Mary; Moscicki, Richard
Cc: Rao, Ashutosh
Subject: Dystrophin

Mary and Rich,

So the never ending saga of cosponsorship has yet another new wrinkle... Glen (NINDS) called to share the following information. For NIH, they contract out speaker travel arrangements. Since three NIH groups are providing travel funding, they need all three NIH contracts to have the same speaker honoraria. Honoraria are both a requirement of the contract and common practice for NIH. To my knowledge, we do not give honoraria (not sure if this is a policy restriction or just part of our culture). So this new caveat presents two options:

1. We continue to have NIH take care of their speakers and we take care of ours as originally planned. Those covered by NIH will receive an Honoraria (\$200 according to Glen) while the FDA funded speakers may or may not receive the same compensation. If not, question of "fairness"...
2. We can add an Interagency Agreement to the Letter of Agreement (LOL... I now know much more about this area than I ever cared to) to transfer funds from NIH to FDA. That would mean that we then become responsible for arranging all of the speakers travel.

Thoughts? Other options? Words of wisdom to make this all end????

Chris

From: [Leptak, Christopher](#)
To: [Moscicki, Richard](#); [Rao, Ashutosh](#); [Gross, Mary](#)
Subject: RE: Dystrophin
Date: Wednesday, January 28, 2015 12:52:59 PM

Correct.

From: Moscicki, Richard
Sent: Wednesday, January 28, 2015 12:52 PM
To: Leptak, Christopher; Rao, Ashutosh; Gross, Mary
Subject: RE: Dystrophin

I am ok with that. Industry speakers I am assuming are coming on their own dollar and would not get honoraria. Rich.

From: Leptak, Christopher
Sent: Wednesday, January 28, 2015 12:48 PM
To: Moscicki, Richard; Rao, Ashutosh; Gross, Mary
Subject: RE: Dystrophin

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Mary

From: [Rao, Ashutosh](#)
To: [Unger, Ellis](#)
Cc: [Leptak, Christopher](#); [Farkas, Ronald](#); [Moscicki, Richard](#)
Subject: FW: Draft Agenda FDA-NIH Dystrophin Workshop 01-26.docx
Date: Wednesday, January 28, 2015 4:56:17 PM
Attachments: [Draft Agenda FDA-NIH Dystrophin Workshop 01-27.docx](#)

Hi Ellis,

At the last FDA steering committee meeting for this workshop, it was proposed that you give the closing remarks at the 5.15 time slot after the panel discussion. Is that okay with you? Latest draft of agenda is attached.

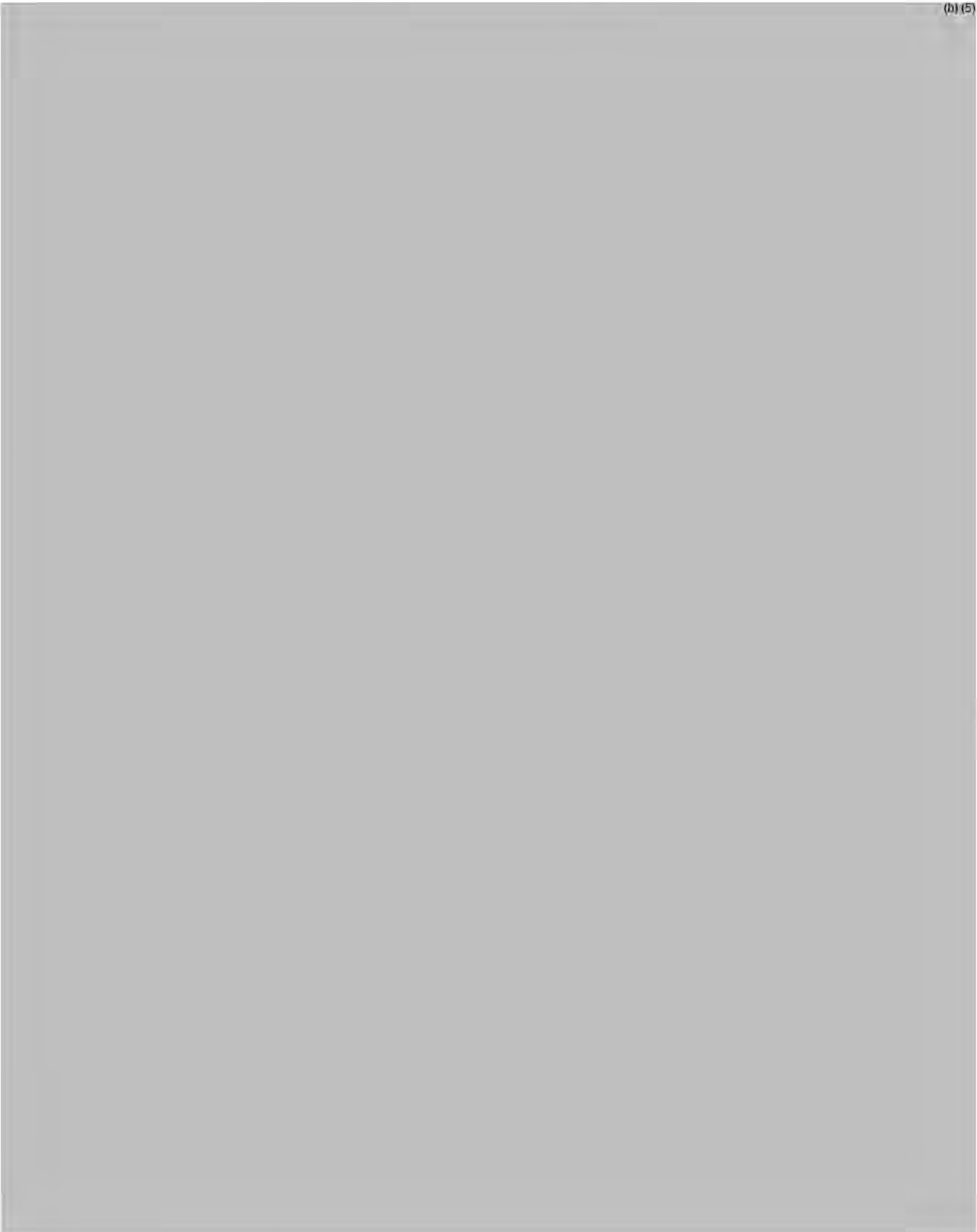
Best,
Ash

From: Leptak, Christopher
Sent: Monday, January 26, 2015 3:40 PM
To: Rao, Ashutosh; Farkas, Ronald; Gross, Mary
Subject: RE: Draft Agenda FDA-NIH Dystrophin Workshop 01-26.docx

Comment on scope included in tracked edits.
Chris

From: Rao, Ashutosh
Sent: Monday, January 26, 2015 3:24 PM
To: Farkas, Ronald; Leptak, Christopher; Gross, Mary
Subject: Draft Agenda FDA-NIH Dystrophin Workshop 01-26.docx

I have made some edits to the draft agenda based on our Friday meeting. Any comments before I send to the 4 pm meeting participants?



From: Leptak, Christopher
Sent: Wednesday, January 28, 2015 11:02 AM
To: Gross, Mary; Moscicki, Richard
Cc: Rao, Ashutosh
Subject: Dystrophin

Mary and Rich,

So the never ending saga of cosponsorship has yet another new wrinkle... Glen (NINDS) called to share the following information. For NIH, they contract out speaker travel arrangements. Since three NIH groups are providing travel funding, they need all three NIH contracts to have the same speaker honoraria. Honoraria are both a requirement of the contract and common practice for NIH. To my knowledge, we do not give honoraria (not sure if this is a policy restriction or just part of our culture). So this new caveat presents two options:

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Thoughts? Other options? Words of wisdom to make this all end????

Chris

From: Nuckolls, Glen (NIH/NINDS) [E] [mailto:nuckollg@ninds.nih.gov]

Sent: Monday, January 26, 2015 2:00 PM

To: Leptak, Christopher; Boyce, Amanda T (NIH); Kaufmann, Petra (NIH); Rao, Ashutosh; Farkas, Ronald; McInnes, Pamela (NIH/NCATS) [E]; Gibson, Jackie J (NIH)

Cc: Gross, Mary; Loewke, Sally A

Subject: RE: Dystrophin workshop FR Notice

Chris,

For NINDS, the document would be signed by Walter Koroshetz. See edits attached.

Glen

From: Leptak, Christopher (FDA/CDER)

Sent: Monday, January 26, 2015 12:49 PM

To: Nuckolls, Glen (NIH/NINDS) [E]; Boyce, Amanda (NIH/NIAMS) [E]; Kaufmann, Petra (NIH/NCATS) [E]; Rao, Ashutosh (FDA/CDER); Farkas, Ronald (FDA/CDER); McInnes, Pamela (NIH/NCATS) [E]; Gibson, Jackie (NIH/NCATS) [E]

Cc: Gross, Mary (FDA/CDER); Loewke, Sally A (FDA/CDER)

Subject: RE: Dystrophin workshop FR Notice

Importance: High

Folks,

Attached is a Letter of Agreement, MOU, whatever term works best for your respective institutions. Please review and provide any suggested edits by **COB Tuesday, 1/27/15**. Of note, this letter is very much in the same light as the previously circulated MOU. From FDA's perspective, we need to capture the information in this format. And although we do not call it an MOU but it appears that NIH does.... Honestly, I think we are just using different terms as the elements are the same.

As this topic has required way to many hours of my life (LOL), I hope that this will suffice for all parties involved.

Best,

Chris

From: Leptak, Christopher

Sent: Monday, January 26, 2015 10:54 AM

To: Nuckolls, Glen H (NIH); Boyce, Amanda T (NIH); Kaufmann, Petra (NIH); Rao, Ashutosh; Farkas, Ronald; McInnes, Pamela (NIH/NCATS) [E]; Gibson, Jackie J (NIH)

Subject: Dystrophin workshop FR Notice

Importance: High

Hello everyone,

Please find attached a draft FR Notice for the dystrophin workshop. Since this workshop is not linked

to a PDUFA commitment or other formal regulatory function, we are recommending that it be kept "short and sweet". Your tracked comments (if any) by **COB Tuesday, 1/27/15** are appreciated.

Thanks

Chris

<< File: Dystrophin Workshop FR Notice 1.26.15.docx >>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD. 20993

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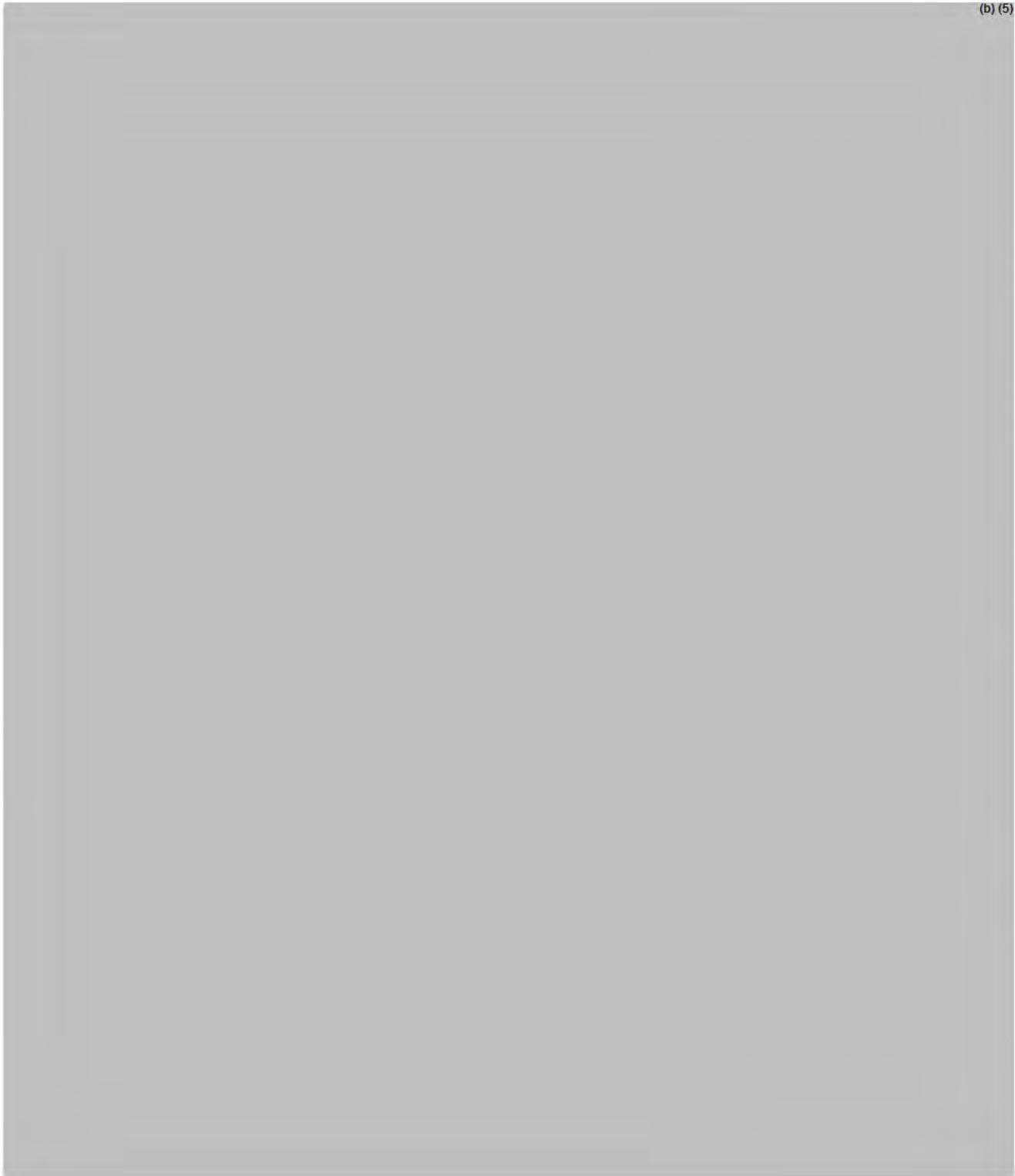
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD, 20993

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Below is a list of invited speakers.

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[REDACTED]

I A N

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[REDACTED]



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From: [Rao, Ashutosh](#)
To: [Moscicki, Richard](#); [Farkas, Ronald](#); [Leptak, Christopher](#)
Subject: Fw: Invitations to participate in the FDA/NIH workshop on dystrophin quantification
Date: Tuesday, January 27, 2015 5:55:19 PM

FYI-

From: Pat Furlong [<mailto:Pat@parentprojectmd.org>]
Sent: Tuesday, January 27, 2015 05:12 PM
To: Nuckolls, Glen H (NIH); John Porter <John@parentprojectmd.org>
Cc: Rao, Ashutosh
Subject: RE: Invitations to participate in the FDA/NIH workshop on dystrophin quantification

Thanks very much Glen and Ash. The agenda looks excellent.

I am really looking forward to the meeting.

Sincerely,

Pat

From: Nuckolls, Glen (NIH/NINDS) [E] [<mailto:nuckollg@ninds.nih.gov>]
Sent: Tuesday, January 27, 2015 5:00 PM
To: Pat Furlong; John Porter
Cc: Rao, Ashutosh (FDA/CDER)
Subject: Invitations to participate in the FDA/NIH workshop on dystrophin quantification

Pat and John,

Ash and I would like to invite you to both participate in the workshop that we're planning "Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data". The meeting will be on March 20 at FDA's White Oak Campus in Silver Spring, MD

We would appreciate if Pat could provide some brief comments related to the meetings scientific goals. Perhaps you could introduce the "Guidance to Industry" document. We would welcome John's help to moderate the final panel discussion. Please see the attached draft agenda (time allocations may change) and list of confirmed participants.

I look forward to seeing you at the DMD Biorepository meeting next Tue. We could discuss the workshop plans then.

Best regards,
Glen

Glen Nuckolls, Ph.D.
Program Officer, Neurogenetics Cluster
National Institute of Neurological Disorders and Stroke (NINDS)
National Institutes of Health (NIH)
6001 Executive Blvd.
Bethesda, MD 20892
glen.nuckolls@nih.gov
301-496-5876

From: [Leptak, Christopher](#)
To: [Rao, Ashutosh](#); [Farkas, Ronald](#); [Moscicki, Richard](#)
Subject: RE: Dystrophin workshop FR Notice
Date: Tuesday, January 27, 2015 10:08:39 AM

Hi Ash,

Completely agree. Likewise, not sure that the PPMD welcoming slot needs to be 10 min; would prefer not to take away time from the other slots to expand that role. The original 5 min is more appropriate.

Chris

From: Rao, Ashutosh
Sent: Tuesday, January 27, 2015 10:06 AM
To: Leptak, Christopher; Farkas, Ronald; Moscicki, Richard
Subject: FW: Dystrophin workshop FR Notice

Good morning,

I am inclined to tell Glen that it would be premature to put down a topic for Pat Furlong without having talked with her.

Additionally, I am not sure that "Framing the scientific discussion for the patient community" is fully within the specific methodology scope of the meeting. Something along the lines of "Perspectives on dystrophin methodology based on the proposed PPMD guidance document" might be more appropriate. Glen can request this topic via email and we can discuss with her before putting it down on the agenda.

Does the topic and strategy sound reasonable? Open to other thoughts and suggestions on this.

Best,
Ash

From: Nuckolls, Glen (NIH/NINDS) [E] [<mailto:nuckollg@ninds.nih.gov>]
Sent: Monday, January 26, 2015 5:59 PM
To: Rao, Ashutosh; Leptak, Christopher; Boyce, Amanda T (NIH); Kaufmann, Petra (NIH); Farkas, Ronald; McInnes, Pamela (NIH/NCATS) [E]; Gibson, Jackie J (NIH)
Cc: Gross, Mary; Loewke, Sally A
Subject: RE: Dystrophin workshop FR Notice

Ash,

I wanted to send Pat and John a draft agenda with their names on it. The draft you sent had 15 min total for Chris, FDA person and Pat. So I changed that to 15 for Chris, 15 for FDA and 10 for Pat. Then 20 for you to do the meeting objectives. See the attached draft to see if that makes sense – ok to send to Pat and John?

Thanks

Glen

From: Rao, Ashutosh (FDA/CDER)
Sent: Monday, January 26, 2015 3:58 PM
To: Nuckolls, Glen (NIH/NINDS) [E]; Leptak, Christopher (FDA/CDER); Boyce, Amanda (NIH/NIAMS) [E]; Kaufmann, Petra (NIH/NCATS) [E]; Farkas, Ronald (FDA/CDER); McInnes, Pamela (NIH/NCATS) [E]; Gibson, Jackie (NIH/NCATS) [E]
Cc: Gross, Mary (FDA/CDER); Loewke, Sally A (FDA/CDER)
Subject: RE: Dystrophin workshop FR Notice

Dear Glen et al,

Please see agenda with minor updates. Will discuss further during t-con.

Ash

From: Nuckolls, Glen (NIH/NINDS) [E] [<mailto:nuckollg@ninds.nih.gov>]
Sent: Monday, January 26, 2015 2:00 PM
To: Leptak, Christopher; Boyce, Amanda T (NIH); Kaufmann, Petra (NIH); Rao, Ashutosh; Farkas, Ronald; McInnes, Pamela (NIH/NCATS) [E]; Gibson, Jackie J (NIH)
Cc: Gross, Mary; Loewke, Sally A
Subject: RE: Dystrophin workshop FR Notice

Chris,

For NINDS, the document would be signed by Walter Koroshetz. See edits attached.

Glen

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To: Nuckolls, Glen (NIH/NINDS) [E]; Boyce, Amanda (NIH/NIAMS) [E]; Kaufmann, Petra (NIH/NCATS) [E]; Rao, Ashutosh (FDA/CDER); Farkas, Ronald (FDA/CDER); McInnes, Pamela (NIH/NCATS) [E]; Gibson, Jackie (NIH/NCATS) [E]
Cc: Gross, Mary (FDA/CDER); Loewke, Sally A (FDA/CDER)
Subject: RE: Dystrophin workshop FR Notice
Importance: High

Folks,

Attached is a Letter of Agreement, MOU, whatever term works best for your respective institutions. Please review and provide any suggested edits by **COB Tuesday, 1/27/15**. Of note, this letter is very much in the same light as the previously circulated MOU. From FDA's perspective, we need to capture the information in this format. And although we do not call it an MOU but it appears that NIH does.... Honestly, I think we are just using different terms as the elements are the same.

As this topic has required way to many hours of my life (LOL), I hope that this will suffice for all parties involved.

Best,
Chris

From: Leptak, Christopher

Sent: Monday, January 26, 2015 10:54 AM

To: Nuckolls, Glen H (NIH); Boyce, Amanda T (NIH); Kaufmann, Petra (NIH); Rao, Ashutosh; Farkas, Ronald; McInnes, Pamela (NIH/NCATS) [E]; Gibson, Jackie J (NIH)

Subject: Dystrophin workshop FR Notice

Importance: High

Hello everyone,

Please find attached a draft FR Notice for the dystrophin workshop. Since this workshop is not linked to a PDUFA commitment or other formal regulatory function, we are recommending that it be kept "short and sweet". Your tracked comments (if any) by **COB Tuesday, 1/27/15** are appreciated.

Thanks

Chris

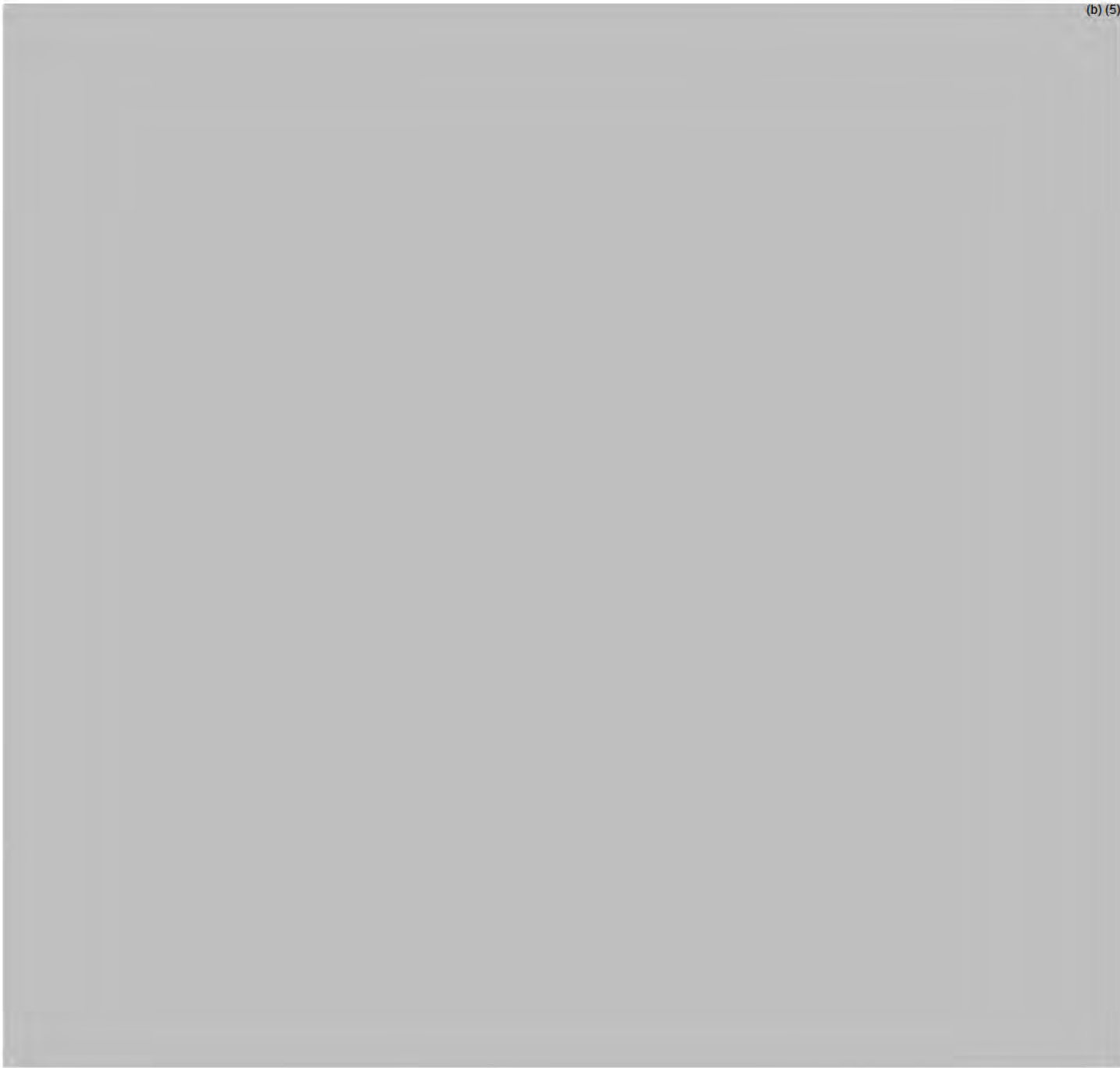
<< File: Dystrophin Workshop FR Notice 1.26.15.docx >>

From: [Kaiser, James](#)
To: [Leotak, Christopher](#); [Gross, Mary](#); [Moscicki, Richard](#); [Temple, Robert](#); [Unger, Ellis](#); [Dunn, Billy](#); [Bastings, Eric](#); [Rao, Ashutosh](#); [Kaiser, James](#); [Rogers, Hobart](#); [Ienzi, Georgiann](#)
Subject: FW: Dystrophin Public Meeting Planning -- Agenda and Background Attached
Date: Friday, January 23, 2015 3:37:34 PM
Attachments: [Dystrophin Workshop FR Notice.docx](#)

Just one edit and a couple of observations on top of Ron's version. -Jim

(b) (5)









From: [Leptak, Christopher](#)
To: [Gross, Mary](#); [Moscicki, Richard](#); [Temple, Robert](#); [Unger, Ellis](#); [Dunn, Billy](#); [Bastings, Eric](#); [Farkas, Ronald](#); [Rao, Ashutosh](#); [Kaiser, James](#); [Rogers, Hobart](#); [Ienzi, Georgiann](#); [CDER WO 1211 conf rm Bldg51 - AR](#)
Subject: RE: Dystrophin Public Meeting Planning -- Agenda and Background Attached
Date: Friday, January 23, 2015 9:55:12 AM
Attachments: [Dystrophin Workshop FR Notice.docx](#)

Hello everyone,

Please find a draft of the FR Notice attached. For our discussion this afternoon, there are a couple of comments for the steering committee's input. In general, since this workshop is not linked to a PDUFA commitment or other formal regulatory function, my advice, based on past experience, would be to keep the FR Notice focused simply as a meeting announcement. Since we will be engaging in a parallel effort to bring the workshop's attention to likely interested parties, the FR Notice would be reach others outside of this targeted outreach.

Best,
Chris

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

From: Gross, Mary
Sent: Friday, January 23, 2015 6:56 AM
To: Moscicki, Richard; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh; Kaiser, James; Rogers, Hobart; Leptak, Christopher; Ienzi, Georgiann; CDER WO 1211 conf rm Bldg51 - AR
Subject: Dystrophin Public Meeting Planning -- Agenda and Background Attached
When: Friday, January 23, 2015 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: CDER WO 1211 conf rm Bldg51 ; TCON number 877 704 7717; PC (b) (4)

Meeting Agenda

1. Update on Co-Sponsorship and IAA
2. Update on FR Notice
3. Discussion of Agenda
 - a. Confirmed Speakers, PPMD Speaker
 - b. Opening and closing remarks speakers?
 - c. Next steps
4. Budget discussion (total cost and how it is being divided up among partners - what is FDA's part)?
5. Public Meeting Outreach
6. Logistics
 - a. Meeting Registration
 - b. Speaker contact
 - c. Timeline
7. Next steps

<< File: Draft Agenda FDA-NIH Dystrophin Workshop 12-23_AR.DOCX >> << File: Dear Speaker1.doc >>
<< File: Doc24.doc >> << File: Scientific Methods to Detect Dystrophinopathies Scientific Workshop.pdf >>

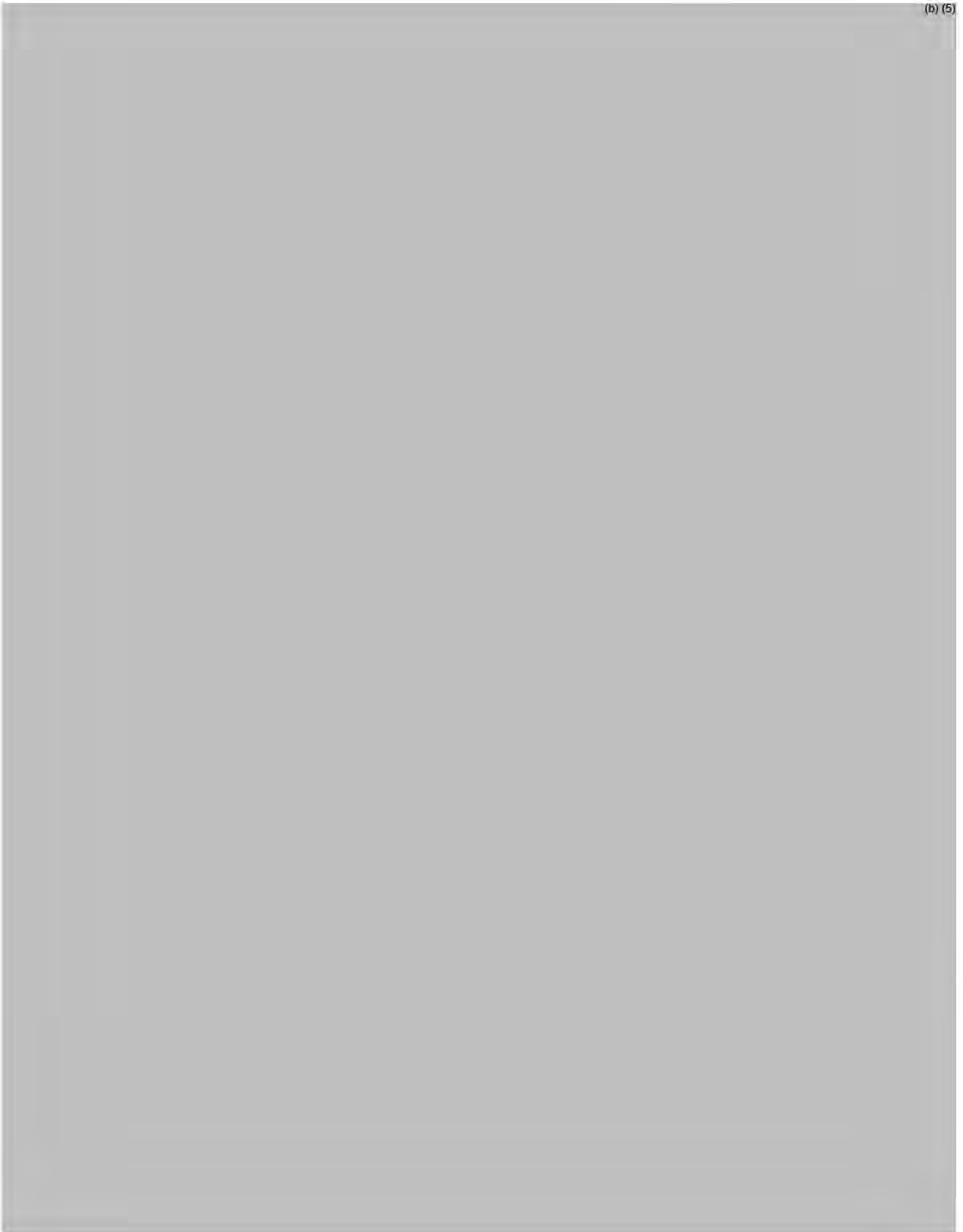
FDA-NIH Dystrophin Methodology Workshop

Location FDA White Oak Campus

Date March 20th 2015 (tentative)

DRAFT-DO NOT DISTRIBUTE

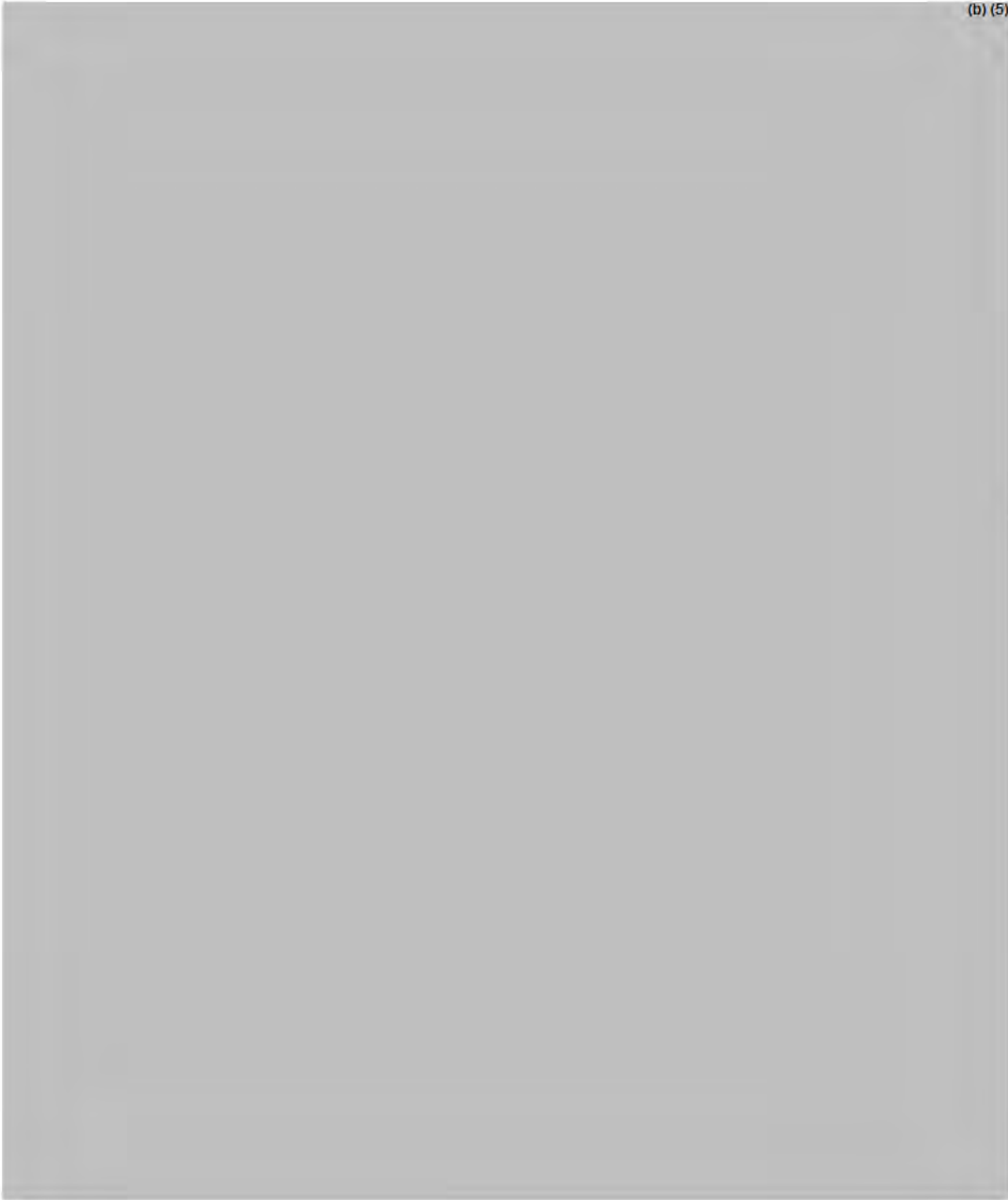
(b) (5)



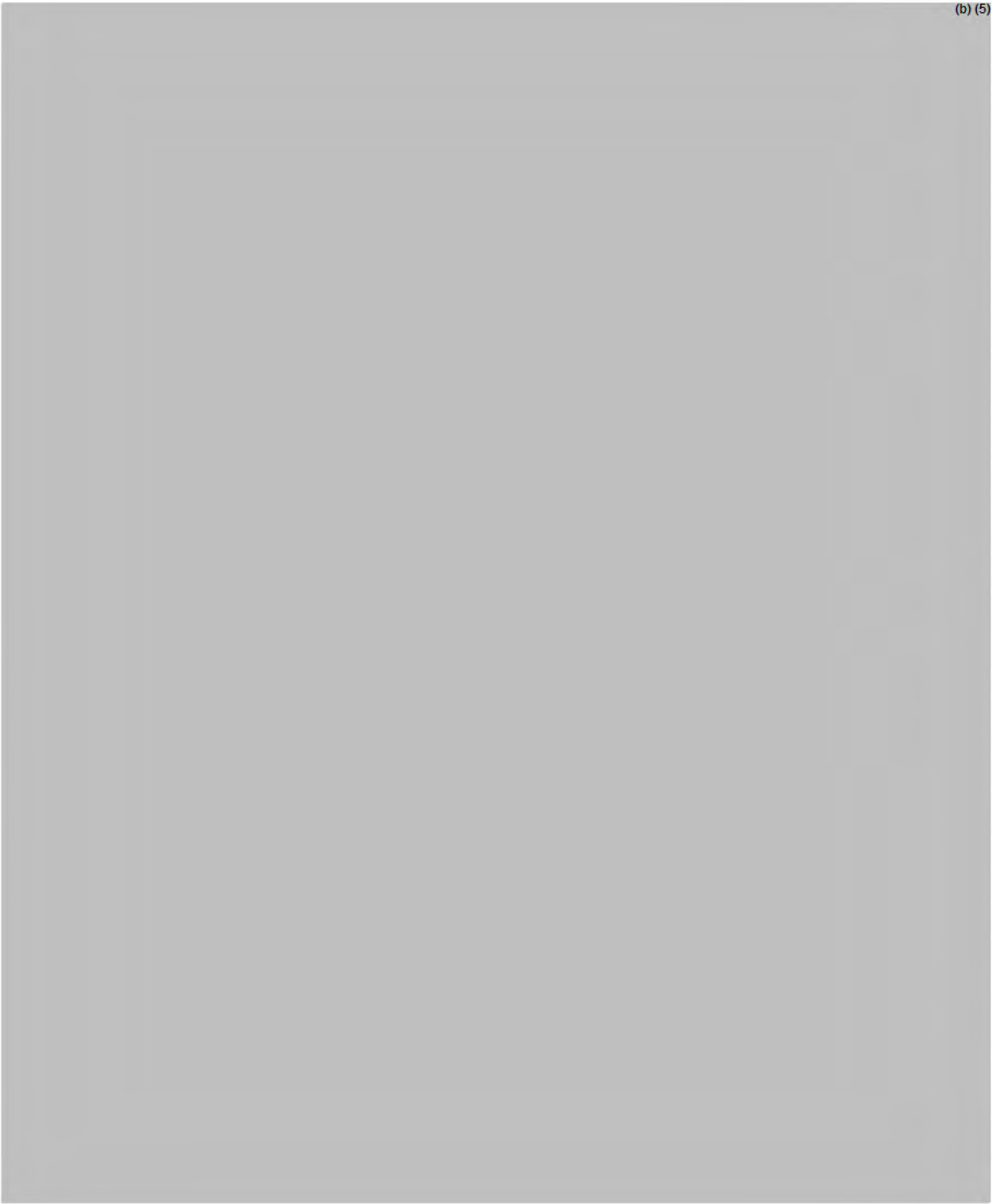




(b) (5)



(b) (5)





(b) (5)



From: [Farkas, Ronald](#)
To: [Leptak, Christopher](#); [Gross, Mary](#); [Moscicki, Richard](#); [Temple, Robert](#); [Unger, Ellis](#); [Dunn, Billy](#); [Bastings, Eric](#); [Rao, Ashutosh](#); [Kaiser, James](#); [Rogers, Hobart](#); [Ienzi, Georgiann](#); [CDER WO 1211 conf rm Bldg51 - AR](#)
Subject: RE: Dystrophin Public Meeting Planning -- Agenda and Background Attached
Date: Friday, January 23, 2015 11:07:41 AM
Attachments: [Dystrophin Workshop FR Notice.docx](#)

Some suggestions for the FR notice

Just heard from Sawchenko that he won't be participating.

Thanks

Ron

From: Leptak, Christopher
Sent: Friday, January 23, 2015 9:55 AM
To: Gross, Mary; Moscicki, Richard; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh; Kaiser, James; Rogers, Hobart; Ienzi, Georgiann; CDER WO 1211 conf rm Bldg51 - AR
Subject: RE: Dystrophin Public Meeting Planning -- Agenda and Background Attached

Hello everyone,

Please find a draft of the FR Notice attached. For our discussion this afternoon, there are a couple of comments for the steering committee's input. In general, since this workshop is not linked to a PDUFA commitment or other formal regulatory function, my advice, based on past experience, would be to keep the FR Notice focused simply as a meeting announcement. Since we will be engaging in a parallel effort to bring the workshop's attention to likely interested parties, the FR Notice would be reach others outside of this targeted outreach.

Best,
Chris

<< File: Dystrophin Workshop FR Notice.docx >>

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

From: Gross, Mary
Sent: Friday, January 23, 2015 6:56 AM
To: Moscicki, Richard; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh; Kaiser, James; Rogers, Hobart; Leptak, Christopher; Ienzi, Georgiann; CDER WO 1211 conf rm Bldg51 - AR
Subject: Dystrophin Public Meeting Planning -- Agenda and Background Attached
When: Friday, January 23, 2015 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: CDER WO 1211 conf rm Bldg51 ; TCON number 877 704 7717; PC (b) (4)

Meeting Agenda

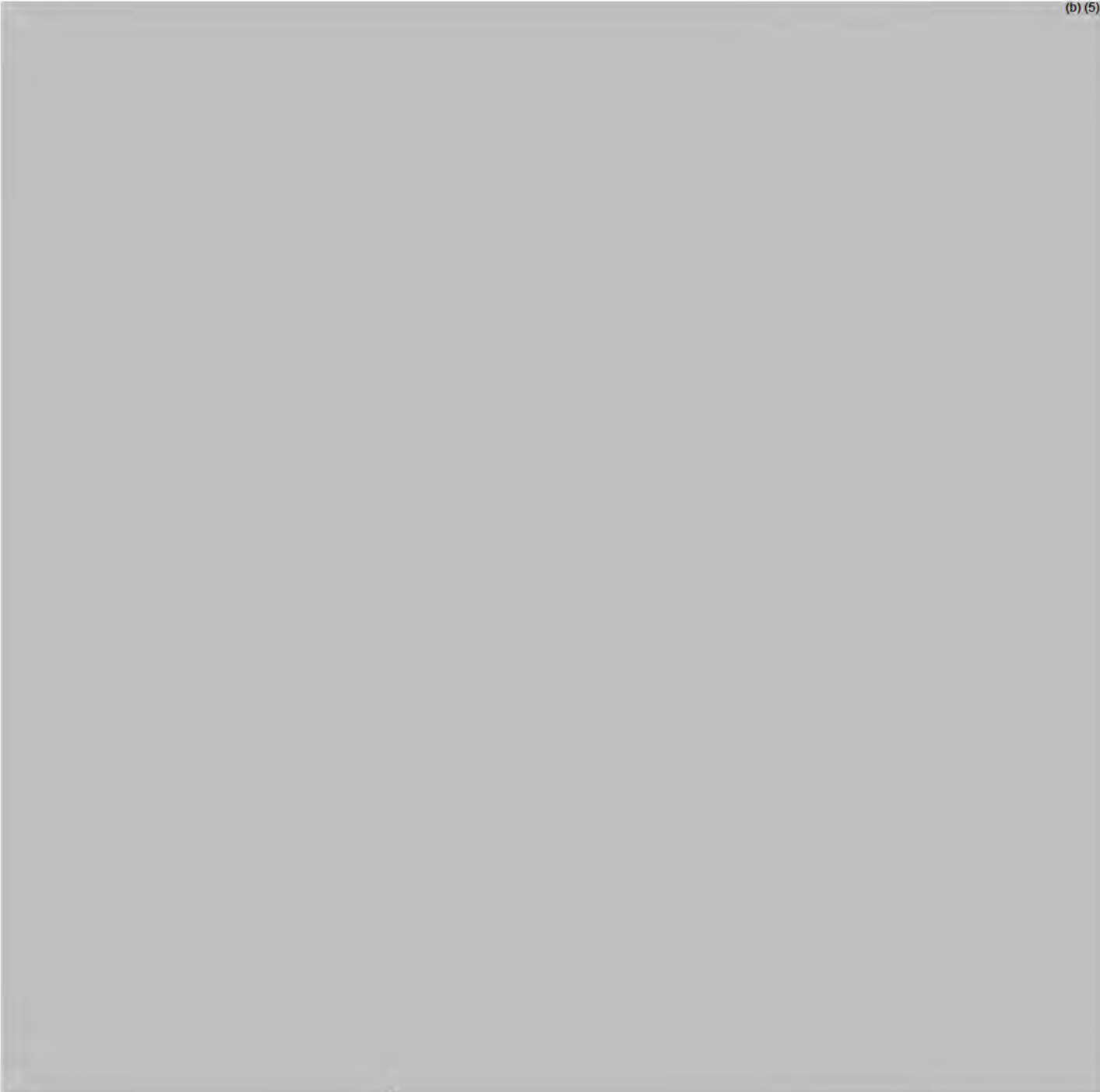
1. Update on Co-Sponsorship and IAA
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<< File: Draft Agenda FDA-NIH Dystrophin Workshop 12-23_AR.DOCX >> << File: Dear Speaker1.doc >>
<< File: Doc24.doc >> << File: Scientific Methods to Detect Dystrophinopathies Scientific Workshop.pdf >>

(b) (5)

(b) (5)





(b) (5)

From: [Gross, Mary](#)
To: [Austin, Christopher P \(NIH\)](#); [jervasti@umn.edu](#); [jsc5@uw.edu](#); [David.Rimm@Yale.edu](#); (b) (6)
[v.sardone@ucl.ac.uk](#); [c.beekman@prosensa.nl](#); [Louise.Rudino-Klapac@nationwidechildrens.org](#);
[zarife.sahenk@nationwidechildrens.org](#); [YHathaout@childrensnational.org](#);
[KevinFlanigan@nationwidechildrens.org](#); [ehoffman@childrensnational.org](#); [Rabi-Tawil@urmc.rochester.edu](#);
[wagnerk@kennedykrieger.org](#); [isweeney@mail.med.upenn.edu](#); [sawchenko@saik.edu](#)
Cc: [Finnegan, Sean J \(NIH\)](#); [Rao, Ashutosh](#); [Leptak, Christopher](#); [Butler, Hope](#); [Ienzi, Georgiann](#); [Moscicki, Richard](#);
[Farkas, Ronald](#)
Subject: FDA-NIH Dystrophin Methodology Workshop
Date: Wednesday, January 21, 2015 2:58:06 PM

Dear Speakers/Panelists – This note seeks confirmation that you are available to participate in the scientific workshop on Dystrophin Methodology co-sponsored by NIH and FDA that will be held at the FDA White Oak campus, 10903 New Hampshire Avenue, Silver Spring, MD on March 20, 2015. The workshop discussion will focus on currently available dystrophin protein quantitative methodologies for human tissue samples. If you have not received an invitation or find you will not be able to participate in the public meeting, please let me know by January 23.

Some of you will be traveling long-distance and will be reimbursed for your expenses. Administrative contacts from either FDA or NIH will be back in touch with you shortly about the necessary paperwork needed for reimbursement purposes.

In addition, we plan to touch base with the speakers and schedule tcons according to panel to consider speaker presentations, panel discussions and respond to your logistical questions. I will be back in touch with scheduling details shortly.

Thank you very much for agreeing to participate and we look forward to working with you on this important topic.

Mary

From: [Gross, Mary](#)
To: [Leptak, Christopher](#); [Moscicki, Richard](#); [Rao, Ashutosh](#)
Cc: [Tenzi, Georgiann](#); [Butler, Hope](#)
Subject: RE: Invitation to speak at FDA-NIH dystrophin methodology workshop
Date: Wednesday, January 21, 2015 8:30:56 AM

Great! Thanks.

From: Leptak, Christopher
Sent: Wednesday, January 21, 2015 8:25 AM
To: Moscicki, Richard; Rao, Ashutosh
Cc: Gross, Mary
Subject: FW: Invitation to speak at FDA-NIH dystrophin methodology workshop

FYI. Good news. Just wish it had not taken almost 3 months to come to a decision...

From: Boyce, Amanda (NIH/NIAMS) [E] [<mailto:boycea@mail.nih.gov>]
Sent: Wednesday, January 21, 2015 8:24 AM
To: Leptak, Christopher
Subject: RE: Invitation to speak at FDA-NIH dystrophin methodology workshop

Chris,

I have approval for \$3000 to travel speakers. Sorry it took so long!

Regards,
Amanda

Amanda Taylor Boyce, Ph.D.
Program Director
Muscle Development and Physiology
Division of Musculoskeletal Diseases
EP/NIAMS/NIH
1 Democracy Plaza
Suite 854
6701 Democracy Blvd.
Bethesda, MD 20892
301-594-5585
boycea@mail.nih.gov

From: Leptak, Christopher (FDA/CDER)
Sent: Tuesday, January 20, 2015 4:21 PM
To: Boyce, Amanda (NIH/NIAMS) [E]
Subject: RE: Invitation to speak at FDA-NIH dystrophin methodology workshop

Hi Amanda,

You are correct in that we agreed to not transfer funds. But, as I found out when I submitted the MOU I drafted, because, there is no funds transferred (i.e., we are each taking care of a subset of speakers), the appropriate doc is an IAA not an MOU. That said, the IAA will outline which groups (CDER, NCATS, etc.) will be responsible for "x" amount of funds or "x" number of speakers.

LOL, honestly, this whole interagency thing has been a headache... um, learning experience.. smile. Each person I speak with has a different take on the "real" process. It has convinced me to write a MAPP when this is done to save the next person some heartache.

Chris

From: Boyce, Amanda (NIH/NIAMS) [E] [<mailto:boycea@mail.nih.gov>]
Sent: Tuesday, January 20, 2015 2:49 PM
To: Leptak, Christopher
Subject: RE: Invitation to speak at FDA-NIH dystrophin methodology workshop

Just to be clear, the IAA is independent of funding, correct? My understanding is that we will be traveling people in and not transferring funds to the FDA. Thanks.

Regards,
Amanda

Amanda Taylor Boyce, Ph.D.
Program Director
Muscle Development and Physiology
Division of Musculoskeletal Diseases
EP/NIAMS/NIH
1 Democracy Plaza
Suite 854
6701 Democracy Blvd.
Bethesda, MD 20892
301-594-5585
boycea@mail.nih.gov

From: Leptak, Christopher (FDA/CDER)
Sent: Tuesday, January 20, 2015 1:37 PM
To: Boyce, Amanda (NIH/NIAMS) [E]
Cc: Rao, Ashutosh (FDA/CDER); Nuckolls, Glen (NIH/NINDS) [E]; Moscicki, Richard (FDA/CDER)
Subject: RE: Invitation to speak at FDA-NIH dystrophin methodology workshop
Importance: High

Hi Amanda,

Touching base again to see if you have a time frame as to when there might be a decision RE co-sponsorship? We need to have this finalized to complete the Interagency Agreement and FR Notice. Do you think you will have an answer by COB Friday 1/23? Otherwise, I would recommend that we move forward with just FDA/NCATS/NINDS that are already on board.

Thoughts?
Chris

From: Boyce, Amanda (NIH/NIAMS) [E] [<mailto:boycea@mail.nih.gov>]
Sent: Wednesday, January 14, 2015 11:26 AM
To: Leptak, Christopher
Subject: RE: Invitation to speak at FDA-NIH dystrophin methodology workshop

FYI, I've sent this up the chain. I'll let you know when I get approval.

Regards,
Amanda

Amanda Taylor Boyce, Ph.D.
Program Director
Muscle Development and Physiology
Division of Musculoskeletal Diseases
EP/NIAMS/NIH
1 Democracy Plaza
Suite 854
6701 Democracy Blvd.
Bethesda, MD 20892
301-594-5585
boycea@mail.nih.gov

From: [Gross, Mary](#)
To: [Leptak, Christopher](#)
Cc: [Moscicki, Richard](#); [Rao, Ashutosh](#); [Ienzi, Georgiann](#)
Subject: Dystrophin Meeting
Date: Thursday, January 15, 2015 1:26:20 PM

Hi Chis – I'm not clear on what's going on with the planning for this meeting, but unless a lot has happened that I'm unaware of, we don't have sufficient time to be ready to hold a public meeting in March. Please advise. Thanks.

Mary

From: [Lentak, Christopher](#)
To: [Moscicki, Richard](#)
Cc: [Unger, Ellis](#); [Rao, Ashutosh](#); [Gross, Mary](#)
Subject: Dystrophin Workshop
Date: Tuesday, January 13, 2015 12:25:39 PM

Hi Rich,

Following up on a couple of points RE to the workshop...

1. What are Janet's thoughts RE NIH's proposal for a patient's perspective speaking slot?
2. Since you will be on vacation, do you know if Janet will be coming to at least part of the meeting?
3. Mary had asked me if we need to submit a formal request for our part of the funding. I didn't think so but sharing with you for your thoughts.

Thanks much

Chris

From: [Ehrlich, Diane T](#)
To: [Leptak, Christopher](#)
Cc: [Ligon, Sharnell \(CDER\)](#); [Moscicki, Richard](#); [Rao, Ashutosh](#); [Farkas, Ronald](#); [Gross, Mary](#); [Bechtel, Christine](#); [Loewke, Sally A](#)
Subject: Letter of Agreement FW: MOU for Dystrophin Workshop
Date: Tuesday, December 09, 2014 3:45:08 PM

Chris,

Chris Bechtel asked me to follow-up on this. When you are ready, send me the letter of agreement and I will obtain Dr. Woodcock's signature. Please copy our group email box CDER EXSEC in all correspondence.

Documenting this process is a great idea. I will discuss the possibility of a MAPP with Office of Management.

Thanks,

Diane

Diane Ehrlich

Public Health Analyst

Office of Executive Programs

Division of Executive Operations

CDER

Food and Drug Administration

301-796-3452

diane.ehrlich@fda.hhs.gov

From: Leptak, Christopher
Sent: Friday, December 05, 2014 10:57 AM
To: Ligon, Sharnell (CDER)
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine; Loewke, Sally A
Subject: RE: MOU for Dystrophin Workshop

Understood Sharnell. That information is most welcome and helpful. I will rework MOU into the letter of agreement form.

As a lessons learned, is there a way to capture this process/information into an SOP or MAPP. Over the past two months, there are been lots of discussions between different parts of CDER and its only near the end that the path has become clear. Although we do not do that many inter-agency types of workshops, it would be helpful for the next person not to reinvent the proverbial

wheel. Is there someone you can suggest that I might contact to see if documenting this information is feasible?

Thanks again for the perspective and assistance,

Chris

From: Ligon, Sharnell (CDER)
Sent: Friday, December 05, 2014 10:35 AM
To: Leptak, Christopher
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine
Subject: RE: MOU for Dystrophin Workshop

Hi Chris,

I actually connected with Mary Hitch in OHCA to get clarification. Since it appears there will be no transfer of funds between FDA and NIH, this should be a letter of agreement instead of an MOU. In this case, signatures do not have to be obtained by OCHA, OCC and Ethics. I have provided a sample letter of agreement that was used for similar public workshops sponsored by us. I am also copying Chris Bechtel on this email, as she is the one who normally handles the signatures, since this is being endorsed by Dr. Woodcock. If you have any questions, please let me know.

Thanks

Sharnell

<< File: Sample Public Workshop-Fellow Letter of Agreement.doc >>

From: Leptak, Christopher
Sent: Friday, December 05, 2014 6:37 AM
To: Ligon, Sharnell (CDER)
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary
Subject: RE: MOU for Dystrophin Workshop

Hi Sharnell,

Based on my outreach, I was not aware that it had to be vetted through those groups. Before doing so, do you know if will have to revetted should the MOU be updated to include additional NIH signatories. I ask as, at present, only one of the

three NIH groups is providing funding but the other two may do so upon formal evaluation later this month.

If it needs to be revetted, I will hold off until we have the final response from those two NIH groups and then update the MOU as needed before submission to OCC, etc.

Thanks for any input you can provide.

Best,

Chris

From: Ligon, Sharnell (CDER)
Sent: Thursday, December 04, 2014 2:56 PM
To: Leptak, Christopher
Subject: RE: MOU for Dystrophin Workshop

Dear Chris,

Can you please let me know if this MOU has been vetted and cleared in Office of Health and Constituent Affairs, OCC and Ethics?

Thanks

Sharnell

Sharnell M. Ligon

Executive Assistant to Dr. Janet Woodcock

Food and Drug Administration

Center for Drug Evaluation and Research

✉ sharnell.ligon@fda.hhs.gov

☎ **Office: 301-796-5253**

7 **Fax: 301-595-7910**

From: Leptak, Christopher
Sent: Wednesday, December 03, 2014 1:22 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Ligon, Sharnell (CDER)
Subject: MOU for Dystrophin Workshop

Dr. Woodcock,

Attached is a signed MOU for the upcoming dystrophin workshop. NIH (NCATS) has agreed to be co-sponsors from a financial perspective and as such, have cosigned the agreement. There is a good chance that NIAMS and NINDS will also provide financial support but since their internal process will not be evaluated until later in the month, we did not want to delay our planning efforts in the meantime. If they should approve a financial commitment, we can amend the MOU with the additional signatures.

Of note, I confirmed with Debbie Lavine, CDER's Co-Sponsorship Liaison, that since this is an inter-agency engagement, we do not currently have a process/form (so MOU should be sufficient) and the other considerations of Co-sponsorship between federal and non-federal groups do not apply.

If you can sign and email back a PDF copy, I will forward to NIH to complete the loop.

Thanks for your consideration,

Chris

<< File: Dystrophin MOU Austin.pdf >>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD. 20993

(b) (5)

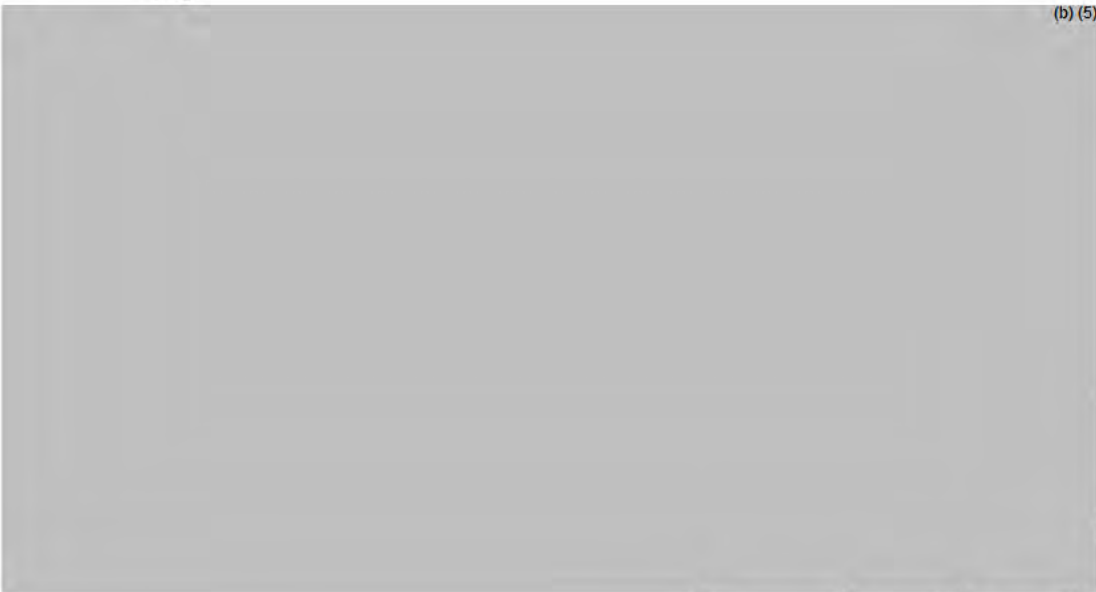




DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
(b) (5) Silver Spring, MD. 20993



SAMPLE

From: [Kaiser, James](#)
To: [Moscicki, Richard](#)
Cc: [Farkas, Ronald](#); [Dunn, Billy](#)
Subject: RE: Request for a Critical Path Innovation Meeting re: DMD
Date: Monday, December 08, 2014 12:42:35 PM
Attachments: [image001.png](#)

Rich – thank you. -Jim

From: Moscicki, Richard
Sent: Monday, December 08, 2014 12:26 PM
To: Kaiser, James
Cc: Farkas, Ronald; Dunn, Billy
Subject: RE: Request for a Critical Path Innovation Meeting re: DMD

Hi Jim, my apologies for not getting back to you sooner. We are interested in helping the DMD community achieve a safe and effective therapy for this very unmet need. Toward this end, an accurate disease model that is predictive of natural hx behavior of the disease would be very interesting. It should not derail our current dystrophin meeting. I would think we should move forward and clearer picture of the “want” here and what has been developed and to learn more about the requester as well. I think we should pursue further. Rich.

From: Kaiser, James
Sent: Tuesday, December 02, 2014 11:37 AM
To: Moscicki, Richard
Subject: Re: Request for a Critical Path Innovation Meeting re: DMD

Rich – I wonder if you had a chance to look over this email.

Jim

From: Kaiser, James
Sent: Monday, November 24, 2014 10:51 AM
To: Moscicki, Richard
Subject: Request for a Critical Path Innovation Meeting re: DMD

Rich – Will you please look at the following and get back to me as to next steps? ShaAvhrée thought it would be a good idea to ask you.

Susan Ward has reached out to me to consider a Critical Path Innovation Meeting with Duchenne Muscular Dystrophy as the disease background. The email trail is somewhat disjointed and not complete below, and for completeness (I hope) I have attached other emails that may help. Dr. Lim of *Faster Cures* had originally sent an email to introducing Dr. Ward to Ameeta and me (that is the one at the bottom of this email). Since then Dr. Ward have been trading some emails to schedule a discussion over the possibility of a CPIM.

I also called Ash about Dr. Ward’s interest last week, just as an FYI.

I Googled the TAP Collaboration (below Dr. Ward’s name in the email below) but didn’t come up

with any hits.

Jim

From: susan j ward [<mailto:susanj@ward.org>]
Sent: Friday, November 21, 2014 6:11 PM
To: Parekh, Ameeta; Kaiser, James
Cc: 'Kimberly McCleary'; 'Mark Lim'; James Signorovitch
Subject: RE: It was nice meeting you

Dear Mark,

It was a delight to speak with you at Faster Cures this week. Thank you so much for your generosity, and for the kind introduction to your colleagues at the FDA. I look forward to any future connection.

Dear Ameeta and James,

I am most pleased to 'e-meet' you. Mark provided enough of an introduction to CPIM to convince me of the need to become much better educated.

For context, the Collaboration Mark refers to is a multi-pharma sponsored research project exploring the feasibility of using growth modeling and latent class techniques to identify distinct clusters of patients with similar longitudinal trajectories of functional outcomes from (initially) the Natural History of patients with Duchenne Muscular Dystrophy (DMD). The premise is that insights drawn from a greater understanding of how longitudinal trajectories cluster may provide i) greater assurance of adequate matching between trials arms, ii) enrichment via enhanced inclusion/exclusion criteria or iii) a supplemental analysis of drug efficacy.

I am interested in better understanding the extent to which the agency has interest in learning about such research projects, and, should there be interest, better understanding the mechanisms by which the results of studies are best communicated. Might I book a call to address these questions with you? Or, if I am a little premature in soliciting guidance, perhaps you could indicate at what point I should get back in touch?

My sincere thanks for any guidance you can provide.

With my best wishes,
Susan

Susan J. Ward, Ph.D.
The TAP Collaboration
617-448-2617
susanj@ward.org

From: Mark Lim (m_lim@fastercures.org) [mailto:m_lim@fastercures.org]
Sent: Wednesday, November 19, 2014 3:49 PM
To: susanj@ward.org; Ameeta.Parekh@fda.hhs.gov; James.Kaiser@fda.hhs.gov

Cc: Kimberly McCleary (KMcCleary@fastercures.org)
Subject: It was nice meeting you

Dear Susan,

It was really nice chatting with you at Partnering For Cures. I wanted to follow-up from our conversation with an introduction to some of our colleagues at the FDA, who might have some thoughts about your multi-pharma collaboration to provide a statistical/mathematical model for predicting the natural progression of Duchenne muscular dystrophy. They are cc'd to this email.

Ameeta is in the Office of Translational Sciences and is a senior advisor in their collaborative efforts. The statistical sciences components of CDER fall under this office. James helps direct their effort to engage stakeholders, such as consortia, to develop regulatory tools, through their Critical Path Innovation Meetings. More information about CPIM can be found at <http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm395888.htm>

I'll drop off this email chain since I wouldn't give any justice in introducing your efforts. I hope these conversations are fruitful!

Happy Holidays!
Mark

Mark David Lim, PhD

FasterCures | A Center of the Milken Institute
Associate Director, Medical Research Innovation
m_lim@fastercures.org | 202.336.8918
twitter: [@markdlim](https://twitter.com/markdlim)

www.fastercures.org



From: [Leptak, Christopher](#)
To: [Ligon, Sharnell \(CDER\)](#)
Cc: [Moscicki, Richard](#); [Rao, Ashutosh](#); [Farkas, Ronald](#); [Gross, Mary](#); [Bechtel, Christine](#); [Loewke, Sally A](#)
Subject: RE: MOU for Dystrophin Workshop
Date: Friday, December 05, 2014 10:57:02 AM

Understood Sharnell. That information is most welcome and helpful. I will rework MOU into the letter of agreement form.

As a lessons learned, is there a way to capture this process/information into an SOP or MAPP. Over the past two months, there are been lots of discussions between different parts of CDER and its only near the end that the path has become clear. Although we do not do that many inter-agency types of workshops, it would be helpful for the next person not to reinvent the proverbial wheel. Is there someone you can suggest that I might contact to see if documenting this information is feasible?

Thanks again for the perspective and assistance,

Chris

From: Ligon, Sharnell (CDER)
Sent: Friday, December 05, 2014 10:35 AM
To: Leptak, Christopher
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary; Bechtel, Christine
Subject: RE: MOU for Dystrophin Workshop

Hi Chris,

I actually connected with Mary Hitch in OHCA to get clarification. Since it appears there will be no transfer of funds between FDA and NIH, this should be a letter of agreement instead of an MOU. In this case, signatures do not have to be obtained by OCHA, OCC and Ethics. I have provided a sample letter of agreement that was used for similar public workshops sponsored by us. I am also copying Chris Bechtel on this email, as she is the one who normally handles the signatures, since this is being endorsed by Dr. Woodcock. If you have any questions, please let me know.

Thanks

Sharnell

<< File: Sample Public Workshop-Fellow Letter of Agreement.doc >>

From: [Ligon, Sharnell \(CDER\)](#)
To: [Leptak, Christopher](#)
Cc: [Moscicki, Richard](#); [Rao, Ashutosh](#); [Farkas, Ronald](#); [Gross, Mary](#); [Bechtel, Christine](#)
Subject: RE: MOU for Dystrophin Workshop
Date: Friday, December 05, 2014 10:34:51 AM
Attachments: [Sample Public Workshop-Fellow Letter of Agreement.doc](#)

Hi Chris,

I actually connected with Mary Hitch in OHCA to get clarification. Since it appears there will be no transfer of funds between FDA and NIH, this should be a letter of agreement instead of an MOU. In this case, signatures do not have to be obtained by OCHA, OCC and Ethics. I have provided a sample letter of agreement that was used for similar public workshops sponsored by us. I am also copying Chris Bechtel on this email, as she is the one who normally handles the signatures, since this is being endorsed by Dr. Woodcock. If you have any questions, please let me know.

Thanks

Sharnell

From: Leptak, Christopher
Sent: Friday, December 05, 2014 6:37 AM
To: Ligon, Sharnell (CDER)
Cc: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gross, Mary
Subject: RE: MOU for Dystrophin Workshop

Hi Sharnell,

Based on my outreach, I was not aware that it had to be vetted through those groups. Before doing so, do you know if will have to be re-vetted should the MOU be updated to include additional NIH signatories. I ask as, at present, only one of the three NIH groups is providing funding but the other two may do so upon formal evaluation later this month.

If it needs to be re-vetted, I will hold off until we have the final response from those two NIH groups and then update the MOU as needed before submission to OCC, etc.

Thanks for any input you can provide.

Best,
Chris

From: Ligon, Sharnell (CDER)
Sent: Thursday, December 04, 2014 2:56 PM
To: Leptak, Christopher
Subject: RE: MOU for Dystrophin Workshop

Dear Chris,

Can you please let me know if this MOU has been vetted and cleared in Office of Health and Constituent Affairs, OCC and Ethics?

Thanks

Sharnell

Sharnell M. Ligon
Executive Assistant to Dr. Janet Woodcock
Food and Drug Administration
Center for Drug Evaluation and Research
* sharnell.ligon@fda.hhs.gov
* Office: 301-796-5253
* Fax: 301-595-7910

From: Leptak, Christopher
Sent: Wednesday, December 03, 2014 1:22 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Ligon, Sharnell (CDER)
Subject: MOU for Dystrophin Workshop

Dr. Woodcock,

Attached is a signed MOU for the upcoming dystrophin workshop. NIH (NCATS) has agreed to be co-sponsors from a financial perspective and as such, have cosigned the agreement. There is a good chance that NIAMS and NINDS will also provide financial support but since their internal process will not be evaluated until later in the month, we did not want to delay our planning efforts in the meantime. If they should approve a financial commitment, we can amend the MOU with the additional signatures.

Of note, I confirmed with Debbie Lavine, CDER's Co-Sponsorship Liaison, that since this is an inter-agency engagement, we do not currently have a process/form (so MOU should be sufficient) and the other considerations of Co-sponsorship between federal and non-federal groups do not apply.

If you can sign and email back a PDF copy, I will forward to NIH to complete the loop.

Thanks for your consideration,
Chris

<< File: Dystrophin MOU Austin.pdf >>

From: [Leptak, Christopher](#)
To: [Moscicki, Richard](#); [Temple, Robert](#); [Unger, Ellis](#); [Dunn, Billy](#)
Cc: [Rao, Ashutosh](#); [Farkas, Ronald](#)
Subject: RE: Dystrophin Workshop
Date: Thursday, December 04, 2014 1:08:30 PM

Good to know Rich. A few weeks should not significantly delay program and if we pushed forward with Feb date, we would be missing multiple key speakers.

Thanks for the input,

Chris

From: Moscicki, Richard
Sent: Thursday, December 04, 2014 11:38 AM
To: [Leptak, Christopher](#); [Temple, Robert](#); [Unger, Ellis](#); [Dunn, Billy](#)
Cc: [Rao, Ashutosh](#); [Farkas, Ronald](#)
Subject: RE: Dystrophin Workshop

I think that's ok. I do have spring vacation about that time when (b) (6); I will have to check. In any case I don't think its critical that I be there if that turns out to be the case. I am a little concerned, about how late its getting to be, not for the submission but for the fact that Sarepta is talking about going ahead and collecting a 4th biopsy on the boys in their initial cohort. Whether February or March may make no difference if they do so soon. They said they would wait to process the biopsies for our direction. I have advised them not to do the biopsies until we see the results of the independent image analysis. Rich.

From: [Leptak, Christopher](#)
Sent: Wednesday, December 03, 2014 4:15 PM
To: [Moscicki, Richard](#); [Temple, Robert](#); [Unger, Ellis](#); [Dunn, Billy](#)
Cc: [Rao, Ashutosh](#); [Farkas, Ronald](#)
Subject: Dystrophin Workshop

Hello,

NIH recently brought to our attention that the Feb 27th date for the workshop is problematic in that a number of speakers will be in attendance at a west coast workshop during that time. I have booked the Bldg 31 conference room for March 20th as an alternative. NIH has shared that there should not be conflicts for the date.

Are you OK with rescheduling and do your own calendars allow for participation on that date?

Thanks
Chris

☎ Office: 301-796-5253

7 Fax: 301-595-7910

From: Leptak, Christopher
Sent: Wednesday, December 03, 2014 1:22 PM
To: Woodcock, Janet
Cc: Moscicki, Richard; Ligon, Sharnell (CDER)
Subject: MOU for Dystrophin Workshop

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If you can sign and email back a PDF copy, I will forward to NIH to complete the loop.

Thanks for your consideration,

Chris

<< File: Dystrophin MOU Austin.pdf >>

Philips, Howard

From: DeMarco, Devota R on behalf of Moscicki, Richard
Sent: Tuesday, July 11, 2017 4:17 PM
To: DeMarco, Devota R
Subject: RM

-----Original Message-----

From: Moscicki, Richard
Sent: Monday, December 01, 2014 11:05 AM
To: Woodcock, Janet
Subject: RE:

I spoke with Ed Kaye, CMO at Sarepta, He explained that MGH was the first site up and was inundated with requests, more than they could handle at the time, but the plan is to reopen the site as they catch up. There will be additional sites around the country including Baltimore which should be up and running soon. There are still plenty of spots in the trial. Should I get back to [REDACTED] (b) (6) and inform him that he should contact the company, that our understanding is that there are still spots in the trial. I have contact information for Sarepta from Ed. On another note, Elias has offered the evening of Dec 9th to meet but I understand you may be traveling. And another note, our Blue Ribbon Recruiting Panel is meeting this week with Korn Ferry. We are slated to discuss the OPQ director search. I wanted to check with you if you think the timing is right for that. If so, I would assume you would want to be part of the initial discussion of search committee, qualifications, desired traits, etc. Rich.

-----Original Message-----

From: Woodcock, Janet
Sent: Sunday, November 30, 2014 5:09 PM
To: Moscicki, Richard
Subject: RE:

Thanks. See you tomorrow. jw

-----Original Message-----

From: Moscicki, Richard
Sent: Sunday, November 30, 2014 5:07 PM
To: Woodcock, Janet
Subject: RE:

Yes I am in tomorrow and will call them. Rich

-----Original Message-----

From: Woodcock, Janet
Sent: Sunday, November 30, 2014 3:36 PM
To: Moscicki, Richard
Subject: FW:

Are you around tomorrow? Could you possibly call your contact at Serepta and find out why they are limiting the trial enrollment! Is causing much heartache among patients and families. jw

-----Original Message-----

From: (b) (6) [mailto:(b) (6)]
Sent: Friday, November 28, 2014 6:00 PM
To: Dunn, Billy; kboniface@sarepta.com; Woodcock, Janet
Cc: Temple, Robert
Subject:

Dear Kara, Janet, Robert & Billy,

My name is (b) (6) and I live in (b) (6). I have two cousins who have Duchenne Muscular Dystrophy. It was brought to my attention that a non-ambulatory clinical trial was opening up at Mass General. Only to find out it was too late for these young boys. Words cannot even begin to express the heartache and disappointment I feel to know there is a possible help, yet is not being offered!

I am pleading with you to please open up more trials or some spots in the existing trial in Mass, so that my cousins and so many others can benefit from this drug. These boys are dying and our only hope is right at our finger tips, yet it is unattainable!

I thank you for your time, but please remember, our time is ticking away and the longer we wait, the more kids will loose their battle against Duchenne.

Sincerely,

(b) (6)

From: [Guidos, Robert](#)
To: [Moscicki, Richard](#)
Subject: FW: Targeted Platform Technology Legislative Language Draft
Date: Tuesday, November 25, 2014 11:58:35 AM
Attachments: [Draft Targ Ther Plat Technology Legislation 112414.doc](#)

FYI.

From: Jenkins, John K
Sent: Tuesday, November 25, 2014 8:21 AM
To: Kweder, Sandra L
Cc: Guidos, Robert; CDER-ORP Requests; CDER OMP; McLatchy, Johanna; Sipes, Grail; Adleberg, Jill
Subject: RE: Targeted Platform Technology Legislative Language Draft

My comments are included in the attached document. As Sandy says, it would be more appropriate for this issue to be handled in FDA guidance, not legislation. We have already told Sarepta of our willingness to apply flexibility to consideration of new molecules derived from its backbone technology for DMD. In fact, we told them that confirmation of clinical benefit of a new drug related to eteplirsen in a different exon could serve as the confirmatory trial for eteplirsen in exon 51 if eteplirsen is approved under AA based on a surrogate of dystrophin production or an intermediate clinical endpoint of 6MW or some other functional measure. They may think that putting this into the statute will "tie our hands" to make us honor what we have said; in my experience the attempt to "tie our hands" in this manner usually work out to "tie our hands" in ways that were not anticipated and are not necessarily beneficial to the party requesting the statutory change.

I would suggest that we offer a counter proposal that FDA develop a guidance to address this issue, not statutory language.

John

From: Kweder, Sandra L
Sent: Monday, November 24, 2014 5:24 PM
To: Jenkins, John K
Subject: FW: Targeted Platform Technology Legislative Language Draft

I have one comment toward the end that sums up my concerns. This seems more appropriate to a guidance on AA than legislation. We already do most of this.

SAndy

From: Guidos, Robert
Sent: Monday, November 24, 2014 1:05 PM
To: CDER-ORP Requests; CDER OMP; Jenkins, John K; Kweder, Sandra L
Cc: McLatchy, Johanna; Sipes, Grail; Adleberg, Jill
Subject: FW: Targeted Platform Technology Legislative Language Draft

ORP, OMP, and OND,

Please see the attached and email below. Please share your comments with Johanna McLatchy (she is out today so I am sending this out) by COB Wednesday, if possible. If you need more time to respond, please let Johanna know.

Bob

From: Woodcock, Janet
Sent: Monday, November 24, 2014 12:55 PM
To: Sipes, Grail; Guidos, Robert
Subject: FW: Targeted Platform Technology Legislative Language Draft

Proposed legislation. Of course, I am not able to analyze on my own. jw

From: Nancy Myers [<mailto:nancy@catalysthcc.com>]
Sent: Monday, November 24, 2014 12:28 PM
To: Woodcock, Janet
Subject: Targeted Platform Technology Legislative Language Draft

Hey JW,

Hope you are back in the pink again!

Following up on a conversation we had last June, Sarepta has been working on the concept of creating a clarification in the AA legislative language that permits a targeted platform technology to be considered for AA and also to allow FDA to consider extrapolated data. I know you all are already doing this, but this is intended to be a clarification like BT was a clarification... it is more the Congressional thumbs up cover that says it is OK for the agency to do this more often.

Here is the legislative language that Hyman Phelps drafted. I think they missed the concept you raised last time of who can extrapolate the data... Sarepta's intent is that only innovators can do that so that we don't open up a huge can of worms, but I think that language needs to be clarified.

Just so you know, this draft was just shared with House E&C staff late Friday evening with the caveat that the language will likely morph, improve and become more polished as we share it with experts and potential allies.

So, would you have a moment to discuss what you think about this now that it is better drafted (though the findings are LONG) and how you think I should best explore this concept inside FDA? This concept has been floated with a number of other groups that will likely be supportive... they have been, though we have not shared the language with them yet. You and FDA obviously have to be comfortable with the approach as a key stakeholder, so I'd like to talk to you about it. Then once I know where you and the policy folks at CDER are (hopefully open to it and not opposed), I was thinking about sharing it with Sally Howard and possibly with Tom Crout in OLA --because I'd like to approach them before they are asked about the concept in the context of 21st Century Cures.

To be clear, this is not intended to be an effort to lower standards. We just think extrapolation of data can be done well in some situations... Sarepta would love FDA to be supportive of this and would like to explore ways to improve this to dovetail what FDA is doing on other fronts. The language is intended to be out in front and push the envelope a bit but not be crazy out there, because that is the only way it will be considered.

Thanks for considering... and let me know how best to proceed.

Nancy

Nancy Bradish Myers
Catalyst Healthcare Consulting, Inc.
7704 Georgetown Pike
McLean, VA 22102
703-448-7448
Nancy@catalysthcc.com

(b) (5)

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

From: [Leptak, Christopher](#)
To: [Austin, Christopher P \(NIH\)](#); [McInnes, Pamela \(NIH/NCATS\) \[E\]](#) (pmcinnes@mail.nih.gov)
Cc: [Moscicki, Richard](#); [Gross, Mary](#)
Subject: MOU for the Dystrophin Workshop
Date: Monday, November 24, 2014 12:29:05 PM
Attachments: [MOU FDA NIH Dystrophin Workshop Final.docx](#)

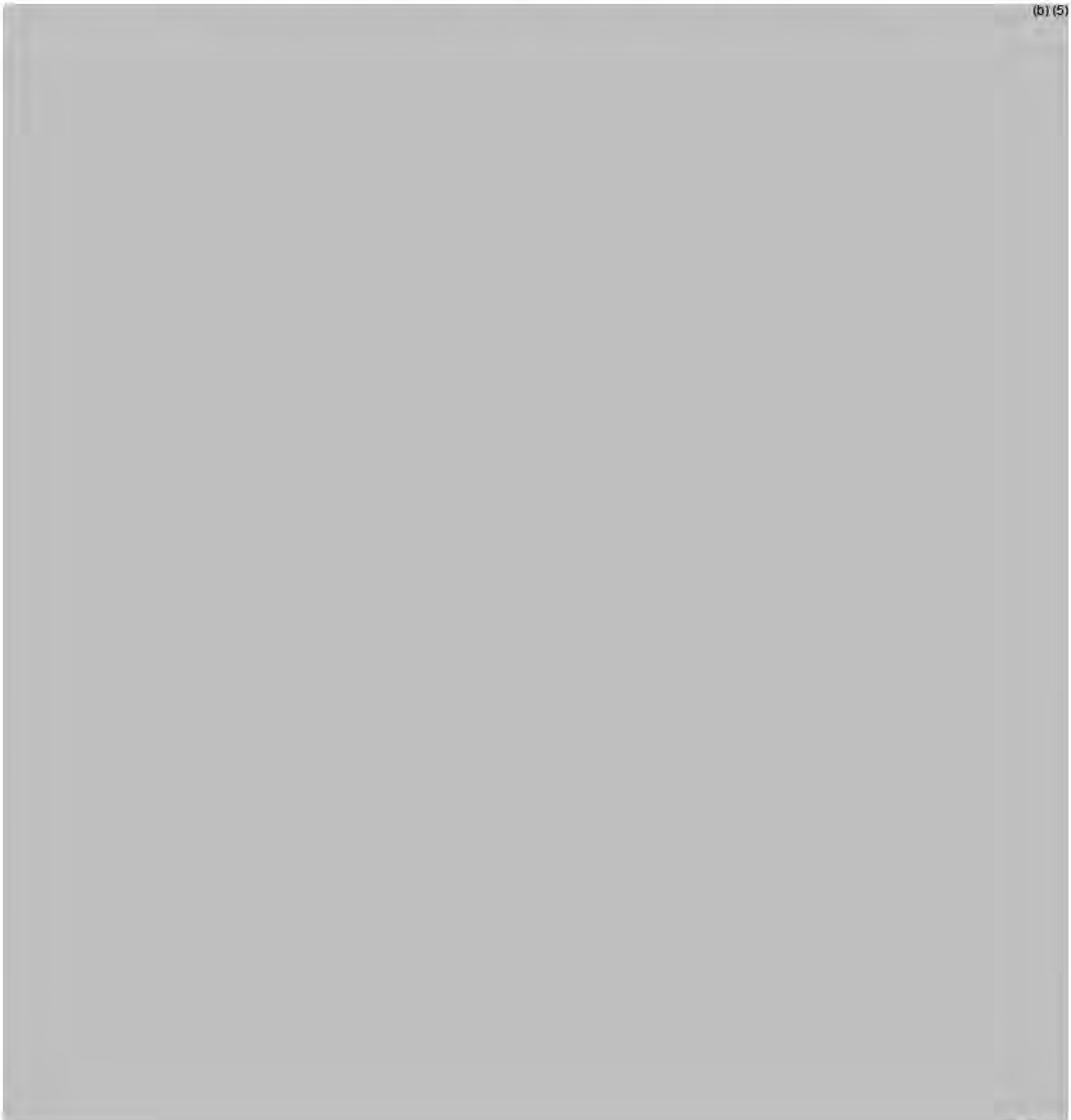
Chris and Pam,

Per our recent discussions, attached you will find a revised MOU for the upcoming dystrophin workshop. If you can sign the document and send me it back in PDF, I will have Janet sign and then send you a copy with both signatures.

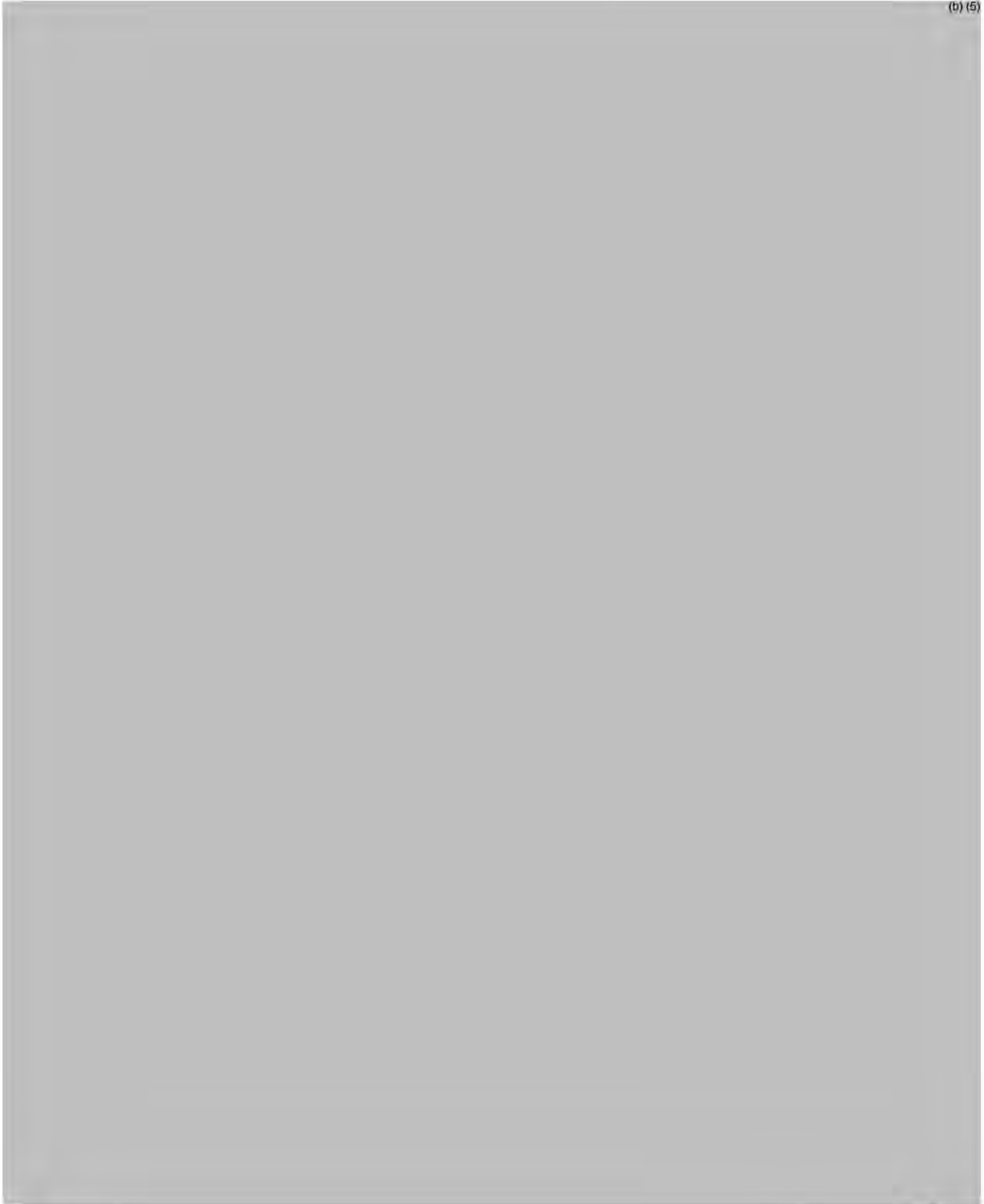
Thank you for your continued support and flexibility in moving this project forward.

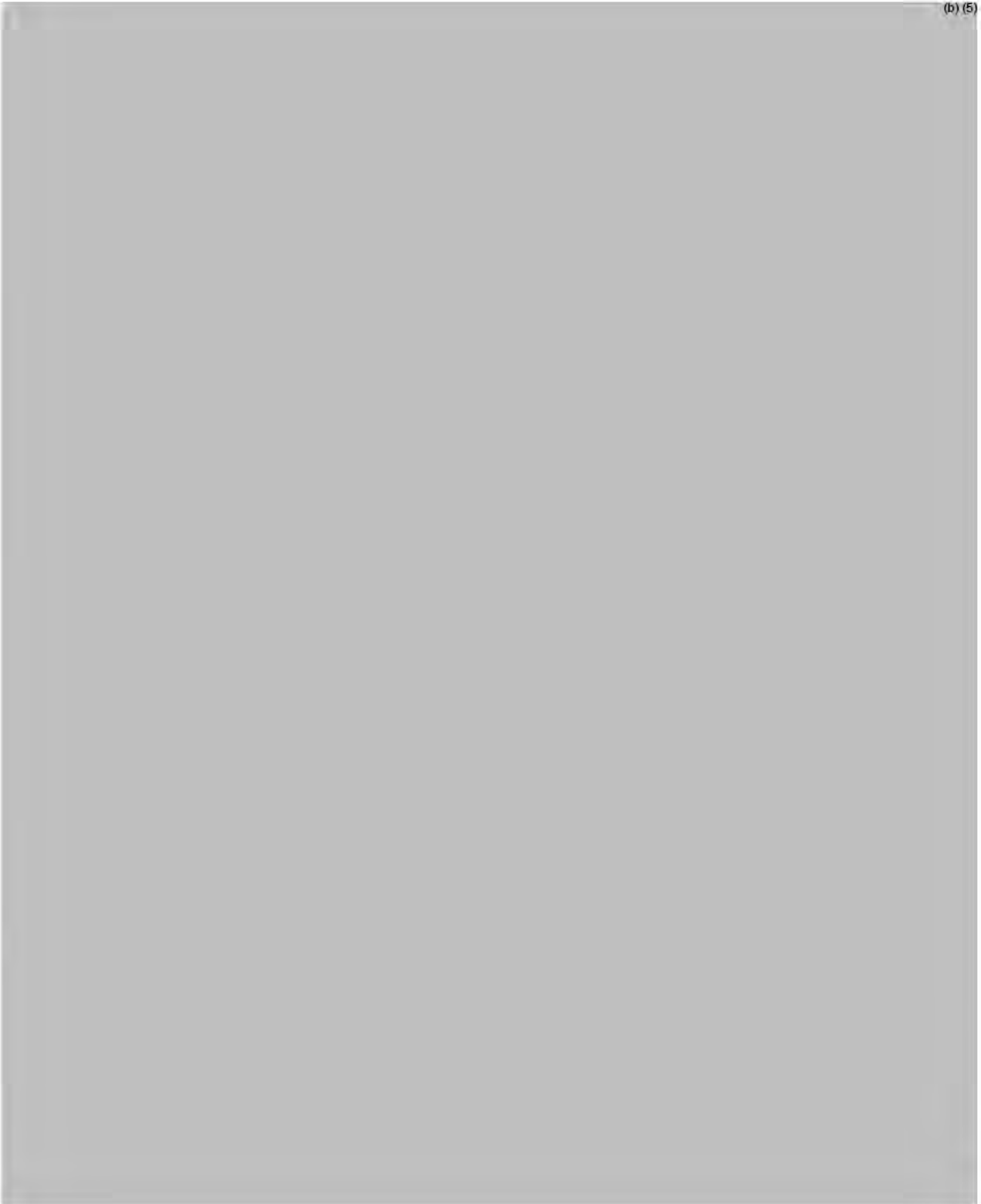
Best,
Chris

Memorandum of Understanding (MOU)
Between
Food and Drug Administration (FDA)/Center for Drug Evaluation and Research(CDER)
And
National Institutes of Health(NIH)/
National Center for Advancing Translational Sciences (NCATS)



(b) (5)





From: [Leptak, Christopher](#)
To: [Rao, Ashutosh](#); [Farkas, Ronald](#)
Cc: [Moscicki, Richard](#); [Loewke, Sally A](#); [Leptak, Christopher](#)
Subject: Dystrophin Speaker List
Date: Thursday, November 20, 2014 10:35:13 AM
Attachments: [Dystrophin Workshop Speaker List.xlsx](#)

Ash and Ron,

Attached is a Dystrophin Workshop speaker list. I combed through my emails, folks' comments on documents, as well as the feedback we got on this past summer's CPIM to form a composite list. For suggestions that were on topics beyond the scope of the workshop, I did not include. And for some that seemed potentially related, I added to the bottom of the sheet as a parking lot.

Once you have a chance to review, I will send to NIH prior to our discussion on Monday.

FYI, I think we should also reach out to CDRH and CBER to see if they can recommend methods speakers (beyond those in the dystrophin community).

Best,

Chris

	A	B	C	D	E	F	G	H
1		PREFIX	LAST NAME	FIRST NAME	Subsession Topic	Job Title/Contact Info	Invited?	Accepted?
8	6	Dr.	Peltz	Stewart	IHC	http://www.ptcbio.com/peltz		
9	7	Dr.	Ishikawa	Y	ELISA	http://www.ncbi.nlm.nih.gov/pubmed/8933672		
10	8	Dr.	Byers	TJ	ELISA	http://www.ncbi.nlm.nih.gov/pubmed/1549217		
11	9	Dr.	Ervasti	Jim	WB			
12	10	Dr.	Chamberlin	Jeff	Exon Skipping			
13	10	Dr.	Hoffman	Eric	Mass Spec	Children's National Med Center, http://rd-connect.eu/contacts/eric-p-hoffman/		
14								
15								
16	SESSION II: Tissue for Dystrophin Analysis							
17	1	Dr.	Bonnemann	Carsten	DMD Path	carsten.bonnemann@nih.gov		
18	2	Dr.	Wood	Bradford	Alternative tissue bx	bwood@nih.gov		
19	3	Dr.	Chamberlin	Jeff	Dystrophin domain structure	http://depts.washington.edu/chamblab/		
20								
21								
22								
23								
24								
25								
26	SESSION III: Natural Disease Variants							
27	1	Dr.	Flanigan	Kevin	DMD/BMD variants	http://www.nationwidechildrens.org/flanigan-lab		
28	2	Dr.	Clemens	Paula	BMD natural history	http://www.neurology.upmc.edu/faculty/clemens.html		
29	3	Dr.	Sweeney	H. Lee	DMD	http://www.med.upenn.edu/apps/faculty/index.php/g20001862/p477		
30								
31								
32								
33		Dr.	Muntoni	Francesco	Exon skipping	http://www.cnmd.ac.uk/research/research_groups/francesco_muntoni		
34		Dr.	McDonald	Craig	Serum biomarkers	IJC Davis		
35								

From: [Leptak, Christopher](#)
To: [Rao, Ashutosh](#)
Cc: [Farkas, Ronald](#); [Moscicki, Richard](#); [Unger, Ellis](#); [Dunn, Billy](#)
Subject: RE: Dystrophin workshop
Date: Friday, November 14, 2014 7:46:12 AM

Ash,

You have had a working relationship with Glen in the past so I think if Glen is willing to be the NIH Co-Chair along with you, your past history could be beneficial in both clarifying the agenda content as well as keep us on track for our workshop goal date. I would be supportive and happy to hear that it was proposed!

Best,
Chris

From: Rao, Ashutosh
Sent: Thursday, November 13, 2014 5:23 PM
To: Leptak, Christopher
Cc: Farkas, Ronald
Subject: Dystrophin workshop

Glen asked if he could serve as the co-chair. He felt that the purpose of the meeting and the short turnaround time required for action may preclude Kurt Fishbeck and Carsten Bonneman from being involved. I am okay with Glen co-chairing, he is an NIH employee and now better understands the nuances of the methodological problems. He currently does not have Flanigan, Mendel, or Hoffman as a current grantee; so I believe he could serve as an impartial referee here. Any thoughts?

From: [Butler, Hope](#)
To: [Gross, Mary](#); [Leptak, Christopher](#); [Moscicki, Richard](#)
Cc: [Ienzi, Georgiann](#); [Abbott, Tanya L](#); [Corum-Lawson, Ashley](#); [Brown, Heather](#); [Clarke, Mary Beth](#)
Subject: RE: Dytrophin Workshop - Budget
Date: Thursday, November 13, 2014 8:33:08 AM

Oh, we had Feb 2—I will update the Conference Request Form. Thanks.

From: Gross, Mary
Sent: Thursday, November 13, 2014 8:27 AM
To: Butler, Hope; Leptak, Christopher; Moscicki, Richard
Cc: Ienzi, Georgiann; Abbott, Tanya L; Corum-Lawson, Ashley; Brown, Heather; Clarke, Mary Beth
Subject: RE: Dytrophin Workshop - Budget

It is currently scheduled for February 27 at WO. Thanks. — Mary

From: Butler, Hope
Sent: Thursday, November 13, 2014 8:22 AM
To: Gross, Mary; Leptak, Christopher; Moscicki, Richard
Cc: Ienzi, Georgiann; Abbott, Tanya L; Corum-Lawson, Ashley; Brown, Heather; Clarke, Mary Beth
Subject: RE: Dytrophin Workshop - Budget

Good Morning, ALL

Since Dr. Woodcock is in support of the public meeting, I will check on funding.

From: Gross, Mary
Sent: Thursday, November 13, 2014 8:05 AM
To: Leptak, Christopher; Moscicki, Richard
Cc: Ienzi, Georgiann; Abbott, Tanya L; Corum-Lawson, Ashley; Butler, Hope; Brown, Heather; Clarke, Mary Beth
Subject: FW: Dytrophin Workshop - Budget

Hi - What will NIH be contributing?

Tanya, Ashley, Hope, Georgi – please see this note below. Thanks.

Mary

From: Leptak, Christopher
Sent: Thursday, November 13, 2014 7:08 AM
To: Moscicki, Richard; Temple, Robert; Rao, Ashutosh; Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric; Kaiser, James; Rogers, Hobart
Cc: Gross, Mary; Loewke, Sally A
Subject: RE: Dytrophin Workshop

Update on the status of the NIH cosponsorship for the Dytrophin Workshop:

Yesterday afternoon, we had a breakthrough and now a path forward for NIH's participation

and cosponsorship for the workshop. Rather than having each of the three NIH subgroups sign the MOU and be listed in the FR Notice, they proposed that we simply list NIH as a whole since at least NCATs is comfortable supporting the MOU as it currently stands. For NIAMS and NINDS, they will need a more flushed out agenda including speaker list before they can commit funding/sign an MOU. As this may take a month or more, it would result in further delay and our inability to meet our Feb meeting objective.

The only downside to this approach is that FDA may need to support travel expenses for an additional four speakers (up to 10 in total) should NIAMS and NINDS ultimately not financially support the workshop. I think this is an acceptable trade-off to keep the project moving forward. Rich, do you agree and would you have access to the additional funding if needed?

Best,
Chris

From: [Gross, Mary](#)
To: [Leptak, Christopher](#); [Moscicki, Richard](#)
Cc: [Ienzi, Georgiann](#); [Abbott, Tanya L](#); [Conum-Lawson, Ashley](#); [Butler, Hope](#); [Brown, Heather](#); [Clarke, Mary Beth](#)
Subject: FW: Dytrophin Workshop - Budget
Date: Thursday, November 13, 2014 8:04:39 AM

Hi - What will NIH be contributing?

Tanya, Ashley, Hope, Georgi – please see this note below. Thanks.

Mary

From: Leptak, Christopher
Sent: Thursday, November 13, 2014 7:08 AM
To: Moscicki, Richard; Temple, Robert; Rao, Ashutosh; Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric; Kaiser, James; Rogers, Hobart
Cc: Gross, Mary; Loewke, Sally A
Subject: RE: Dystrophin Workshop

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Best,
Chris

From: [Leptak, Christopher](#)
To: [Unger, Ellis](#); [Moscicki, Richard](#); [Dunn, Billy](#)
Cc: [Farkas, Ronald](#); [Rao, Ashutosh](#)
Subject: RE: Dystrophin Workshop
Date: Wednesday, November 05, 2014 8:00:04 AM

Thanks for the input Ellis.

Rich and Billy, your thoughts? NIH is pushing fairly hard to steer some of the meeting content towards therapeutic targets and levels of dystrophin that have clinical meaningfulness.

From: Unger, Ellis
Sent: Tuesday, November 04, 2014 11:10 AM
To: Leptak, Christopher; Moscicki, Richard; Dunn, Billy
Cc: Farkas, Ronald; Rao, Ashutosh
Subject: RE: Dystrophin Workshop

Chris,

I don't know enough about utrophin to comment, but I think that discussion of methods to quantify dystrophin will represent a full day of work, and would not want to get distracted with clinical trials or utrophin.

As far as the need for an MOU vs. an Inter-agency agreement, I would rely on the knowledge of others.

Ellis

From: Leptak, Christopher
Sent: Sunday, November 02, 2014 5:15 PM
To: Moscicki, Richard; Unger, Ellis; Dunn, Billy
Cc: Farkas, Ronald; Rao, Ashutosh; Leptak, Christopher
Subject: Dystrophin Workshop
Importance: High

<< File: MOU FDA NIH Dystrophin Workshop ghn (2).docx >>

Rich, Ellis, and Billy,

Attached is a draft MOU for the dystrophin workshop. The tracked edits are those made by NIH to the original proposal. There are a couple of comments for consideration.

Honestly, I have been receiving mixed messages RE what is necessary for an inter-Agency meeting co-sponsorship. The span has been from a simple MOU to a detailed Inter-Agency Agreement. Since the most recent (and it seems prevailing advice) is that a simple MOU is sufficient, I am of the mind to get this agreed upon before the tides have a chance to turn again.

Since we will need to have the MOU in place before we can start clearance of the FR Notice (still being drafted and needs to be in clearance within the next week in order to be posted in time for the Feb 2 meeting date), your input by **COB Wed Nov 5th** would be most appreciated.

Best,

Chris

Memorandum of Understanding (MOU)
Between
Food and Drug Administration (FDA)/Center for Drug Evaluation and Research(CDER)
And
National Institutes of Health(NIH)/
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)/
National Institute of Neurological Disorders and Stroke (NINDS)/
National Center for Advancing Translational Sciences (NCATS)

(b) (5)



(b) (5)

(b) (5)



From: [Jenkins, John K](#)
To: [Temple, Robert](#); [Unger, Ellis](#); [Walsh, Sandy](#); [Moscicki, Richard](#)
Cc: [Yao, Stephanie](#); [Dunn, Billy](#); [Farkas, Ronald](#)
Subject: Re: Urgent media inquiries, Sarepta clarifications - WSJ and Bloomberg
Date: Friday, October 31, 2014 2:06:57 PM
Attachments: [image001.png](#)

I think Monday should be fine, but again want to be sensitive that it does not appear that we are criticizing National Childrens or their staff. I think they were trying to do a good job, but were operating in an "academic" environment, not one of the same rigor we expect to support a primary endpoint for approval.

John

From: Temple, Robert
Sent: Friday, October 31, 2014 01:59 PM
To: Unger, Ellis; Jenkins, John K; Walsh, Sandy; Moscicki, Richard
Cc: Yao, Stephanie; Dunn, Billy; Farkas, Ronald
Subject: RE: Urgent media inquiries, Sarepta clarifications - WSJ and Bloomberg

I should think that Ellis's illustration of disparity could be given, perhaps with an explanation that uncertainty about the reliability of measures does not indicate that we believe fraud has occurred. Do all agree that our response can be delayed till Monday?

From: Unger, Ellis
Sent: Friday, October 31, 2014 1:55 PM
To: Jenkins, John K; Temple, Robert; Walsh, Sandy; Moscicki, Richard
Cc: Yao, Stephanie; Dunn, Billy; Farkas, Ronald
Subject: Re: Urgent media inquiries, Sarepta clarifications - WSJ and Bloomberg

I would think our response could wait until Monday.

And BTW, the actual "disparity" was the technician's count of positive fibers in some images - some counts she performed in our presence were markedly different than her earlier counts.

Ellis Unger

Sent from my Blackberry

From: Jenkins, John K
Sent: Friday, October 31, 2014 01:47 PM
To: Temple, Robert; Walsh, Sandy; Unger, Ellis; Moscicki, Richard
Cc: Yao, Stephanie; Dunn, Billy; Farkas, Ronald
Subject: Re: Urgent media inquiries, Sarepta clarifications - WSJ and Bloomberg

We also have a guidance about the use of imaging endpoints in clinical trials that spells out the principles for how to standardize conduct of assays and how to implement rigorous analysis procedures. We may be able to point to that in our response.

John

From: Jenkins, John K

Sent: Friday, October 31, 2014 01:22 PM
To: Temple, Robert; Walsh, Sandy; Unger, Ellis; Moscicki, Richard
Cc: Yao, Stephanie; Dunn, Billy; Farkas, Ronald
Subject: Re: Urgent media inquiries, Sarepta clarifications - WSJ and Bloomberg

We also need to be careful not to appear to criticize National Childrens and Dr. Mandel. This was an early Phase 2 trial not intended to support registration. We have asked that they re analyze the data using standardized measurements like we expect for this type of data to support an NDA, not repeat the study. Such a request is not that uncommon.

John

From: Temple, Robert
Sent: Friday, October 31, 2014 12:48 PM
To: Jenkins, John K; Walsh, Sandy; Unger, Ellis; Moscicki, Richard
Cc: Yao, Stephanie; Dunn, Billy; Farkas, Ronald
Subject: RE: Urgent media inquiries, Sarepta clarifications - WSJ and Bloomberg

I can't tell how available Ellis is, but he and Rich will, I think, need to explain why we found the dystrophin measurements unreliable or not sufficiently reliable. It will be important to emphasize that all agree well-documented increases in dystrophin levels are an important component of evidence that would be used by the sponsor to support approval of eteplirsen, so that it is important to support their reliability.

From: Jenkins, John K
Sent: Friday, October 31, 2014 12:38 PM
To: Walsh, Sandy; Unger, Ellis; Moscicki, Richard
Cc: Yao, Stephanie; Dunn, Billy; Temple, Robert
Subject: Re: Urgent media inquiries, Sarepta clarifications - WSJ and Bloomberg

I suggest Rich and Ellis draft something since they attended the inspection and wrote the report.
John

From: Walsh, Sandy
Sent: Friday, October 31, 2014 12:31 PM
To: Unger, Ellis; Moscicki, Richard; Jenkins, John K
Cc: Yao, Stephanie; Dunn, Billy; Temple, Robert
Subject: Urgent media inquiries, Sarepta clarifications - WSJ and Bloomberg

Good afternoon,

I have media inquiries from the Wall Street Journal and Bloomberg/Business Week about FDA making contradictory and inconsistent statements about Sarepta, particularly the "marked disparities" information. If we were not talking about "fraud" what were we talking about? Can we better clarify what we said in our statement in that *"FDA is concerned that the methods used to measure dystrophin were not adequately robust to support an NDA submission."*

WSJ and Bloomberg are seeking FDA comment and clarification on this today if possible, but I can tell them we'll be in touch on Monday if necessary.

Their inquiries are included below to better specify what they're being asked. Do you want to

comment further today beyond what we put last night? Thoughts?

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



Bloomberg Inquiry

Hi, Sandy.

Thanks again for getting back to me by phone. Happy Halloween to you and yours!

Please see the language below from the FDA guidance to Sarepta that suggested that something was awry at the Columbus hospital test site. The words "uncovered marked disparities" suggested to me (and others) that marked disparities had been covered/concealed/obscured. "Disparities" in the context of a medical trial is pretty disturbing in and of itself. Pile on "concerns about the reproducibility of data," and it's really starting to sound like FDA had developed deep suspicions about the trial methods and integrity. Then the FDA comes back and says, nope, we weren't talking about "fraud." OK, now I'm pretty confused. What WAS the FDA talking about?

"The study 201/202 clinical site inspection conducted in May, 2014, after the issuance of the April 15, 2014, guidance letter, uncovered marked disparities in the immunohistochemistry methodology and concerns about the reproducibility of the data. The lack of confirmation of robust dystrophin measurement during the site visit necessitates including the independent assessment of dystrophin-positive fibers and 168-week efficacy data from study 201/202 in the NDA."

Happy to discuss in person or by phone. I intend to write more about the hunt for a Duchenne treatment.

Paul

WSJ Inquiry

Hi Guys,

An analyst at the RW Baird brokerage wrote an investor note about FDA and Sarepta. I want to know if FDA has any comment. This is from his note:

"We find it difficult to completely fault Sarepta for misinterpreting FDA communications as we find

several statements from the agency over the last week completely contradictory. Notably the FDA stated in meeting minutes:

The study 201/202 clinical site inspection conducted in May, 2014, after the issuance of the April 15, 2014, guidance letter, uncovered marked disparities in the immunohistochemistry methodology and concerns about the reproducibility of the data. The lack of confirmation of robust dystrophin measurement during the site visit necessitates including the independent assessment of dystrophin-positive fibers and 168-week efficacy data from study 201/202 in the NDA.

The use of the words "marked disparities," "concerns about the reproducibility of the data," and "lack of confirmation" carry a very clear connotation that no one who has ever spent a week in a lab could misconstrue. Yet in last night's response the FDA stated:

As described by Sarepta in its October 27 statement, the need for additional data and analyses to support the NDA was reinforced by an FDA inspection of the clinical site where dystrophin analyses had been conducted. It is important to note that the agency did not find any evidence of fraud at this site, as has been perceived by some. FDA is concerned that the methods used to measure dystrophin were not adequately robust to support an NDA submission.

We think that viewing those two statements side by side shows enormous inconsistency in the message the FDA is trying to communicate. But we note that the messages are intended for two separate audiences: the first was meant only as a private communication with Sarepta and the second a public response resulting from the dissemination of that private communication.

So while the FDA may find fault in Sarepta's communication, the agency should bear its fair share of blame.

From: [Jenkins, John K](#)
To: [Unger, Ellis](#); [Woodcock, Janet](#); [Dunn, Billy](#); [Temple, Robert](#); [Rawlings, Kimberly](#); [Whyte, John](#)
Cc: [Moscicki, Richard](#); [Jenkins, John K](#)
Subject: RE: Was there fraud - the guidance indicated there was?
Date: Wednesday, October 29, 2014 9:08:49 AM

As I read the letter from April and the recent meeting minutes it becomes clear to me that what "changed" was our making clear to the sponsor what information was considered necessary to make an NDA submission complete for review. The sponsor made various requests that they be allowed to submit some of the information we had requested in the April letter during the course of the review, and we stated our position that these data were necessary to form a complete application. I think what was missing was any direct reference to the requirements for a complete NDA in the April letter. I think we "assumed" the sponsor would understand that the data were required, but given their inexperience they appear to have assumed they could submit the information "late" during our review. Such as view is inconsistent with the PDFUA V goals letter and its call for applications that are complete at the time of submission. This requirement was put in place under the "program" to allow us to plan our review from the outset and meet the various review milestone dates, including planning for the advisory committee meeting. The sponsor's proposed timeline for submission of critical data, such as the reanalysis of the biopsies, is incompatible with the timeline required to substantially complete our review in advance of the advisory committee meeting.

So, while I don't think we added new requirements for the NDA, the sponsor clearly misinterpreted our communication to them and the requirements under PDUFA V and were planning for a rolling submission AFTER the PDUFA clock started. We can still offer, and should encourage them to take advantage, of a rolling submission, but the PDFUA clock will not start until the application is complete. Of course, we can work to shorten our review timelines and expedite the review, but the ability to do that will be impaired by the need to plan for the advisory committee meeting, something that has not happened with most other "expedited" reviews.

Is OComm/ODEI working on a statement we can issue?

John

From: Unger, Ellis
Sent: Tuesday, October 28, 2014 10:52 AM
To: Woodcock, Janet; Jenkins, John K; Dunn, Billy; Temple, Robert; Rawlings, Kimberly; Whyte, John
Cc: Moscicki, Richard
Subject: RE: Was there fraud - the guidance indicated there was?

Janet, et al,

I'm attaching the inspection report from our site visit to Nationwide Children's Hospital in late-May (there was no 483 issued), the letter we wrote Sarepta on 4/15/14, and the minutes from a couple weeks ago.

With respect to the dystrophin analysis, in the April 15 letter, at the bottom of page 2 (at 2), we wrote:

"After examining the source data and images you provided in support of dystrophin protein expression from eteplirsen treatment, we remain skeptical about the persuasiveness of the data, and concerned about serious methodological problems explained previously."

On page 3, we urge them to initiate two trials ASAP.

We'll need to meet to discuss a strategy, but Billy is away at a meeting for the next two days,

Ellis

From: Woodcock, Janet
Sent: Tuesday, October 28, 2014 9:51 AM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Temple, Robert; Rawlings, Kimberly; Whyte, John
Cc: Moscicki, Richard
Subject: RE: Was there fraud - the guidance indicated there was?

Yes I am getting besieged with emails from the community. It would be good to have a response strategy. I'm also interested in whether we actually said anything different. jw

From: Jenkins, John K
Sent: Tuesday, October 28, 2014 8:00 AM
To: Unger, Ellis; Woodcock, Janet; Dunn, Billy; Temple, Robert; Rawlings, Kimberly
Cc: Moscicki, Richard; Jenkins, John K
Subject: RE: Was there fraud - the guidance indicated there was?

Ellis

Can we confirm that the recent advice we provided re what was needed to consider the NDA complete was the same as the advice they were given last spring? The media reports suggest we asked for more data, so we will need to be clear on this point if we are going to make a statement. I think the likelihood of being able to issue a joint statement with Sarepta is nil. Also, was a 483 or inspection report issued for the inspection of Children's? The 483 would be publicly available, but perhaps not the inspection report. We could check with Nancy Sager on whether we could release that report. Unfortunately the community is interpreting our concerns about the quality/interpretation of the data from the biopsies as "fraud," which is not what was found or described in the report. I copied Rich since I know he had conversations with Frank Sasinowski at the NORD meeting last week about Sarepta's plans. I think it would be helpful if we could arrange a meeting today or later this week to review the current state and consider what statement we could issue.

John

From: Unger, Ellis
Sent: Monday, October 27, 2014 7:20 PM
To: Woodcock, Janet; Jenkins, John K; Dunn, Billy; Temple, Robert