FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUG ADVISORY COMMITTEE (PCNS)

Thursday, September 28, 2017

9:00 a.m. to 3:54 p.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

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PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. ALEXANDER: Good morning. My name is Caleb Alexander. I'd like to welcome you and remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so.

I'd also like to identify the FDA press contact, Sandy Walsh. If you're present, could you please stand or raise your hand. Thank you. I see you over there.

Once again, my name's Caleb Alexander. I'm the chairperson of the Peripheral and Central Nervous System Drugs Advisory Committee, and I'll now call this meeting to order. We'll start by going around the table and introducing ourselves. Why don't we start with the FDA to my left and go around the table?

DR. TEMPLE: Good morning. I'm Bob Temple. I'm the deputy director of ODE I, acting deputy.

Thanks.

DR. UNGER: Good morning. I'm Ellis Unger. I'm director of the Office of Drug Evaluation I, in the Office of New Drugs in CDER at FDA.

DR. DUNN: Good morning. I'm Billy Dunn. I'm the director of the Division of Neurology Products.

DR. BASTINGS: Good morning. I'm Eric Bastings, deputy director of the Division of Neurology Products.

DR. KOZAUER: Good morning. I'm Nick Kozauer. I'm a clinical team lead in the Division of Neurology Products.

DR. KESSELHEIM: Good morning. My name's Aaron Kesselheim. I'm an associate professor of medicine in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital and Harvard Medical School.

DR. GREEN: Morning. I'm Mark Green. I'm a professor of neurology, anesthesiology, and rehabilitation medicine, and director of headache and pain medicine at the Icahn School of Medicine

at Mt. Sinai in New York.

DR. ALEXANDER: And once again, I'm Caleb Alexander. I'm an associate professor of epidemiology and medicine at John Hopkins, and I codirect the Center for Drug Safety and Effectiveness there.

DR. PERLMUTTER: I'm Joel Perlmutter, professor of neurology, radiology, neuroscience, physical therapy, occupational therapy at Washington University, and I direct the Movement Disorders Center there.

DR. FOUNTAIN: I'm Nathan Fountain from the University of Virginia, where I'm a professor of neurology, and direct the epilepsy program there.

DR. MIELKE: I'm Michelle Mielke from the Mayo Clinic, where I'm a professor of neurology and epidemiology.

DR. KRYSCIO: Good morning. I'm Dick Kryscio from the University of Kentucky. I'm a professor of statistics and biostatistics and associate director of the Alzheimer's Disease Center.

MR. LISON: Good morning. I'm Wyatt Lison. I'm a partner with Feinstein Doyle Payne & Kravec. I'm the acting consumer representative.

MR. WATKINS: Good morning. I'm Jeff Watkins. I'm a Duchenne's community patient representative from Annapolis, Maryland.

DR. OVBIAGELE: Good morning. I'm Bruce Ovbiagele. I'm professor and chair of neurology at the Medical University of South Carolina.

DR. GORDON: Good morning. My name is Mark Gordon. I'm the industry representative. I'm a neurologist and senior director at Teva Pharmaceuticals.

DR. ALEXANDER: Great. Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is to ensure that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the

record only if recognized by me. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it to Moon Hee Choi who will read the conflict of interest statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the Authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with Federal Ethics and Conflict of Interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of

interest, or when the interests of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services, which the government may expect from the employee.

Related to the discussions at today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C., Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application, NDA 200896, ataluren for oral suspension, sponsored by PTC Therapeutics, for the treatment of patients with dystrophinopathy due to a nonsense mutation in the dystrophin gene. This is a particular matters meeting during which

specific matters related to PTC Therapeutics' NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Mark Gordon is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Gordon's role at this meeting is to represent industry in general and not any other particular company. Dr. Gordon is employed by Teva Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on

the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ALEXANDER: Thank you. We'll now proceed with the FDA's introductory remarks from Dr. Billy Dunn, director of the Division of Neurology Products.

FDA Opening Remarks - Billy Dunn

DR. DUNN: Thank you, Dr. Alexander. Good morning. I've made the unwise decision of preparing somewhat lengthy remarks while I'm suffering from a cold, so I beg your patience if I have any troubles with that, but I'm very pleased to be here.

Good morning to you all. Good morning to the committee. Welcome to all our committee member, guests who have traveled here, and all the

folks who are joining us by electronic means for this important meeting.

I want to thank the committee for your willingness to be here, your eagerness to consider the important topics we will discuss today, and your forthrightness in sharing with us your perspectives on the application under consideration.

I want to especially thank the public attendees, both in person and those that are joining us by audio or video broadcast, for their commitment to finding a treatment for Duchenne's muscular dystrophy and related conditions.

I particularly want to thank the patients who are joining us today. For those of you who have requested an opportunity to address the committee, or who have provided written comments to the committee, we look forward to and are deeply appreciative of your input. Your efforts to be here are truly invaluable. Thank you.

We are here today to discuss the development of ataluren for the treatment of patients with

dystrophinopathies resulting from nonsense mutations in the dystrophin gene, including patients with nonsense mutation Duchenne's muscular dystrophy, the population that was enrolled in the studies under consideration.

There is, without question, a profound unmet medical need in DMD. Despite available treatments, there is a clear need for improved therapeutic options for this serious and rare disease, and there are no approved treatments that specifically target nonsense mutation DMD.

The natural history of DMD is relentlessly progressive, despite the many advances that have been made in its treatment over the years. We are highly sensitive to the urgency needed for the development of effective treatments for DMD and to the importance of bringing all tools, approaches, and mechanisms that might be available to ensure the efficient development of such treatments.

Although we may hear assertions today made to the contrary, I assure the committee that we are aware of and responsive to this context. I also

unambiguously assure the committee that this application and its preceding regulatory interactions have always been considered in this light.

Indeed, in this area, and all other diseases, in which issues such as these are present, which are, frankly, a substantial portion of the diseases and development programs we in the neurology division deal with, we understand these factors, bear them well in mind, and make a point to consider them in all our interactions with all sponsors throughout the development process.

One need look no further than our recent drug approvals in the neurological space to see examples of our attentiveness to these issues. It is worthwhile to explicitly note that our concerns with this application, about which you have read in the background materials and will hear and discuss today, exist even with the recognition that DMD is a rare disease with a relentlessly progressive course that has an enormous unmet medical need.

Even in the face of these needs, we have

fundamental concerns about the nature of the analyses and observations that have been offered by the applicant that are intended to provide convincing evidence of that ataluren's effectiveness.

Prior to discussing, briefly, the nature of these concerns, because of the strength of our disagreement with the applicant, I want to emphasize that despite our differing views on the data in the application, the applicant and the agency do not have a contentious relationship.

Indeed, despite the inherently difficult nature of discussions at which fundamentally different viewpoints are expressed, our conversations with the applicant have been thoughtful exchanges marked by careful scientific consideration of the relevant issues.

It has always been apparent to me that the applicant has listened carefully to our concerns. And similarly, we have always listened attentively, sincerely, and with an open mind to the arguments advanced by the applicant. Dr. Peltz, who is

observing these proceedings, and the team he has assembled, are to be commended for their steadfast commitment to patients with DMD.

We are here today under unusual circumstances. We are reviewing this application under a condition known as filing over protest. When the agency refuses to accept or file a submitted application because it is deficient in some manner that precludes its acceptance, the regulations stipulate, that, after some discussion, an applicant may insist that it be filed, in essence requiring the agency to review the application despite the agency's previously stated written objections to doing so and over the FDA's protest.

The applicant has opted for this approach for ataluren. I will spend a moment discussing a bit of the regulatory history of this application in order to describe how we have arrived at this point.

The applicant first submitted an application in 2011. The application was based on the study

known as Study 007. This study failed. Although the applicant performed numerous additional analyses of the trial, these analyses were post hoc and unconvincing. Because it was clear on face that the application could not be approved based on the data submitted, we refused to file the application.

Soon after the decision to refuse to file the application, we held a meeting with the applicant to discuss the concerns that we had with the application. At this meeting, we discussed with the applicant the need for an additional study that could be informed by the results of Study 007.

After the meeting with the applicant, but before issuance of our final meeting minutes, we elected to hold an additional internal meeting to carefully consider the applicant's additional arguments, and it was clear that the presented data could not support approval. It was also clear that a second adequately designed study should be performed. These conclusions and recommendations were communicated to the applicant.

After receiving this guidance, the applicant appealed the decision to refuse to file the application, in what is known as a Formal Dispute Resolution Request. After considering the applicant's arguments, the appeal was denied, and the decision to refuse to file the application was upheld.

The applicant submitted a revised application in 2015. This application was based on a study known as Study 020, which was informed by additional hypotheses generated from further post hoc analyses of the results of Study 007.

It was a larger study than Study 007 and was enriched for patients with baseline characteristics predicted by the applicant to increase the ability to identify a drug effect, if present. Study 020 also failed.

Like Study 007, the applicant performed numerous additional analyses of the trial, but these analyses were exploratory or post hoc and unconvincing. Because it was again clear on face that the application could not be approved based on

the data submitted, we again refused to file the application.

Soon after this decision, we held a meeting with the applicant to discuss the concerns with the application. After careful reconsideration of the applicant's various arguments, we discussed with the applicant the need for an additional study to support the hypothesis-generating findings of Study 007 and 020. We indicated a willingness to work closely with the applicant on the design of such a study.

After receiving this guidance, the applicant appealed the decision to file the application with a second Formal Dispute Resolution Request. As part of the appeal process, an additional meeting with the applicant was held to discuss the substance of the appeal. After considering the applicant's arguments, the appeal was denied, and the decision to refuse to file the application was again upheld.

In the denial of the appeal, the applicant was strongly advised that the most efficient path

forward, as previously communicated, was the prompt conduct of another trial. Following the receipt of this advice, the sponsor opted to file the application over the agency's protest, and our review of the application has been ongoing.

Today, you will hear presentations from various members of the review team outlining our concerns with this application that relate to the evidence intended by the applicant to support the effectiveness of ataluren.

Dr. Bob Temple, who is the deputy center director for clinical science, of the Center for Drug Evaluation and Research, and the acting deputy director of the Office of Drug Evaluation I, will discuss the issues associated with the interpretability of exploratory assessments of multiple endpoints and subgroups in clinical trials and the need to prospectively test hypotheses formed on the basis of such subgroup analyses from failed clinical trials.

Dr. Veneeta Tandon, a clinical reviewer in the Division of Neurology Products, will discuss

efficacy considerations related to Studies 007 and 020, including concerns about the inverted U-shaped dose response seen in Study 007, with the high dose performing similarly to placebo; a discussion of the exploratory analyses of both studies that led to our decisions to refuse to file the application; a review of the patient populations evaluated in each study, including the applicant's derivation of a post hoc subgroup of Study 007, the so-called ambulatory decline-phase population, and its use to enrich Study 020; and a discussion of the applicant's assertion that this enrichment strategy did not succeed, with a presentation of an FDA analysis that suggests that this was not an explanation for the study's failure.

Dr. Xiang Ling, a statistical reviewer in the Office of Biostatistics, will discuss details concerning the results of the two failed studies, including a discussion of the 300 to 400 meter baseline 6-minute walk distance exploratory subgroup that became the focus of the applicant after Study 020 did not meet its primary endpoint

and the difficulties in interpreting the exploratory findings presented by the applicant.

Dr. Tandon will return and offer additional thoughts on the interpretability of the 300 to 400 meter subgroup with regards to other factors in addition to 6-minute walk distance that can influence prognosis, and how the evolving science regarding how best to use prognostic factors to predict disease progression in DMD trials reinforces the importance of testing seemingly logical exploratory findings in a prospective fashion. She will also discuss our concerns regarding additional post hoc supportive analyses and observations that have been offered by the applicant.

Finally, she will comment on the highly relevant experience with ataluren for the treatment of nonsense mutation cystic fibrosis and its important lessons for the nonsense mutation DMD experience.

Dr. Atul Bhattaram, Dr. Ash Rao, and Dr. Jim Weaver, from the Offices of Clinical

Pharmacology and Biotechnology Products, will provide an integrated discussion of FDA's analytical and methodological concerns regarding the applicant's explanation for the inverted U-shaped pattern of 6-minute walk distance in Study 007, in which the high dose of ataluren had results essentially indistinguishable from placebo.

These considerations are critical, as such an inverted U-shaped pattern of efficacy is extremely unusual for drugs that are known to be effective. Integrated into this discussion will be the conclusions reached by the team that the dystrophin data that have been submitted with this application are not interpretable due to a number of methodological shortcomings.

Dr. Nick Kozauer, a team leader in the Division of Neurology Products, will provide a summary of our findings to conclude the agency's presentation.

A few additional points merit specific mention. First, and perhaps most importantly, it is important to keep in mind at all times what we

are and are not taking issue with. We are not arguing about the numbers. We are not here today to endorse or rebut the magnitude of reported change, the meaningfulness of a given observation, or the pattern of effects observed on a panel of exploratory endpoints.

Our concern is much more fundamental and regards the basics of the scientific method – the need to formulate hypotheses, rigorously gather data to prospectively test the predictions based on the hypotheses, and if the data suggest a need to alter the hypotheses, do so, and then rigorously test again.

We have no concern with identifying promising patterns via exploratory analyses. This is the essence of scientific discovery and is something to be encouraged. What should be approached with great caution is the tendency to draw conclusions when the data suggest a need to alter the hypothesis and test again.

You will hear from us no discouragement regarding a hopeful interpretation of the

applicant's observations thus far, and we have offered to work closely with the applicant to plan an efficient and rigorous prospective evaluation of the applicant's revised hypothesis in a well-designed clinical trial.

Indeed, we commend the applicant for taking such a thoughtful approach to exploring Study 007 and enriching Study 020 based on those explorations. This a very sensible approach. It is unfortunate that Study 020 was unsuccessful, but it, in turn, has now provided the opportunity for additional thoughtful explorations that may serve as the basis for enrichment of a future study.

You will hear today many lines of reasoning and argument that may seem compellingly supportive of ataluren's efficacy, but it is essential to recognize that these findings are observations that require prospective evaluation. We do not believe they are sufficiently interpretable or persuasive without further testing.

On a related note, it is likely that you will hear many assertions of statistical

significance today. Statistical significance may be achieved when a prospectively identified outcome is tested according to a rigorously defined pre-specified analysis plan.

In the setting of multiple analyses, and especially after the primary analysis has failed, all other comparisons that reach p-values under 0.05 are usually described as nominally significant. In this situation, there is potential for an increased false positive rate.

It is important to remember that nominal significance represents significance in name only without adjusting for multiple comparisons involving multiple endpoints and multiple doses. In fact, no result you will hear today is statistically significant. Both studies failed on their primary outcome, and all other observations are exploratory and only capable of achieving nominal significance.

I mentioned previously that Dr. Tandon will be discussing the experience with ataluren in nonsense mutation cystic fibrosis, and I will offer

a few comments in this regard, as this related development program is illuminating.

An initial clinical study in nonsense mutation cystic fibrosis failed on its primary analysis. Despite this failure, the applicant reported trends favoring ataluren on various analyses. The applicant then reported positive findings from a post hoc analysis that excluded patients taking aminoglycoside antibiotics, and then offered a mechanistic explanation that aminoglycoside antibiotics interfered with the activity of ataluren.

A second larger clinical study was conducted that enrolled only subjects with nonsense mutation cystic fibrosis who were not taking aminoglycoside antibiotics. In March of this year, the applicant announced that this second study failed. Further development in nonsense mutation cystic fibrosis was discontinued.

The parallels with the nonsense mutation DMD program are striking: a failed initial study; post hoc identification of a promising subgroup

accompanied by a seemingly reasonable explanation for why that subgroup should derive unique benefit; and a second study designed to evaluate that subgroup of interest that failed.

These results remind us that hypotheses derived from exploratory analyses of negative trials, even when they appear to be supported by seemingly logical and plausible explanations, may often be misleading and need to be prospectively tested.

In sum, the applicant has presented observations resulting from numerous exploratory analyses of two failed trials. It is notable that the exploratory subgroup the applicant identified in Study 007 to inform the enriched design of Study 020 is not the subgroup of interest now proposed by the applicant. The applicant has identified a new subgroup of interest in Study 020, a subgroup for which seemingly plausible explanations will be offered.

As you will hear, the applicant has attempted to buttress the new subgroup observations

in Study 020 by returning to Study 007 and examining this newly-defined subgroup there, a somewhat circular pattern of support.

It is also notable that in 2011 the applicant argued, just as strongly as it does now in the current application, that the exploratory results presented at that time were compelling, but we now know that Study 020 did not support those exploratory findings from Study 007.

As is obvious in our previous extensively documented opinions, we believe an additional study to support the hypothesis-generating findings of those two studies is needed. This issue is not simply statistical. It is a fundamental concern about the interpretability and persuasiveness of exploratory observations and the importance of experimental design.

None of this is to say that the applicant has not presented thoughtful work that has identified potentially promising trends in the data, and I must reiterate my previous comments congratulating the applicant on the conduct of

Study 020 and our offer to work closely with the applicant on a subsequent study.

Indeed, we are pleased to see that the applicant has recently initiated recruitment into an additional long-term trial, Study 041, that is informed by the information gleaned from Study 007 and 020.

It is also notable that the enrollment criteria for Study 041 have been even further refined from those used for the exploratory analyses of Study 020, which speaks to the continually evolving nature of the understanding of how best to enrich clinical trials in DMD.

Because this application is being reviewed under the filing over protest provisions, there are some unusual aspects to its regulatory history. Our careful previous consideration of the data and issues, prior to and upon submission, resulted in definitive conclusions being reached on multiple occasions about the approvability of this application, and those conclusions have been clearly documented.

Nonetheless, after being filed over protest, we have been committed to a complete and fair review, as we always are. The review team has worked hard and carefully to consider, with a fresh eye and an open mind, the arguments in the application and as is evident by the presentations you will hear today, we continue to have significant concerns regarding the strength of the data in the application.

Given the importance of these fundamental issues related to the need for a scientifically rigorous approach to the interpretation of trial data, we believe that it is important for the committee to discuss this matter, and we have thus convened this meeting today. We look forward to your comments.

I conclude by offering quotations from two widely separated eras. The first comes from a series of articles in the New England Journal of Medicine called, "The Changing Face of Clinical Trials," that was inaugurated in June of 2016. This series deals with contemporary challenges in

the design, performance, and interpretation of clinical trials.

Amongst the many excellent articles the series has already offered is one from September of 2016 by authors Dr. Stuart Pocock and Dr. Greg Stone entitled, The Primary Outcome Fails, What Next?

Within that article, when answering the question, "Do subgroup findings elicit positive signals?" the authors state: "Although it is appropriate to consider subgroup findings in any major trial, for a trial in which the overall result for the primary outcome is neutral or negative, such considerations are often misleading, since the potential for harm is often implied for the partner subgroups.

"Such qualitative interactions are rarely plausible unless a strong mechanistic underpinning is present, and the analyses are typically not adjusted for multiple comparisons. Even if the findings from statistical tests of interaction are significant, such findings should usually be

perceived as useful for generating hypotheses at best.

"Indeed, we find it hard to think of an example in which an apparent benefit in a subgroup in a trial with a negative outcome has led to confirmation in a subsequent trial."

With regard to the question in the article, "Do secondary outcomes reveal positive findings?" the authors state: "If the primary outcome is negative, positive findings for secondary outcomes are usually considered to be hypothesis generating."

The second quotation comes from Andreas Vesalius, the founder of modern human anatomy, and one of the most important early champions of empiricism in medicine, and dates from the 16th century. In his "Epistle on the China Root," he states: "I am not accustomed to saying anything with certainty after only one or two observations."

Thank you for the substantial efforts you have made in preparing for and attending this

meeting, and thank you for the important work you will do today. Dr. Alexander, thank you for the time to offer my comments. I return the proceedings to you.

DR. ALEXANDER: Thank you very much. We'll move to the applicant presentations in just a minute, but I wanted to give Dr. Onyike an opportunity to introduce himself.

DR. ONYIKE: Yes, I'm Chiad Onyike, associate professor of psychiatry at Johns Hopkins University.

DR. ALEXANDER: Thank you for joining us.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any

financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We now proceed with PTC Therapeutics presentations.

Applicant Presentation - Murad Husain

DR. HUSAIN: Members of the advisory committee, FDA, good morning. I am Murad Husain, senior vice president of regulatory affairs at PTC Therapeutics.

PTC began its journey to find treatments for Duchenne's muscular dystrophy almost two decades ago when Dr. Stuart Peltz, our CEO, founded the

company based on his research in RNA biology. We wouldn't have come this far without the support of many others. We thank each one of the over 400 patients and their families who took part in our DMD studies of ataluren, many of whom are here today to share their experience.

We would also like to thank the hundreds of healthcare professionals who helped design and conduct our clinical studies. We thank you, members of the advisory committee, for listening to our presentation with an open mind and weighing the questions posed by FDA based on your clinical and scientific judgment.

Nonsense mutation DMD is a rare, progressive, genetic disease that leads to cumulative irreversible muscle loss resulting in loss of ambulation and eventually early death. There are approximately 1800 patients in the U.S. with nonsense mutation DMD and only approximately 700 are able to walk. Unfortunately, patients with nonsense mutations have no treatment options that address the underlying cause of the disease.

We are here today because the FDA needs advice about whether ataluren has sufficient data to conclude that ataluren is effective. The FDA has provided a balanced statistical review highlighting both the evidence of effectiveness and limitations of our application.

However, the clinical review has stated a strict definition of statistical significance, p-value of less than 0.05 for the primary endpoint, suggesting that the inability to achieve this level of statistical significance alone should preclude approval. For this, FDA is holding ataluren to a different standard than prior NDA reviews for rare diseases.

FDA's interpretation requests clinical context in light of Duchenne's natural history, which has evolved during the development of ataluren. The persuasiveness of the efficacy and safety data must consider the knowledge about the non-linear disease trajectory, the unmet medical need, and the rarity of the disease.

Ataluren's benefit-risk is positive. You

will see during the course of this presentation that multiple lines of evidence support the ability of ataluren to product dystrophin, which was the basis for prior accelerated approval. You will also see the preservation of key functional milestones, including slowed muscle function decline, delayed loss of individual muscle functions, preservation of both ambulation and pulmonary function, and the safety profile is favorable.

Starting with Study 004, we have demonstrated the production of full length dystrophin in both patient biopsies and cultured myotubes in only 28 days of treatment. Subsequently, Study 007 was the first specific controlled study in DMD to use the 6-minute walk test as an outcome. We learned the need to enrich the patient population, but also saw consistency in results in favor of ataluren 10, 10, 20 dose. We also observed a bell-shaped dose concentration response, which was subsequently confirmed in animal studies.

Study 020 missed its primary endpoint based on our failure to enrich the population as intended from Study 007 learnings. It's important to interpret the results using the clinical context of the natural history. The results are compelling in the prespecified transition phase of the disease, as you will see later on in our presentation. In addition, this trial demonstrated consistent preservation of function in favor of ataluren across multiple endpoints.

Patients transitioned to a long-term open level extension study called Study 019. From this study, we demonstrated preservation of pulmonary function when compared to natural history. Finally, we continue to study ataluren's benefit with both post approval global registry and a new long-term placebo-controlled trial. These data supported approvals outside the United States.

We also have real world evidence of ataluren's benefit. Ataluren is currently available in more than 25 countries since the first approval in Europe in 2014. The safety profile

continues to be favorable in more than 700 patient-years of exposure with about 95 percent patient retention. The global registry collecting real-world evidence has been established and continues to enroll patients.

Our proposed indication is for the treatment of dystrophinopathy resulting from a nonsense mutation in the dystrophin gene. With this background, let me share the agenda for today's presentation.

Dr. Ellen Welch will present ataluren's mechanism of action. Dr. Kevin Flanigan from Nationwide Children's Hospital will provide an overview of the disease and its natural history. Next, Dr. Joe McIntosh will present the efficacy and safety data supporting the positive benefit-risk of ataluren. Lastly, Dr. Craig McDonald from the University of California Davis will conclude with his clinical perspective.

We also have additional experts with us today. All external experts have been compensated for the time and travel to today's meeting.

Thank you. I now turn the lectern to Dr. Welch.

Applicant Presentation - Ellen Welch

DR. WELCH: Good morning. I'm Ellen Welch, senior vice president of genetic disorders and translational medicine at PTC. I've been working in the area of nonsense suppression for more than 20 years, and today I'll review ataluren's mechanism of action as a small molecule that specifically enables readthrough at premature stop codons, and I'll show you how ataluren produces dystrophin.

So let me start by reviewing what a nonsense mutation is. A nonsense mutation is a single point alteration with DNA. Approximately 13 percent of the DMD patient population have their disorder due to the presence of a nonsense mutation. As a consequence of that mutation, when DNA is transcribed into RNA, as shown here, the protein coding region is changed to introduce a premature stop codon, indicated here by the orange stop sign.

The cellular machinery begins making protein

by decoding the mRNA three nucleotides at a time, starting at the five prime end of the mRNA. When the ribosome encounters a premature stop codon, protein synthesis is interrupted before a full-length protein can be synthesized, shown here by the gray spheres. This is best thought of as introducing a period in the middle of a sentence.

When ataluren is present, it interacts with the ribosome, allows an amino acid to be incorporated at the site of the premature stop codon, indicated by the orange sphere. The ribosome continues on to synthesize the rest of the protein, honoring the normal termination codon to produce a functional protein. Ataluren is specific for premature stop codons and does not read through normal termination codons.

Also, ataluren's mechanism of action is distinct from exon-skipping drugs. Ataluren exhibits a bell-shaped concentration response. This property has been observed in several nonsense mutation models, including myotubes derived from DMD patients and mice.

Two examples are presented on this slide. On the left-hand graph, myotube cultures derived from 35 different nonsense mutation patients were treated with increasing concentrations of ataluren and monitored for the production of dystrophin. We observed a bell-shaped concentration response.

We see a similar response in the myotube cultures derived from nonsense mutation DMD mice in the graph on the right. On average, the peak readthrough activity is observed at similar concentrations.

Ataluren's readthrough activity follows a two-binding site model on the ribosome, similar to other ribosome binding drugs such as aminoglycosides. When the drug binds to the high-affinity binding site, readthrough of the premature stop codon in the dystrophin mRNA is favored, and dystrophin is produced, highlighted in dark blue.

In contrast, when both the high- and low-affinity sites are occupied, translation termination is favored and readthrough is reduced,

highlighted in the light blue region of the curve. This is the mechanism behind the bell-shaped dose response. Ataluren's ability to enable readthrough at nonsense codons in dystrophin has been demonstrated in multiple cell and animal models, including zebrafish, mice, and humans.

Shown here are muscle tissues from the nonsense mutation DMD mouse. After treatment with ataluren for 28 days, dystrophin is produced and correctly localized to the muscle membrane, as shown by the green staining. The dystrophin protein produced is functional and is able to protect the muscle from injury.

Now I'll show you a similar experiment in patient cells. In this ex vivo study, we grew myotube cultures from pretreatment muscle biopsies taken from patients who participated in our Proof of Concept Study 004. We then treated with ataluren, and used immunofluorescence to measure spectrin and dystrophin proteins. Some of the technical aspects of the image analysis are depicted, including the use of spectrin to identify

the myotubes, as indicated by the gridlines in the upper right.

In the lower right, full-length dystrophin is clearly produced in the ataluren-treated myotubes when compared to the untreated cells. All nonsense mutation patients responded to ataluren treatment in culture, independent of the premature stop codon type or the location within the mRNA.

We've also demonstrated production of dystrophin in muscle biopsies from patients exposed to ataluren for 28 days in our Study 004, and Dr. McIntosh will present these data later.

In summary, ataluren treatment enables readthrough of nonsense codons to produce functional dystrophin protein. Several studies show that ataluren is specific to premature termination codons and does not read through normal termination codons.

Ataluren exhibits a bell-shaped concentration response. The activity of ataluren has been confirmed in many different nonsense mutation models, and is supported by a large number

of independent public publications.

I'd now like to introduce Dr. Kevin Flanigan, who will review the DMD natural history and clinical endpoints.

Applicant Presentation – Kevin Flanigan

DR. FLANIGAN: Good morning. Thank you for the opportunity to provide an overview of the unmet medical need, the evolution of the natural history, and clinical trial challenges for Duchenne's muscular dystrophy.

My name is Kevin Flanigan, and I'm the director of the Center for Gene Therapy and chief of the Neuromuscular Division at Nationwide Children's Hospital. I've treated patients with Duchenne's muscular dystrophy for over two decades, so I understand the urgency of gaining treatments for this devastating disease.

Duchenne's muscular dystrophy is a relentlessly progressive rare and ultimately fatal childhood genetic disorder. DMD is characterized by a decline in ambulatory function that rapidly accelerates once a transitional threshold is

reached.

Duchenne's is always progressing, but when assessed with the current clinical tools, we see patients have a stable or improved measure of ambulation when very young, followed by a non-linear and rapidly progressing decline later on. This leads to loss of ambulation around 13 years of age and premature death due to respiratory and cardiac dysfunction.

DMD is caused by a lack of functional dystrophin protein. Dystrophin is an essential muscle cell protein that acts as a shock absorber, protecting the muscle cell from load-induced damage. Deficiency of dystrophin leads to damage to the muscle cell membrane and progressive and irreversible loss of muscle fibers. Eventually, loss of skeletal muscle fibers, which are replaced by fat, leads to rapid loss of muscle function. Our ultimate treatment goal is to slow or stabilize disease progression.

Patients with nonsense mutation DMD have an absence of dystrophin. It's commonly accepted that

small amounts of functional dystrophin will predict clinical benefit. This understanding comes from published natural history studies, comparing to rare cases where patients spontaneously produce small amounts of dystrophin. Recently, the FDA used small levels of dystrophin production as the basis for accelerated approval.

While difficult to quantify, two predominant methods are used to confirm the existence of dystrophin. One of them is immunofluorescence, which has been shown in multiple studies to be a reliable and reproducible method to detect dystrophin change. However, the exact relationship between the level of dystrophin and muscle function has not been determined.

Let me share an example of a patient with this devastating disease. Here you see a young boy, age 9. You can observe his rise from the floor, which is compromised, taking him several seconds to fully stand and requiring the use of compensatory techniques, but he has a reasonable reserve capacity in muscle strength function that

allows him to walk and ambulate in typical day-to-day activities.

Here we see the same young man at age 17, and we can observe the inevitable progression of Duchenne's. Despite supportive treatment, his muscle weakness has progressed. He can't sit up or transfer between the bed and chair, or independently perform even the most basic activities of daily living. This is the common disease progression for patients with DMD.

When he's placed back on the bed, you can observe his knee and ankle contractures caused by the immobility. At night, he unfortunately requires respiratory assistance, due to weakness of the diaphragm. The early need for mechanical ventilation underlines the urgent need for any treatment that can change disease progression.

This relentless progression of disease is what I eventually see in all of my patients with Duchenne's dystrophy. It's a devastating disease for these boys and their families.

There's a sequence of important and

irreversible loss of functions in DMD. Early manifestations include the loss of ability to rise from the floor, loss of ability to climb stairs, loss of ambulation, and late physical manifestations leading to a requirement for respiratory assistance.

These endpoints all measure different aspects of disease progression. Age at the loss of one milestone, such as loss of ambulation, is prognostic for age of loss of subsequent milestones. These changes help us to monitor and measure disease progression in our patients over their lifetimes.

One of the most important things we have learned during the last several years is that the rate of decline does not occur in a linear fashion for each milestone. It's important to assess treatments for DMD based on this overall progression and imperative to recognize that even small delays from one milestone to the next can be dramatic in the life of a patient with Duchenne's.

Now let me discuss the sources of

independent data supporting this non-linear decline, particularly in regards to the 6-minute walk test. When we analyze the trajectory of patients using the 6-minute walk test, we can see from recently published natural history studies that patients can be grouped into phases.

Data published by Pane show patients with a baseline 6-minute walk distance of greater than 400 meters tend to be stable over a one-year period. As you can see from this graph, it may take two years or more for an observable decline to occur. This concept is also supported by other independent published assessments.

Conversely, patients with baseline 6-minute walking distances of less than 300 meters tend to decline rapidly and abruptly over a one-year period, and we can fully appreciate the biologic rationale of this rapid decline.

This graph shows the change in one-year intervals in the 6-minute walk test versus the fat infiltration, as measured by magnetic resonance spectroscopy of the vastus lateralis muscle.

Patients remain stable over a long period of time, shown by those patients above 400 meter 6-minute walking distance, during which the percent of fat in muscle increases. When the fat fraction reaches a limit of around 80 percent, which often coincides with a 6-minute walking distance of 300 meters, patients tend to lose ambulation.

This schematic summarizes the insights gained from natural history observations I just described. This includes a stable phase, a transition phase, and an accelerated decline phase, linked to the patient's baseline 6-minute walk distance.

Over a one-year period, patients in the stable phase are unlikely to show change, whereas patients in the accelerated decline phase are at high risk of loss of ambulation. As a result, this transition phase is the most sensitive phase to assess change in the 6-minute walk distance in a one-year period.

The description I just explained has been previously acknowledged by the FDA in materials to

this committee. From eteplirsen's FDA briefing book, there is acknowledgement of a sharp decline in patients with baseline 6-minute walk distance of under 300 meters. From drisapersen's FDA briefing book, there is acknowledgement of the stability of patients with baseline 6-minute walk distance of greater than 400 meters.

This supports the need to use the subgroup of patients with baselines between 300 and 400 meters to assess patients in one-year clinical trials.

While the 6-minute walk test has been used several times in recent clinical trials, it's important to analyze other commonly used endpoints. When patients remain ambulatory, muscle function endpoints, like the timed functional test and the North Star Ambulatory Assessment, provide additional information on the clinical progression of DMD patients. In fact, the FDA DMD guidance of 2014 recommended use of multiple endpoints to evaluate efficacy, seeking to broaden evaluation of clinical effects and measure change.

As discussed previously, progressive loss of functions including the ability to perform tasks and loss of pulmonary function are hallmarks of DMD, and preserving such functions is key to any treatment. Since the North Star is a key instrument to assess the ability of patients to perform different tasks, let me review that instrument in more detail.

The North Star evaluates physical function across 17 different measures, ranging from hopping to the ability to stand. Each measure is given one of three scores, with 2 being able to perform the function, 1 being able to perform with difficulty, and zero being complete loss of that given function.

While the endpoint can be summarized in a composite score, a new and more clinically interpretable way to analyze this endpoint is to assess the preservation of each function. Let me share with you some natural history data for loss of function as measured by this endpoint.

This chart shows the loss of function in one

year for patients in the largest North Star data set derived in the U.K. The 17 functions are listed on the left. As you can see, even in such a short period of time, a large proportion of functions are lost in DMD patients.

In summary, Duchenne's muscular dystrophy is a devastating, relentlessly progressive disorder that results in irreversible muscle loss and early death. It's commonly accepted that an increase in dystrophin leads to clinical benefit. The small number of patients in the non-linear muscle function decline make DMD difficult to study, therefore, it's essential to consider the current understanding of the natural history and all available data.

Lastly, a critical treatment goal is to preserve muscle function since loss is progressive and irreversible.

Thank you. Dr. McIntosh will now discuss ataluren's efficacy and safety data.

Applicant Presentation - Joe McIntosh

DR. McINTOSH: Good morning. My name is

Joe McIntosh, and I'm the senior vice president and head of clinical development at PTC Therapeutics. Today, I will discuss the evidence in support of ataluren's efficacy.

As you have seen previously, the evidence of ataluren's benefit comes from multiple studies. In Study 004, we assessed dystrophin production in patients. In Study 007, defined the dose of ataluren and provided us with an understanding of the need to enrich patients. This study also showed a consistent effect of ataluren in the selected dose across key endpoints.

Study 020 reinforced the consistency effect across key endpoints and further highlighted the need to interpret the results in light of natural history. Lastly, our long-term open-label study, Study 019, provides additional data on the preservation of pulmonary function in non-ambulatory patients.

The totality of these studies show evidence of effectiveness. The many results in favor of ataluren demonstrate patient benefit, which cannot

be attributed to chance.

Firstly, we see production of dystrophin. Secondly, there's consistent results across two randomized controlled trials from the four endpoints with greater benefit in the subgroup of patients who are in the transition phase.

Finally, ataluren shows preservation of functional milestones. In particular, we see delay in loss of individual muscle functions on the North Star and preservation of loss of ambulation, as well as pulmonary function.

Let me start with Study 004. Study 004 enrolled 38 patients and consisted of three dose cohorts. Patients who were treated with ataluren for 28 days, and then were followed up for an additional 28 days. Plasma samples were obtained at day 1 and day 28 to determine drug concentrations.

To measure dystrophin production, analysis was performed on muscle biopsies. For these biopsies, the entire extensor digitorum brevis muscle was obtained from one foot during the

pretreatment period and from another foot on day 28.

We assessed dystrophin with three independent methods: direct quantification and qualitative assessment to find immunohistochemistry, as well as ex vivo expression in cultured myotubes.

The mean change from baseline in dystrophin expression was 11 percent after 28 days of ataluren treatment, with 61 percent of patients showing some increase in dystrophin level. Importantly, the method used for quantification were standardized.

In addition, a qualitative assessment defined as the concordance of increase in dystrophin staining by at least 2 out of 3 blinded readers, this assessment showed an increase in dystrophin in 34 percent of patients. Importantly, the biopsy also demonstrated that dystrophin was produced and correctly located in the cell membrane.

We also conducted an ex vivo assessment where myotubes were cultivated from each biopsy.

In this assessment, all samples showed increase in dystrophin production, as highlighted by Dr. Welch.

While Study 004 did demonstrate production of dystrophin, the sample size was insufficient to discern a dose-response relationship. Primarily, because 9 of the 12 patients receiving the high dose were in the dose concentration selected for the 10,10,20 milligram dose as shown here.

We later determined that 19.3 micrograms per milliliter is the upper bound at which exposure is associated with optimum readthrough, as highlighted in gray. This overlapping exposure is why dystrophin responses were absorbed in all three doses and a clear dose response was not observed in this study.

The results of Study 004 are important for two reasons. Study 004 shows proof of dystrophin production in a short a period as 28 days in nonsense mutation DMD patients, and the FDA has approved another therapy for Duchenne's based solely on dystrophin production.

Let me now move to the randomized controlled

trial, beginning with Study 007. This was the first randomized, placebo-controlled study in nonsense mutation DMD. It assessed two dose regimes of ataluren. The study enrolled a broad patient population, as you can see from the eligibility criteria.

Patients were followed over a 48-week period. Data on multiple clinical endpoints were gathered, including the primary endpoint, which is the 6-minute walk test as well as the timed function tests.

Here we show the change from baseline over 48 weeks for the ITT population. There was no difference for placebo, shown in orange, compared to the high dose shown in gray, consistent with ataluren's bell-shaped concentration relationship. However, there was a difference of 26 meters in favor of ataluren with the 10,10,20 milligram dose shown in blue, compared to placebo at week 28. Early separation was seen and maintained throughout the study duration.

The timed function test endpoints, including

the 10 meter walk/run, 4-stair climb, and 4-stair descent, which are muscle function tests normally performed in 5 to 8 seconds, these numerical changes in favor of ataluren were seen across these endpoints.

Effect sizes ranged from 1 second in the 10 meter walk/run to 2.4 seconds for stair climb. This translates to approximately 20 to 40 percent preservation of function.

To put these results into perspective, corticosteroid studies in DMD have shown that a 1.5 second change correlates to a benefit of maintaining ambulation for indicial 3.5 years. Based on these results, we conducted Study 020.

Study 020 was a 48 week randomized, placebo-controlled trial to assess the benefit of ataluren at the 10,10,20 milligram dose. In 2011, after Study 007, there was an understanding for the need to enrich the patients when using 6-minute walk test. This led us to use the eligibility criteria for baseline 6-minute walk distance between 150 and 80 percent predicted for

age and height.

This slide shows the range of baseline 6-minute walk test in distances in two studies. Study 007 enrolled a broad heterogeneous population with a baseline 6-minute walking distance ranging between 75 and 533 meters. The distribution quartiles are shown here.

The FDA assert that Study 020 was successfully enriched. However, the strategy used for Study 020 did not enrich for the desired population. Importantly, the population distribution shows the same proportion of patients with a baseline 6-minute walk distance above 400 meters compared to Study 007, instead of limiting the number of stable patients as intended.

We did prespecify the three to 400 meter subgroup for analysis in an effort to assess patients in the transition phase. So let's look at the results.

Here you see the change in 6-minute walk test distance over a 48 week period in the ITT population. The results were numerically in favor

of ataluren, with an overall difference of 13 meters at week 48. In addition, we saw a benefit in favor of ataluren-treated patients across three timed function tests. These results are similar to those seen in Study 007.

The positive benefit seen across key outcomes, over two well-controlled placebo studies is part of the compelling evidence. This consistency in favor of ataluren adds to the body evidence of effectiveness.

As Dr. Flanigan explained, each endpoint measures different aspects of the disease course. The probability that all these endpoints would favor ataluren by chance is less than 1 percent.

We conducted a meta-analysis to provide additional supportive data and provide a better estimate of the treatment effect in a larger heterogeneous patient population. When combining both studies, we see a positive benefit in favor of ataluren across the 6-minute walk test in each of the timed function tests.

I will now review the 6-minute walk data in

light of the natural history described by Dr. Flanigan.

We now understand that for clinical trials over one-year duration, it is important to assess the change in 6-minute walk distance for patients with a baseline between 300 to 400 meters, representing the transition phase. We prespecified this group in Study 020 and have retrospectively analyzed Study 007 in light of this new understanding.

In both Study 007 and 020, this group represents about 40 percent of all enrolled patients, making this group sufficiently large to interpret the results. Importantly, baseline demographics were balanced for these groups.

Here are the findings. The effect of ataluren when analyzed using the understanding of natural history is consistent across both studies, resulting in a difference of more than 40 meters.

Different from the FDA's clinical reviewer's interpretation, the results in Study 007 subgroup were driven by the 75 percent of patients on

steroids who demonstrated a response in excess of 30 meters in favor of ataluren, and not by the small number of patients who were not receiving steroids.

Looking across the three key timed function tests, we see even more robust results of up to 4.4 seconds, consistent across endpoints and trials. The effect size for each of these endpoints is well and above the 1.15 second improvement, which is regarded as clinical meaningful.

I will now review the ability of ataluren to preserve functional milestones. The loss of milestone has substantial impact on patients and their families, as they are progressive and in many cases, irreversible. Therefore, preserving these functions as long as possible is extremely important.

Preservation of loss of ambulation is of paramount importance for patients. In Study 007 and Study 020, the incidence of loss of ambulation was smaller in ataluren-treated patients when

compared to placebo. As expected from the natural history, patients with a 6-minute walk test greater than 400 meters did not lose ambulation in a one-year period.

Of those Duchenne's patients in the transition phase, no ataluren-treated patients lost ambulation, whereas, 8 to 9 percent of placebo-treated patients lost the ability to walk. In the accelerated decline phase, patients with a baseline 6-minute walk test of less than less than 300 meters, shown on the right, loss of ambulation is frequent, and once more we see numerical benefit in favor of ataluren-treated patients.

While loss of ambulation is arguably the most important milestone for an ambulatory DMD patient, every function is intrinsically important. The ability to climb and descend stairs has been historically assessed in the clinic due to its importance in daily activities for patients.

On the left, we see loss of ability to climb 4 stairs. On the right is loss of 4 stair descent. In both Study 007 and 020, ataluren-treated

patients demonstrated greater preservation in stair climb and stair descent, compared to placebo.

As Dr. Flanigan discussed, the North Star is more clinically interpretable when evaluating the percentage of patients who have lost any of their 17 functions. Here you see all of the functions for placebo patients in Study 020. These data are consistent to the national history data presented earlier today by Dr. Flanigan.

As you see, about 20 percent of functions present at baseline are lost in a one-year period. When comparing the placebo to ataluren-treated patients in blue, it is evident that ataluren-treated patients experience preservation of 15 out of the 17 functions, representing a 31 percent reduction in risk of functional loss.

These data suggest that ataluren can preserve functions such as running, jumping, hopping, which are meaningful to patients. Lastly, the ability to maintain respiratory function is directly linked to survival.

I will now show you a natural history

comparison from our long-term open-label study, Study 019. In this chart, you see the distribution of forced vital capacity in DMD patients in a cohort from the CINRG study, contemporaneous to those in Study 019.

There are two important points noted here. One is the age at which patients start declining, and the second is the overall decline. As you can see, this cohort of patients start to decline at 12.5 years.

When this matched cohort is compared directly with patients in Study 019, we see the decline phase is delayed by four years. In addition, Study 019 shows preservation of lung function by 13.8 percent compared to those of the same age in the CINRG natural history control arm.

Delaying respiratory decline is associated with delayed time to mechanical ventilation and reduced risk of death, demonstrating the importance of these results.

To conclude, the totality of data from Studies 004, 007, 020, and 019 enable

interpretation of ataluren's efficacy. Together, these data provide evidence of effectiveness.

Study 004 showed production of dystrophin in patients. Study 007 and 020 demonstrated consistency of results across key muscle function tests. In addition, when interpreted in light of the current understanding of natural history, both studies showed a larger difference in patients in the transition phase.

Furthermore, the meta-analysis allows us to overcome some of the issues associated with heterogeneity, including those patients in the stable phase, and show additional benefit. Lastly, preservation of functional milestones was observed across multiple measures, which is of critical importance to patients.

We ask you to consider the totality of data when evaluating ataluren's benefit in this devastating disorder that lacks current treatment alternatives.

I now will briefly present the safety data from the two placebo-controlled studies.

Ataluren's clinical trials have generated one of the largest and most comprehensive safety databases of DMD therapies. Our database include 445 patients with DMD treated with ataluren, of which 389 have been treated for more than 48 weeks.

In the two placebo-controlled studies, observed adverse events were mostly mild to moderate in severity and occurred at a similar frequency to that of placebo. Overall, incidence of serious adverse events and AEs leading to discontinuation was low in both trials with an incidence being equal to or less than the incidence seen in placebo.

Some of the most frequently reported adverse events include mild GI disturbance as well as common symptoms of pediatric illness, such as nasopharyngitis. The adverse events were also observed in placebo-treated patients. More in depth information on safety is provided in our briefing book.

Based on the view of safety data, we conclude that ataluren was well-tolerated and has

demonstrated a favorable safety profile for this devastating disease. The overall safety profile in ataluren patients was comparable to placebo. Most adverse events were mild in severity, and there was a low incidence of serious adverse events.

Additionally, no new risks have been identified from long-term treatment of ataluren or from postmarketing data, supporting the long-term safety of ataluren for this rare and universally fatal condition.

Let me now turn to Dr. Craig McDonald to provide his clinical perspective.

Applicant Presentation - Craig McDonald

DR. McDONALD: Thank you. My name is Craig McDonald. I am the director of the Neuromuscular Medicine Research Center at the University of California Davis. Over the past 25 years, I've been involved in the treatment of over 800 patients with Duchenne's. Sadly, the majority of these patients are no longer with us.

I've been a principal investigator on industry sponsored clinical trials in Duchenne's

for multiple companies. I'm also the director of the Cooperative International Neuromuscular Research Group, CINRG, Duchenne's Natural History Study, funded by the federal government and patient organizations.

During the next few minutes, I would like to highlight my perspective on the needs of patients in relation to the data presented today. Nonsense mutation DMD patients are in urgent need of effective and safe therapies. The disease is relentlessly progressive as you've seen from Dr. Flanigan and Dr. McIntosh's presentations.

Even in a one-year period, there is substantial loss of function. Time is of the essence. Interventions are needed now to help DMD boys and young men preserve muscle and respiratory function in order to extend their quality and duration of life.

Loss of function is sequential in Duchenne's muscular dystrophy. We know loss of ambulation is overwhelming for patients and their families. It's a watershed event in their lives. Duchenne's

natural history data show that age at loss of ambulation predicts the age at subsequent loss of upper limb function and the age at need for mechanical ventilation.

As you've seen today, ataluren slows the progression of disease as observed by the 6-minute walk test, timed function tests, and North Star Ambulatory Assessment, all of which are predictive of loss of ambulation.

Delaying loss of ambulation with ataluren is expected to lead to delays in subsequent loss of function, including loss of upper limb function and delayed time to needing mechanical ventilation, which are directly linked to quality and duration of life.

Delaying disease progression allows a patient longer autonomy, which is a patient's and parent's main hope. The ataluren data are remarkable in their consistency. If we only look at the four key muscle function endpoints from the two randomized controlled trials, we see that all favor ataluren.

An integrated analysis shows that the likelihood of this result being due to chance alone is 0.8 percent. This aligns with the statistician's analysis from the FDA's briefing book where they state that there is a possible signal of treatment effect.

We also see that ataluren patients from both Study 007 and Study 020 were less likely to lose ambulation. This further reinforces evidence of efficacy, reducing the possibility that this is a chance finding.

If we next consider the NSAA loss of function, we see that 15 of 17 measures favor ataluren. Again, we see further evidence of efficacy continuing to diminish the likelihood for a chance finding.

Finally, we have evidence supporting a dramatic delay in pulmonary decline for ataluren-treated patients when compared to historical control data. When calculating the probability for these consistent treatment benefits, we can conclude there is substantial

evidence of efficacy for this devastating disease. The totality of the data supports a treatment benefit with ataluren.

Let me show you what access to ataluren will mean to patients. As Dr. McIntosh showed earlier, it's encouraging to see the ability of ataluren to preserve pulmonary function, since this has been directly linked to mortality.

The critical threshold of a 1-liter absolute forced vital capacity has been shown in the CINRG database to be associated with a four-fold increase in mortality over time, when controlling for age. In fact, when we compare the critical milestone of reaching a 1-liter forced vital capacity for patients in Study 019, to those in a similar cohort in CINRG, we see a demonstrable benefit in terms of ataluren.

By age 19, approximately 50 percent of the CINRG cohort have reached a threshold FVC value associated with an increased risk of death, whereas only 15 percent of ataluren-treated patients have progressed to this level of impairment. This

important result cannot be ignored since the risk of death is 4 times greater for Duchenne's patients progressing below a 1-liter forced vital capacity in comparison to age matched patients not progressing below this critical threshold.

Another meaningful measure of loss of function important to patients is the North Star Ambulatory Assessment. The FDA briefing document states that a decline from a 2 to 1 score on the NSAA is an equally valid clinical change compared to a 1 to zero score change.

As clinicians treating Duchenne patients, we know that these are actually different transitions. The change for a North Star score of a 2 to a 1 may actually be quite subtle for a Duchenne patient.

(Short video played.)

On the left, you will see a patient who has transitioned from a score of 2 to 1 on the rise from floor. He slowly pushes off the knee to compensate, thus producing a score of 1, rather than a score of 2. On the right is a patient who has transitioned from a 1 to a zero score. You can

see the tremendous difficulty he has in rising from the floor, and he is unable to accomplish the task.

Thus, the analysis of NSAA loss of function, a shift to a zero score, that we recently published in The Lancet, is an objective and clinically meaningful hard endpoint. The transition from a 2 to a 1 score, proposed by the FDA to be equivalent, does not carry the same clinical meaningfulness.

The 31 percent reduction in loss of function with the NSAA is important to patients. The evidence of ataluren effectiveness for preservation of function needs to be considered in light of the known natural history.

Based on the NSAA data, the placebo arm of Study 020 is representative of the expected functional decline in Duchenne patients treated with steroids who don't have access to ataluren. This is confirmed by the United Kingdom North Star network data on 514 patients presented earlier by Dr. Flanigan.

We can see remarkable consistency in the data between these groups. Therefore, we would

expect a significant percentage of DMD patients to lose functions each year. The need is urgent, because ataluren provides preservation of NSAA functions.

Here is a plot of cumulative NSAA functions over a one-year period as independently assessed by Professor LJ Wei from Harvard. On average, placebo patients lose significantly more functions than ataluren-treated patients. We see a clear early separation in risk reduction for functional loss, which increases over time.

Our patients and their families can't afford to wait for additional data when the totality of evidence already shows that ataluren is effective. Any delay in access will result in unnecessary loss of function.

Today, I'm not here representing myself, but the voice of all the patients I've cared for throughout the years. This day marks an important opportunity to continue to advance the treatment landscape in DMD.

Ataluren demonstrated persuasive results in

the treatment of nonsense mutation DMD, a disease that is complex to treat and to study. I urge you to use best clinical and scientific judgment when reflecting upon the question in front of you.

The FDA recently approved another drug for a different rare subset of DMD patients based on production of low levels of dystrophin, and I have treated patients with this drug and continue to see benefits. But most importantly, we have many lines of clinical evidence demonstrating what we ultimately need, delaying the loss of functional milestones that are watershed events for patients. I've had the privilege to offer ataluren to my patients and have seen compelling results so far.

Additionally, we see a favorable safety profile. Needing an opportunity to provide an efficacious treatment far outweighs the possible risk. The final decision you will make today should be based upon informed clinical judgment and not based on missing a primary endpoint. The data are sufficient to conclude that ataluren is effective and with minimal safety issues. There is

no reason to not make this treatment available to our patients now. Thank you.

Clarifying Questions

DR. ALEXANDER: Thank you very much. We now have some time for clarifying questions for PTC Therapeutics. Please remember that all participants from the panel, the FDA, and PTC should state their name for the record before you speak. And if you can, it's helpful if you direct your questions to a specific presenter.

Dr. Green?

DR. GREEN: Was there any consistency in the duration of steroid treatment? There was a slide that -- I have to pull it out -- it said more than 6 months, but was there a consistent amount?

DR. McINTOSH: Sorry. Just for my clarification, in terms of the question, you're asking consistency in how steroids were used in the study?

DR. GREEN: Well, and the duration of use, and the timing of use.

DR. McINTOSH: Yes. We stratified by

steroid duration, so patients had to -- by 6 months or more than 6 months, all patients had to be on steroids for Study 020, and it was balanced, yes.

DR. ALEXANDER: Dr. Ovbiagele?

DR. OVBIAGELE: Yes, thank you. The question I had was about the positive benefit seen for ataluren comparing Study 007 versus Study 020. When you look at the magnitude of the benefits, since of course the primary outcome wasn't significant for either one -- so we're looking at the nominal and numerical benefits -- it does seem as if it was greater for Study 007 than 020. Study 007 was smaller and less selective.

Do you have an explanation for that, please?

DR. McINTOSH: Yes. When we look at the timed function tests, we see remarkable consistency across both studies. There are numerical differences in the 6-minute walk data between Study 020 and Study 030. That's really due to the performance of the 6-minute walk test in the stable patients and the unstable patients.

In Study 020, we didn't see effect in those

two subgroups in the transition zone, which is the 3[00] to 400 group, where we feel it's most appropriate to find a drug effect in a one-year study, we see consistency across studies.

DR. OVBIAGELE: No. What I was referring to was when you just compare not just the 6-minute walking test, but actually all the outcomes that you mentioned, the primary and the secondary ones. Do you actually see the magnitude of the effect?

Again, that's what we're looking at because, again, neither study attained significance, but it seems to be broad. I wondered, just to make sure that we understand the plausibility of all of this, what your thoughts were.

DR. McINTOSH: Yes. I think this slide here best demonstrates a comparison of both studies. This slide shows both studies, the 6-minute walk test, 10 meter walk/run, 4-stair climb, and 4-stair descent across both studies. In the timed function tests, what we see is clear consistency with a similar response across all of those timed function

tests. The 6-minute walk test, there is some numerical difference, but the consistency is still fairly striking.

If we move, as you rightfully said, the timed function tests -- this is a plot comparing the timed function tests across both studies, and what we feel it shows is consistency for these timed function tests in both studies.

DR. ALEXANDER: Thank you. Mr. Watkins?

MR. WATKINS: Yes. A question for Dr. McDonald. You'd mentioned your observation of your patients in response to a recently approved drug for DMD, and then also your observations of the response for ataluren.

Can you compare the two in your mind? Are there similar benefits that you've observed in your patient population, based on your observations?

DR. McINTOSH: Thank you.

DR. McDONALD: This is Craig McDonald from the University of California. I think one important point is that these are drugs that have different mechanisms of action. We're seeing early

dystrophin levels at 28 days in ataluren. So I think the possibility to actually show a treatment effect in a one-year trial is actually there, looking at the appropriate population.

I think really the totality of evidence and the consistency of endpoints favoring ataluren is really, in my mind, unprecedented with dystrophin restoration strategies in a one-year trial. The effects for the other drug you mentioned I think are seen over a longer duration of a period of time because it takes longer for dystrophin to be produced.

MR. WATKINS: Thank you.

DR. ALEXANDER: Thank you. Dr. Fountain?

DR. FOUNTAIN: Yes. This is actually a follow-up to that question, and that is that, if I understand it right, you have quite a few patients in ongoing longer term trials. And you showed the pulmonary function test data that appears to be preserved compared to the historical controls.

Do you have other data besides the pulmonary function tests over a longer duration?

DR. McINTOSH: The data that we do have -- and I'll get Dr. Craig McDonald to present it because it's part of the 019 study, loss of ambulation. What we did in that study is also compared loss of ambulation.

Could we have the slide please? This is essentially the loss of ambulation data essentially for Study 019. Study 019, as we showed, is one of the studies where we have almost four years -- so 3 and a half years of exposure. And the real advantage of having that is that we can really observe outcomes data, which is more clinically relevant.

I will now hand it over to Dr. McDonald to speak you through the results of that data.

DR. McDONALD: This is long-term extension data from Study 019 where patients have had several years of treatment with ataluren. What you can see here is a median age of loss of ambulation of 16.3 years. Now the best external source of natural history control data is actually seen in the next slide, and here we see data that is now in

press from our CINRG group in The Lancet.

To demonstrate this, this is loss of ambulation data in 330 Duchenne patients, with the red line there showing the proportion of patients maintaining ambulation on steroids. The blue line are those not treated with steroids. The median age at loss of ambulation in those 330 patients is 13.4 years, with a 95 percent confidence interval of 12.5 years to 14 years.

On the right, this compares with the long-term ataluren-treated patients, which showed median loss of ambulation of 16.3 years, which is 2.3 years prolonged beyond the 95 percent confidence interval we see for the 330 Duchenne patients followed long-term. Thank you.

DR. FOUNTAIN: Are you collecting other data as well or just the pulmonary and the ambulation?

DR. McINTOSH: In that study, we collect the outcomes data, which is the pulmonary data as well as the timed function test and 6-minute walk test data.

DR. FOUNTAIN: Is there any reason to think

then it's just a final follow-up to this that longer term wouldn't be better? Is there some physiologic reason? Do you think to keep making dystrophin, that would help? If you started earlier, it would help more; if you continue it longer it would help more. So the longer you're on it, the more benefit it would have would seem to be.

Is there some reason you think that wouldn't be true?

DR. McINTOSH: I'd like to hand this over to Dr. Craig McDonald.

DR. McDONALD: It's a mechanism-based treatment to produce dystrophin and preserve muscle fibers. Clinically, we believe that earliest treatment is essential. We would want to treat patients as soon as the diagnosis is made to try to preserve as much muscle function as possible, knowing that it may take two or three years to actually demonstrate benefits in that group.

However, we also know that even in the patients in the rapidly decline phase, we're also

seeing benefits in terms of preservation of pulmonary function. There's also some extension data that shows stability of upper limb function as measured by the performance of upper limb, measure the PUL.

DR. ALEXANDER: I'd like to ask a question. My name is Dr. Alexander. So doctors who say no to that Study 020 failed because of failure to enrich the population appropriately, which I understand, but that is a reasonable comment about -- I mean that comment could be made about any study that fails.

So I'm just trying to understand more in terms of the temporal sequence, why were stable patients included in Study 020? Was it known prior to the conduct of that study? Was there a failure to appropriately reach the targets for recruitment of the right patients? Or was it only learned after that study was analyzed, that there was a failure to enrich for the right population?

DR. McINTOSH: This is an important point to clarify. We need to understand that the evolving

nature of our learnings as we designed these studies. Study 007, which was the first placebo-controlled study to use the 6-minute walk test, the results from that study, we learned we needed to enrich the patient population and need to remove stable patients. However, we did not know how to do that appropriately. At the time, the natural history data was not forthcoming. There was no natural history data on the 6-minute walk test.

As Dr. Dunn had explained, we did some sub-analysis and we looked at a particular group. We identified an exclusion criteria. We said we'll remove patients who can walk 80 percent predicted for their height and age, and that will move the stable patients. When we actually used that criteria, what it did not do was remove stable patients, unfortunately.

The temporal evidence that showed that the greater than 400 group are a stable patient group and would be difficult, we only came out with the Pane publication in 2014. I think now it is quite

recognized, and I think in the last two applications, which this committee is aware of, with drisapersen and eteplirsen, there's been acknowledgement of the floor and ceiling effects associated with the 6-minute walk test.

DR. ALEXANDER: If you were designing the study all over again, are there other changes you'd make, other than to focus exclusively on patients with a 6-minute walk distance of 300 and 400 meters?

DR. McINTOSH: Absolutely. I mean we've had a lot of learnings from these two clinical trials, and the DMD space is rapidly evolving. What we have categorically learned is, A, you need longer studies. Short-term studies, one-year studies, create significant challenges and require the need to enrich.

So longer studies for sure and also to focus on a decline-phase population. You need to exclude stable patients, and you need to exclude patients who are very unstable, and those are the principles we're moving forward with our study.

DR. ALEXANDER: Thank you. Dr. Kesselheim?

DR. KESSELHEIM: This is Dr. Kesselheim. My question was sort of answered by that response. But my question was about the transition phase and whether clinicians prospectively can identify patients based on what phase they're in, and do they change their treatment patterns differently. As a relationship to that on slide 56, I was just wondering what the X-axis time measure is.

DR. McINTOSH: Thank you. I'll refer to Dr. Craig McDonald who's an expert in natural history of Duchenne's to answer that.

DR. McDONALD: Craig McDonald from the University of California. Again, with regard to the sequence and whether clinicians can identify patients in the transition phase, I think we certainly use a variety of measures. The same measures that are actually used in these clinical trials, where we're seeing consistent ataluren treatment effects, some of the measures are more prognostic.

The rise from floor value is really more of

a prognostic measure rather than a measure that's predictive of a treatment effect. The Pane data was actually available in 2014, showing stability of ambulatory function in those higher functioning groups.

But yes, we can -- I think clinically using the same endpoints such as the timed function test, 6-minute walk, and North Star, we can identify patients in transition versus the stable phase. Thank you.

DR. ALEXANDER: Dr. Perlmutter?

DR. PERLMUTTER: Joel Perlmutter from Washington University. Again to Dr. McDonald, if I may. When you showed us the data from your Lancet paper in press, comparing the steroid treated versus the ataluren, were those two studies contemporaneous, or was that a historical control, and were the ataluren subjects or participants also taking steroids?

DR. McINTOSH: Thank you. Dr. McDonald?

DR. McDONALD: Yes. The data I presented earlier was a natural history data, which was

conducted contemporaneously with the ataluren trials. This was conducted in 20 sites worldwide. A hundred percent of patients in that red curve are treated with steroids; 94 percent of the patients in the Study 019 group were treated with steroids, and they were actually balanced on a variety of other factors.

DR. ALEXANDER: Dr. Fountain and then Dr. Mielke.

DR. FOUNTAIN: In reference to slide 81 about the North Star data, you mentioned that there was an improvement, but it looks just at -- eyeballing, it would appear that it's true that 8 of 17 are better, but 6 of 17 are worse, and 3 of 17 look about the same.

So is slide 82 an aggregate data, or is it something else or some subgroup? Because a fundamental question is how well we're able to separate out what is coincidentally or could be found by accident. So just eyeballing it, 6 of 17 look worse, 8 of 17 look better, so that's pretty close; and 3 of 17 are the same.

Is the analysis of that of all factors and are they weighted, or something like that?

DR. McINTOSH: Thank you. I'd like to invite Dr. Marcio Souza to answer.

MR. SOUZA: Marcio Souza, PTC Therapeutics. Slide 81 is actually a comparison between two placebo or untreated cohorts. Just to show, as you rightly so said, Dr. Fountain, this is very balanced. This validates the placebo.

Our slide in the core -- if I could bring back the comparison between ataluren and placebo, please -- shows a difference in 17 out of the 15 [sic] items. And when we compute the difference, not only the number of items, but the magnitude of the difference, we see a 31 percent risk reduction for a patient into this relatively short period of time, of one year, of losing of function, if that given patient would be placebo versus ataluren, reinforcing, once again, not only the unmet needs of losing as much 20 percent in one year, or more in some functions, but also very high treatment effects. Thank you.

DR. ALEXANDER: Dr. Green, and then we'll come to you Dr. Mielke.

DR. GREEN: It has to do with the placebo slide as well. Given a somewhat modest therapeutic gain and admittedly probably acceptable SAEs, even though they occurred in both groups, were patients able to detect -- because sometimes adverse events aren't severe; they're just detectable -- detect what group they had been allocated to?

DR. McINTOSH: Study 020 was robustly blinded and masked. No specific AEs would have specifically unblinded the patients at all.

DR. ALEXANDER: Did that address your question?

DR. GREEN: Well, you have no specific information whether they were able to correctly allocate the group they were in, or their caretakers?

DR. McINTOSH: Let me invite Dr. Marcio Souza to answer that question.

MR. SOUZA: Marcio Souza, PTC Therapeutics. They were not only allocated blindly by the system,

the IVRS system, but all the sibling pairs were allocated to the same group as per the protocol. There's no difference in the formulation in terms of anything that could lead to unblinding, and there was no difference in adverse events in any of the groups that could lead to inadvertently unblinding.

On top of that, the FDA inspection that occurred already, at PTC, did not find any example that could be leading to unblinding.

DR. ALEXANDER: Thank you. Yes, Dr. Dunn?

DR. DUNN: Yes. I just wanted to make sure Dr. Green -- your question I think was not so much -- and maybe I misunderstood you -- was not so much about the methods of randomization and allocation, but I think you were asking the sponsor if they had any objective assessment of the effectiveness of the blinding maneuvers; is that correct?

(Dr. Green nods yes.)

DR. DUNN: Okay. I don't have an answer to that for the sponsor. I just wanted to make sure

that that was clear to the sponsor so they could offer any information they had in that regard. I think Dr. Green was asking if you had performed any post-study assessment of the effectiveness of your blinding maneuvers.

DR. McINTOSH: We haven't done any specific assessments to look for, but there's been nothing in the study that has alluded to the fact that this was not a well-controlled and blinded study.

DR. GREEN: Again, I was interested in the patients and the caretakers equally.

DR. McINTOSH: During the study, we had no issues with caretakers. And talking about something that would significantly show unblinding, we have no data to suggest there'd be any issues with our blinding.

DR. ALEXANDER: Dr. Mielke?

DR. MIELKE: I had a question going back to The Lancet neurology article again, and looking at the curves. Would you mind putting that figure up again?

DR. McINTOSH: Is it on the North Star data?

Loss of ambulation. Thank you.

DR. MIELKE: Again, looking at the red curves and the blue curves, there is a slight difference in terms of corticosteroid use, but was there any difference in terms of where they started from, given the terms of their 6-minute walk test?

DR. McINTOSH: Yes. I'd like to invite Dr. Craig McDonald, who did this analysis.

DR. McDONALD: We do have demographic information at baseline comparing the CINRG natural history cohort published in The Lancet, and the patients participating in Study 019. They were well-balanced on age at entry. They were well-balanced in terms of proportions on steroids. They were well-balanced on proportions taking deflazacort.

The CINRG data did not have long term 6-minute walk data, because this was a relatively new endpoint that had been recently validated. But we did have 10 meter walk/run data, and the two populations were well-balanced with regard to baseline 10 meter walk/run function. Thank you.

DR. ALEXANDER: Dr. Kesselheim?

DR. KESSELHEIM: Yes, it's Aaron Kesselheim again. I was comparing slides 48 and 52, which are the Study 007 and Study 020. It looks like in 48, the separation between the low-dose ataluren line and the placebo line occurred relatively early in the treatment, whereas in Study 20, it occurs relatively late, in slide 52.

I was just wondering if you had an explanation for why that might have looked differently.

DR. McINTOSH: Study 007 we saw, as you rightfully said, early separation. What we noted in Study 020 is the separation occurred a little bit later. We don't really fully understand why that was, but we still do see separation, and that separation continues throughout the latter part of the treatment period.

DR. ALEXANDER: Thank you. Dr. Onyike?

DR. ONYIKE: The transition phase can be defined or viewed as a category, or it could be viewed as a continuum. To the extent that one

might view it as a continuum, it would stand to reason that people who are closer to 400 would fail milestones earlier or might be declining faster than those who are closer to 300.

My question then is do you have descriptions of the baseline values for the clinical outcomes for the placebo group versus the treatment group -- I'm sorry, for the treatment group versus the CINRG comparisons?

Because my thinking would be that if the median scores on the 6-minute walk distance, if they differ, if the placebo group are closer to 400 than the treatment group, that could explain the findings.

DR. McINTOSH: Just for me to clarify, when you're talking specifically about patients in the transition phase, you're saying did the prognostic disease factors balance across both treatment arms, in that specific group, to ensure that there's no imbalance?

DR. ONYIKE: It would appear to me that you are using the transition phase as a category.

DR. McINTOSH: Yes.

DR. ONYIKE: And that pretends that people who are 300 are equivalent to those who are at 400, and I'm not sure that is true.

DR. McINTOSH: This is an excellent point. We have done baseline demographics for the 3[00] to 400, so this is obviously critically important. We did stratify at 350. The good news about stratifying at the midpoint, that it means it ensured that there was balance within this to three to 400 baseline group.

What we see, generally, across the prognostic indicators of function like stair climb, stair descent, 6-minute walk -- stair descent and run/walk, it's very balanced. The only difference is the ataluren patients were a little bit older, so that would bias potentially against. But when you look at the actual function of these patients, these patients were functionally comparative.

DR. ALEXANDER: Mr. Watkins?

MR. WATKINS: Yes. Do you have any ideas on why ataluren was not successful in the CF studies

versus the apparent positive benefits that you're presenting today in Duchenne?

DR. McINTOSH: CF is obviously very different from, A, genetically, you have two mutations, as in Duchenne's you only have one, as well as pathophysiologically, you have a lot of infections in cystic fibrosis, which are confounded.

What we saw is in our preclinical models, as well as in our phase 2 study, we saw restoration of the CFTR protein, the target protein. We did the experiment to look at CF in one study, we had an interaction with Toby [ph]. We reran it. Then the benefitting was not sufficiently large to pursue that indication.

DR. ALEXANDER: My name is Caleb Alexander. I have a question about statistical significance. And I'll be the first to say I'm not a biostatistician, but I'm trying to reconcile -- and I think we'll hear from the FDA later, regarding their take on tests that are maybe of nominal significance, but not capital S, statistically

significant.

So I'm trying to understand the statistic that we heard that the likelihood of endpoints being positive, being positive by chance alone, was 0.8 percent. On the one hand, we have these two trials that failed their primary endpoints, if I understand what we've heard, so we're looking at a variety of different secondary endpoints that were not prespecified.

But can you say a little bit, but simplifying it for the non-biostatisticians in the room, about how we interpret this value of 0.8 percent?

Then I guess the other point to this is that both briefing documents have discussed an absence of adjustment for multiple comparisons. Are those not possible to do post hoc? I realize there may still be lots of problems about doing those, but are those not possible to do?

DR. McINTOSH: Excellent. There are two questions there about that one analysis around .08, and I'd like to invite Professor LJ Wei who did the

analysis from Harvard to discuss this.

DR. WEI: Thank you very much. LJ Wei from Harvard. Could you put up the slides, please?

Sir, if you allow me just to make some comments before I make a comment about this totality evidence across two studies, across the key outcomes.

The FDA, who is sitting here, discuss how we define substantial evidence from a clinical trial. My understanding right now, FDA is using p less than .05 for primary endpoint. That's their definition. In fact, American Statistical Association, which is the largest statistical society, recently issued a formal statement saying don't use a p less than .05. It doesn't make too much sense.

Furthermore, in the workshop we had with FDA, Duke University, I remember Dr. Temple was sitting there too, we discussed how we can improve drug development for rare disease drugs, and three things we came out.

First one, moving beyond p less than .05,

depending on how rare the disease, we should choose the level we're talking about. What is the second lesson we learned? Utilize multiple endpoints, not a single endpoint. Third one, utilize the natural history data, helping us evaluate the treatment.

So PTC today is presenting to you exactly those three areas.

DR. ALEXANDER: So how is this value of 0.8 percent derived?

DR. WEI: Yes. Let me explain to you, sir. Let's think about 007, the blue dots on the right-hand side means in favor of treatment; on the left-hand side of zero means in favor of placebo. You notice the 4 blue dots? They're all on the right hand side of zero. If we move to the right panel, 020, 4 blue dots are also on the right hand side of zero.

Let's think about it. Suppose I have a coin. I said suppose there's a fair coin -- that means 50 percent, you're getting heads, 50 percent you're getting tail. If you toss a coin, you get heads, you put a blue dot on the right. If you get

tails, you put it on the left. Then I ask myself, what is the chance you toss the coin eight times, you got eight heads? The chances are .004, but of course the tosses are not independent because they came from the same data.

So we actually can use a statistical methodology to figure out the 0.8 percent chance to get this profile if there is no difference at all, so the chance is so small.

DR. ALEXANDER: Okay. Thank you. And were adjustments made for multiple comparisons?

DR. WEI: Well, sir, this is also a very philosophical issue. How in the world we can handle so-called multiplicity from a statistical point of view -- if you think about drug development, if you really think about multiplicity, we should go back to phase 1, phase 2, phase 3. I tell you, if we do that, no one is going to approve the drug, period.

So something is going on. It's a little bit artificial when we're talking about multiplicity. Thank you.

DR. ALEXANDER: Okay. Thank you.

Dr. Onyike, and then that will be the last question for the session.

DR. ONYIKE: Yes, if I may revisit my earlier question, how did the groups compare at baseline with respect to the 6-minute walk?

DR. McINTOSH: Sure. For the transitions in patients, or for the ITT?

DR. ONYIKE: For the transition.

DR. McINTOSH: Okay.

DR. ONYIKE: For the groups that were randomized, basically.

DR. McINTOSH: Okay. For the transition zone, I'd like to highlight the third column there. Placebo patients had a 6-minute baseline walk test of 342, and ataluren had 351. When you look at the other covariants of the disease prognosis, which is climb stair, climb descent, raise from spine, and run/walk, they're all very similar in balance. So these prognostic indicators imply that the patients have a similar disease severity.

DR. ONYIKE: Thank you.

DR. McINTOSH: Thank you.

DR. ALEXANDER: Thank you very much. We'll now take a 15 minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves, or with any member of the audience, and we'll resume promptly at 11:15 a.m. Thank you.

(Whereupon, at 11:00 a.m., a recess was taken.)

DR. ALEXANDER: Thank you, and welcome back. We'll now proceed with the FDA presentations.

FDA Presentation - Robert Temple

DR. TEMPLE: I'm Bob Temple. I'm deputy director of ODE I. I'm going to talk generally about some principles of subgroup analysis, not so much the data that's been presented to us. But it's worth noting that a lot of the discussion and disagreement has something to do with looking at subsets of the entire trial, so that's what I'm going to be talking about.

The general principle that the study endpoints in a trial, that are going to be analyzed

to demonstrate effectiveness have to be identified before the study is completed -- we even like it best if they're identified before the study started -- is universally expressed and is a critical part of study planning, and really everybody knows this.

The overall term expressing the concern about multiple endpoints is generally referred to as multiplicity, and it involves a recognition that false conclusions can be reached if you look at a whole lot of endpoints and pick the one that wins. There's also concern with potential bias in selecting endpoints, if new endpoints are selected with the data in hand, for obvious reasons. So in designing trials, there is particular attention to specifying the primary endpoint.

It's worth noting that the same issues arise when you're looking at subgroups of the population; men/women, old/young, people with varying degrees of disease seriousness, and things like that, which is mostly what we're talking about today. We're not looking at new endpoints so much as subsets.

That's the case today, where subsets of the disease based on severity or baseline characteristics, or whatever, where a clearly negative study as originally planned, negative based on all the randomized patients, is said to be a positive study in a population subset chosen after completion and with knowledge of the data.

It does seem worth noting that in most cases, these subsets that are chosen don't look crazy. They look plausible. That's what makes them attractive. But everybody knows this, and they're worried about it anyway.

In an ICH, International Conference on Harmonization Guidance called E-9, which talks about statistical principles, there are a number of statements in there that recognize this.

"Redefinition of the primary variable -- that would also include a subset of the population based on a baseline characteristic; that's my addition, not ICH E-9 -- after unblinding will almost always be unacceptable since the biases this introduces are difficult to assess."

The guidance also says under the heading of Sub-groups, Interactions, and Covariates, "Acknowledging that subset variations are of great interest and can be planned" -- they note that we are -- and I would endorse this -- we're very interested in whether there are subgroups in the population that respond differently. We always analyze that sort of thing.

In some cases, it's perfectly possible to find that a relevant subgroup, based on a variety of factors, is the right group to study. We endorse things like prognostic enrichment, where you identify the people who have enough disease to show something, and predictive enrichment, where you identify who the responders are. The attractive areas are genetic enrichment, but there could be other bases for picking.

What ICH says, "In most cases, subgroup or interaction analyses are exploratory and should clearly be identified as such. When exploratory, these analyses should be interpreted cautiously, and any conclusion of treatment efficacy or lack

thereof, or safety based on exploratory subgroup analyses is unlikely to be accepted." That's what ICH E-9 says.

"Exploratory trials cannot be the basis of the formal proof of efficacy, although they may contribute to the total body of relevant evidence." So it's a very strong position that you don't go nosing around.

In a masterly piece of timing, a recent New England Journal of Medicine article from September 1, 2016, Stuart Pocock and Stone addressed the issue of what to do with studies when the primary outcome fails. They note that there may be reasons for hope, based on such a study, notably when a small trial comes close to nominal significance, but they are very skeptical when the overall result is neutral. That's a judgment call of course.

"Indeed," they say, "we find it hard to think of an example in which an apparent benefit in a subgroup in a trial with a negative outcome has led to confirmation in a subsequent trial." I'm

not necessarily quite as negative as that. I think these are worth pursuing.

Maybe it's because of my enthusiasm for enrichment, but I think the idea of looking at subgroups that look good in formal studies is a pretty good idea because the groups could have differences in effect size, differences in degree of spontaneous variability, all those things.

I would say we generally would encourage sponsors to look closely at what seemed to be possible responder subsets, and that is in fact what PTC has done. Unfortunately, they didn't really work. So subset findings we believe need study, not acceptance and belief.

In a paper in the Annals of Internal Medicine called "Clinical Trials: Discerning Hype from Substance," a somewhat aggressive title, Tom Fleming illustrates the risks of unplanned subset analyses, and he particularly cites a trial of Actimmune in idiopathic pulmonary fibrosis. No significant effect was seen on progression-free survival, which was the primary endpoint, or on

overall mortality, but mortality leaned with a nominal p of 0.08 or 0.15, depending on how you looked at it, in the overall study.

That wasn't totally negative. There was some reason for optimism, and very exciting to everybody. In the mild-to-moderate subset, there was a marked reduction in mortality, 21 versus 6 -- pretty impressive, right? -- with a nominal p-value of 0.004.

So they did the confirmatory study, which was absolutely the right thing to do, and they did it in people with mild to moderate disease, and there was no effect at all. On drug, the mortality was 14.5 percent, placebo was 12.7. Those kinds of things are very sobering, because 21 versus 6 looks pretty good. The PTC experience to date supports the reasons for being cautious.

The Fleming example, and there are many more, of failing to confirm a subset finding is not a reason not to study a subset that appears to respond in a subsequent trial, especially if the subset is plausible, which they usually are, and

the finding looks strong.

PTC's experience with ataluren in DMD, and as you've already heard, in cystic fibrosis as well, showed that it is possible to responsibly assess plausible subsets in a prospective trial, of course, and also suggests that one should try to control one's expectations because these do not always work out.

The experience also clearly shows why a study planned to support the subset hypothesis is really needed, because they fail a lot, and why, as Pocock, Fleming, FDA and many others have explained repeatedly, the subset findings are not credible on their own. Maybe there are some exceptions to that, but I can't really think of any.

As you've heard, the initial controlled study of ataluren, Study 007, compared 2 doses of ataluren to placebo with a primary endpoint of change in 6-minute walk distance.

There's no question that the study leaned in a favorable direction for the low dose, although it showed no hint of an effect at the high dose, which

I believe considerably undermines the lean. As you know, there's been some attempt to explain why the dose-response curve is umbrella-shaped, but as you'll also hear, we don't necessarily agree with that.

As explained in the division memorandum, the various post hoc analyses, some of which led to nominal p-values of less than 0.05, were not considered statistically valid and were weakened further by the absence of effects on secondary physical function.

So we did not agree to approve the drug based on those subset analyses, but suggested a new randomized trial, looking at the apparent responder subset, people with the walking distance in a certain range.

The company did that. They did a study in patients with a baseline walking distance greater than 150 and less than 80 percent predicted, and that's what Study 020 was. They also changed certain requirements for age and steroid use; a terrific reasonable prognostic enrichment strategy

or maybe it was even predicted enrichment. I'm not sure.

PTC plainly responded appropriately to our refusal to file. They did the new study. But unfortunately, as you've heard already, Study 020 didn't show a statistically significant effect on 6-minute walking distance. The nominal overall p-value was 0.21. ("I'm embarrassed. If I keep quoting p-values maybe we'll learn not to do that anymore.")

In addition to that, the mean effect size observed was very modest, 13 meters, far smaller than the 46-meter effect seen in the subset of Study 007 that led to this enrichment strategy. That's sobering, too.

For Study 020, as you've heard, PTC urges, after clear failure on the primary endpoint, and with reasons that are not implausible, a different assessment, based on yet another subgroup, now patients with baseline 6-minute walking distance of 300 to 400 meters.

As I said, these are always plausible.

That's the whole point of these after-the-fact subsets. They're always plausible, but they're chosen with data in hand. You already know the outcome, and that's an important bias problem. Such subset study results need to be studied in controlled trials, and that's what we've been urging.

You already heard about this, and I don't want to dwell on it too much, but PTC's experience with ataluren in nonsense mutation cystic fibrosis is further reason for being sober. The 2014 press release reported favorable results in a placebo-controlled trial on FEV1 and pulmonary exacerbations with a nominally significant effect in patients not receiving aminoglycosides. That was plausible because they might interfere with the drug, and there were laboratory data to support that.

They announced at that time that they were going to conduct a confirmatory study, which they did. The results were announced in March of 2017. There was really no effect at all. The p-values

for FEV1 were 0.534, as close to nothing as you can get, and 0.401 for exacerbations. Again, a perfectly plausible subset plan didn't really work out.

Thank you. I'm going to stop there. I could take questions if anybody wants to. Or are we not doing that?

DR. ALEXANDER: Thank you, Dr. Temple. I think we'll move on, but we may come back to you with specific questions for you.

The next speaker from the FDA.

FDA Presentation - Veneeta Tandon

DR. TANDON: Good morning. I am Dr. Veneeta Tandon, a clinical reviewer in the Division of Neurology Products. In the initial part of this presentation, I will be giving you an overview of the FDA efficacy review of the ataluren NDA.

The statistics reviewer, Dr. Ling, will then present detailed analyses of the efficacy data. I will be back again to emphasize several important additional efficacy considerations for the committee.

Subsequently, Drs. Bhattaram, Rao, and Weaver will discuss the applicant's analyses that attempt to support the presence of an inverted U dose-response relationship of ataluren. Dr. Kozauer will then summarize the agency's presentation, with some final remarks.

As you heard from the applicant earlier today, the ataluren development program included Study 004, which was a small, 4-week, uncontrolled, dose-ranging trial. Three dose regimens given 3 times a day was studied in patients with nonsense mutation DMD, who were at least 5 years of age.

The goal of this study was to evaluate the pharmacodynamic effect of ataluren on in vivo and in vitro dystrophin production from muscle biopsies at baseline and at the end of 4 weeks. You will hear about the results from this study from other FDA presenters later this morning.

In addition, the ataluren development program included two randomized, placebo-controlled studies of 48 weeks duration. Study 007 was conducted in patients with nonsense mutation

Duchenne muscular dystrophy, who were randomized in a 1 as to 1 as to 1 ratio to receive placebo, a low dose or a high dose of ataluren, given 3 times a day.

Patients were required to be at least 5 years of age, with baseline 6-minute walking distance of at least 75 meters. Patients were not required to be taking steroids to be enrolled.

For the second study, 020, the enrolment criteria were modified to enrich based on a post hoc subgroup analyses from Study 007. Patients were equally randomized to receive either placebo or low dose of ataluren.

The enrolled patients were required to be between 7 to 16 years of age, have a baseline 6-minute walking distance of at least 150 meters, but less than 80 percent of their predicted value based on patients height and weight. Unlike Study 007, this study required that patients be on a stable dose of steroids for at least 6 months. Both studies employed similar stratification factors, with the exception of steroid use.

In the upcoming slides, I will present only the high level results from Study 007 and Study 020. Dr. Ling will present the detailed results from these studies.

Now let me give you an overview of Study 007, which was conducted first. The primary endpoint was the change from baseline in 6-minute walking distance at week 48. The results of the analyses of the endpoint for both doses of ataluren that were evaluated in this study were negative when compared to placebo with p-values of 0.05 and 0.48, respectively, for the low and high dose of ataluren.

It is important to note here that the high dose performed similarly to placebo, and numerically worse than the low dose. This is a very unusual result when drugs are effective.

This study also included 50 secondary endpoints. Although the analyses of these endpoints would have been exploratory regardless, since the primary analyses were negative, there was also no planned control for multiple comparisons in

the protocol. All but two were negative for both doses. Again, the high dose performed similarly to placebo and numerically worse than the low dose for all secondary endpoints.

Based on post hoc assessment, the applicant postulated that the failure of the high dose to show a trend towards benefit is related to an inverted U-shaped dose response of ataluren. Drs. Bhattaram and Weaver's presentation later this morning will discuss why FDA does not find this hypothesis persuasive.

After the results of Study 007 were known, the applicant conducted multiple post hoc analyses on the data from Study 007 to find a nominally significant result in favor of ataluren. In all of these post hoc analyses, the numerically worse performance of the high-dose ataluren was dismissed by the applicant.

As you will hear later today, we do not find this scientifically justified and very much believe that the high-dose results must be considered in the interpretation of the study findings.

Post hoc analyses changed both statistical methods and study populations. The unblinded change of the statistical method included adding a post hoc interaction term to the primary mixed model repeat measure analysis and conducting post hoc permutation tests on this refined MMRM.

In addition, unblinded changes were made to study population after looking at the data. After looking at the data, the applicant chose not to consider the baseline 6-minute walking distance value from two patients because of injuries that the applicant stated would have affected assessments. These changes favored ataluren and were not based on any prospectively planned approach.

The applicant referred to this application as the corrected ITT population and used the corrected ITT population in all post hoc analyses that were included in the NDA. The applicant submitted an NDA in 2011 that was based on results of these post hoc analyses. As you have heard earlier from Dr. Dunn, the FDA refused to file that

application.

In addition to the post hoc analyses that I just discussed, the applicant subsequently identified a new post hoc subgroup of patients from Study 007 referred to by the applicant as the ambulatory decline-phase population or abbreviated as ADP, and for which the applicant believed a treatment benefit was present.

This group was identified after several additional sequential post hoc changes that narrowed the age, the 6-minute walking distance criteria, and required the use of steroids.

The applicant then went on to conduct Study 020, which was a larger trial that was empirically enriched using enrolment criteria that were identical to the post hoc ADP population from Study 007.

As Drs. Dunn and Temple have stated, the agency very much encourages this sort of prospective enrichment to test exploratory hypotheses. This study was well-powered with a sample size more than 3 times the size of the ADP

group in Study 007, enrolling 230 patients compared to 63 patients that met the ADP population criteria in the low-dose arm of ataluren in Study 007.

Based on the applicant's theory regarding the reason for the numerically worse performance of the high dose in Study 007, Study 020 evaluated only the low dose of ataluren. Despite the enrichment of Study 020 and the larger sample size, the primary endpoint changed from baseline 6-minute walking distance at week 48 was clearly negative with the p-value of 0.21.

Additionally, all but one of the trials secondary endpoint, which could only be considered exploratory since the primary analysis failed, were nominally negative.

The applicant attributed the failure of Study 020 to the fact that patients in Study 020 had a higher than intended baseline 6-minute walking distance relative to the post hoc ADP population from Study 007. However, an FDA analysis that will be presented by Dr. Ling during her statistical discussion comes to a different

conclusion and shows that these factors do not explain the failure of Study 020.

The applicant analyzed nine different subgroups in Study 020. It is important to remember that these analyses can only be considered exploratory since the primary analysis of the trial failed. In addition, even if the primary analysis of the trial was positive, these analyses would still be exploratory, as there was no plan for multiple comparisons in the protocol. That is no control for type 1 error to account for the possibility that some results may be positive by chance alone.

Five out of these nine subgroups were based on different baseline 6-minute walking distance cutoffs. The only one of the nine subgroup that normally favored ataluren included patients with a baseline 6-minute walking distance between 300 and 400 meters.

The applicant then went back and looked at these subgroups in a new post hoc analysis of Study 007, using a post hoc statistical method.

Based on this exploratory finding, the applicant submitted the current NDA application in 2015, which the agency refused to file.

You will hear more about these results in the subsequent statistical presentation by Dr. Ling. I will now hand over the presentation to Dr. Ling.

DR. ALEXANDER: We're just going to pause for one minute while we make some AV adjustments.

(Pause.)

FDA Presentation - Xiang Ling

DR. LING: Good morning, everyone. My name is Xiang Ling. I'm the statistical reviewer of this application. In this presentation, I will give an overview of the statistical analysis results for the efficacy studies 007 and 020.

The primary endpoint for Study 007 was a change from baseline in 6-minute walking distance at week 48. The primary analysis was a mixed model repeated measures, noted as MMRM.

As specified in the statistical analysis plan, the original 6-minute walking distance data

were replaced with the ranks in analysis because the data were not normally distributed. We call this rank-transformed data.

Holm's analysis method was specified to adjust for multiplicity of testing the two doses. The primary analysis did not show a statistically significant treatment difference for the low dose compared to placebo. The nominal p-value is 0.15 and the p-value adjusted for multiplicity was 0.3. There was virtually no treatment difference between the high-dose group and placebo.

Sensitivity analyses were specified in the analysis plan to be performed if the primary analysis had been positive. These analyses were considered exploratory in the setting of a failed primary analysis. The results are presented in the bottom half of this table.

ANCOVA on the last available data was performed to assess the possible impact of missing data. In this study, the amount of missing data was very limited, about 3 percent. Analysis using ANCOVA on rank-transformed data yielded similar

results as the primary analysis did. The adjusted p-value for the low dose was 0.32. Again, there was no treatment difference between the high dose group and the placebo.

Another analysis was permutation test performed to assess the possible impact of dynamic randomization, that was utilized in this study. As the permutation test does not rely on normality assumption, the analysis was performed without rank transformation.

The adjusted p-value for the low dose was 0.15 based on the permutation test, which was similar to the p-value of MMRM on untransformed data, indicating that the dynamic randomization didn't have a significant impact on the efficacy result.

The secondary endpoint for Study 007 were considered exploratory, as there were no planned type 1 error control for testing the secondary endpoints. Over 50 secondary endpoints were explored. Only two of them reached nominal statistical significance, based on the prespecified

analysis methods.

Nominal statistical significance means that the p-value of the test is less than 0.05, without adjusting for multiple comparisons involving multiple endpoints and multiple doses.

The statistical significance for the two endpoints would be lost if the p-value was adjusted only for the multiplicity of testing the two doses and not considering a failed primary endpoint and multiple secondary endpoints.

Here are the results for the timed function tests. Again, these are exploratory analyses. A total of 16 analysis results were presented in this table for the 4 endpoints and the 2 doses on rank-transformed data and untransformed data. The 6-stair climb for the low dose using untransformed data was the only one that reached nominal statistical significance.

The applicant identified a post hoc subgroup in Study 007 that suggested a nominally significant treatment effect in favor of the low-dose ataluren. This subgroup was referred to as an ambulatory

decline-phase subgroup, and was defined by three factors: age between 7 and 16 years, 6-minute walking distance between 150 meters and 80 percent predicted for age and height, and steroids use for a minimum of 6 months.

Subsequently, a large phase 3 study known as Study 020 was designed to study the enriched ambulatory decline-phase population. The enrollment criteria for Study 020 included these three factors that were used to define the ambulatory decline-phase population.

Patients were randomized only to the low dose of ataluren or placebo. The study enrolled twice as many subjects as Study 007 and over 3 times as many subjects in the Study 007 ambulatory decline-phase subgroup.

Despite that the study had a larger sample size and was enriched based on the post hoc subgroup finding from Study 007, the study failed to reach statistical significance for the primary endpoint. The p-value is 0.21 based on the prespecified analysis method. The numerical

treatment difference was 13 meters, much smaller than the 44 meters for Study 007 ambulatory decline-phase subgroup.

To explain the failure of Study 020, the applicant argued that 80 percent of the predicted 6-minute walking distance inclusion criteria was set too high to adequately exclude stable patients. The mean baseline 6-minute walking distance was 23 meters higher in the Study 020, than in the Study 007 ambulatory decline-phase subgroup.

To investigate the potential impact of the inclusion of stable patients and the higher baseline 6-minute walking distance in Study 020, we conducted an analysis attempting to create a group matched closer to the Study 007 ambulatory decline-phase subgroup. In this analysis, the most stable patients were excluded so that the mean baseline 6-minute walking distance for this subgroup was similar to the Study 007 ambulatory decline-phase subgroup.

The numeric difference between the ataluren and the placebo based on this analysis was similar

to the primary analysis. After the primary endpoint failed, the analysis of secondary endpoints were for exploration only. A total of 4 endpoints were explored. One of them, the 6-stair descent, reached nominal statistical significance.

The subgroup analysis for Study 020 were planned as exploratory analysis, as no type 1 error control was specified for testing subgroups. A total of nine subgroups were explored and five of which were based on baseline 6-minute walking distance.

Of all the subgroups, the baseline 6-minute walking distance of 300 meters to 400 meters was the only one that reached nominal statistical significance in favor of ataluren. The adjacent subgroups of less than 300 meters and the larger than 400 meters favored placebo numerically. Further exploration of the subgroup showed larger treatment effects in the subgroup of 300 to 400 meters on most of the function tests, except for the test of 10-meter run or walk.

This chart depicts the result of the primary endpoints by baseline 6-minute walking distance category for Study 007 and Study 020. The subgroup analysis for Study 007 were not prespecified and were done retrospectively after the data was unblinded.

The bars are the estimated mean differences between ataluren and placebo on the week 48 change in 6-minute walking distance. The red ones are for the high dose in Study 007, green bars are for the low dose in Study 007, and the blue bars are for Study 020. The nominal p-values shown for the ambulatory decline-phase population and the 300 to 400 meter subgroup are considered exploratory.

Positive differences indicate that ataluren is numerically better than placebo. We can see that Study 007 showed greater treatment differences compared to Study 020 for the low-dose ataluren. However, the direction of the numerical treatment differences in the less than 300 meters and the larger than 400 meters subgroup were not consistent between the two studies. The high dose did not

reach nominal statistical significance for any of the subgroups.

In summary, both studies failed to demonstrate that ataluren had a treatment effect on the primary endpoint, change in 6-minute walking distance at week 48. There was no treatment difference between the high-dose group and placebo in Study 007, and the high dose was not studied in Study 020.

In Study 007, the adjusted p-value for the low-dose group was in the range 0.08 to 0.32. In Study 020, the numerical treatment differences were 13 meters and the p-value was 0.21. The data suggested a signal of treatment effect for the low-dose ataluren. Both studies showed a statistically non-significant numerical change in the primary analysis, favoring the low-dose ataluren.

In the subgroup of patients with 6-minute walking distance of 300 to 400 meters, a numerical treatment difference on 6-minute walking distance was seen in both studies. A numerical

treatment difference was seen on most of the timed function tests in Study 020. However, these results were difficult to interpret based on the following observations.

First, the high dose didn't have a favorable trend. Second, multiplicity adjustment was not prespecified for testing the 300 to 400 meter subgroup in Study 020. This subgroup was the only one reaching nominal statistical significance out of the nine prespecified subgroups.

Third, the numerical treatment difference on 6-minute walking distance was not similar between the two studies; 44 meters in Study 007 versus 13 meters in Study 020 in the ambulatory decline-phase patients.

I will hand over to Dr. Tandon.

FDA Presentation - Veneeta Tandon

DR. TANDON: Thank you, Dr. Ling.

I'm Dr. Veneeta Tandon again from the Division of Neurology Products. I will now discuss four key efficacy considerations for the committee that include prognostic factors for DMD clinical

studies; analyses of the North Star Ambulatory Assessment; the post hoc pooled analysis discussed by the applicant; and summary of applicant's development of ataluren for the treatment of nonsense mutation cystic fibrosis.

As you have heard from both the FDA statistical presentation and the applicant this morning, an exploratory analysis of a subgroup of patients with the baseline 6-minute walking distance of 300 to 400 meters from Study 020 nominally favored ataluren. This finding needs some additional context.

While we fully agree that 6-minute walking distance at baseline can help make some prediction about the likelihood of DMD patients to lose ambulation or remain stable over 48 weeks, recent literature clearly supports that baseline 6-minute walking distance alone poorly predicts progression in trials, as would any other single prognostic factor in these patients.

A recent publication by Goemans et al. in 2016 suggests that there are many prognostic

factors in addition to baseline 6-minute walking distance, such as corticosteroid use, duration, and age, that also do not explain all of the variability in the disease progression.

All of these factors combined actually account for about 30 percent of the variability in 6-minute walking distance progression. In fact, Dr. Goemans further suggests that broadening the prognostic model by adding additional factors, including rise time, 10 meter walk/run, 4-stair climb, height and weight, may even still only explain 60 percent of the variability in 6-minute walking distance progression.

In fact, it is quite clear that many attractive and seemingly logical patient subgroups could be defined based on some or all of these factors, and may be worth testing.

The manner in which various prognostic factors, including 6-minute walking distance, are best used to enrich clinical trials in DMD remains an area of evolving science. This, in fact, is further evident in the design of Study 041, which

is the applicant's ongoing efficacy trial to test the exploratory result of Study 020.

The enrollment criteria for the primary analysis in Study 041 have further evolved from Study 020 and are now based on baseline 6-minute walking distance and a minimum rise from supine time. Ultimately, in a trial that failed on its primary analysis without prospective testing, there is no way to be confident that the exploratory results in the 300 to 400 meter subgroup are attributable to drug. Other known and unknown factors, or chance alone, may explain these results.

As discussed by Dr. Dunn, the FDA has actively encouraged the applicant to pursue such an approach and is very willing to work with them on the most efficient trial design for this purpose.

The applicant has also made an argument regarding the effectiveness of ataluren based on exploratory analysis of the North Star Ambulatory Assessment or NSAA. The NSAA was an exploratory endpoint in Study 020. Both preplanned analyses of

the total NSAA score using ordinal or transformed linear scores, which were also exploratory, were negative with p-values of 0.13 and 0.27, respectively. The applicant then conducted additional post hoc analyses on patients performance on individual items of the scale.

The NSAA consists of 17 functional items, each of which is shown on the left of this bar chart. Each item is scored from 2 to zero. As displayed on the slide on the right, a score of 2 indicates that the patient is able to perform the task. A score of 1 indicates that the patient is able to perform the task with difficulty, and a score of zero indicates that the patient is unable to perform the task.

The applicant presents an analysis of the number of patients that have lost the ability to perform a task that has declined from a score of either 2 or 1 to zero. Again, the figures shown here depict each individual item of the NSAA on the Y-axis and the number of patients who declined to zero on the X-axis.

The orange bars represent the number of patients on placebo who declined, and the blue bars report the number of patients on ataluren who declined. The applicant notes that more placebo-treated patients declined from a score of either 2 or 1 to a score of zero, compared to ataluren-treated patients in most items during the trial. As you can see in this bar chart, the orange bars are longer on most items.

What is also important to consider, however, is that the decline in patients who progress from 2, meaning being able to perform a task, to a 1, meaning performing the task with difficulty. This is also clinically important as it shows that the disease has progressed during the study.

When FDA conducted this analysis, it became apparent that more ataluren-treated patients declined on 10 items of the NSAA scale than more placebo-treated patients declined on only two items. The number of patients declining was similar between treatment groups for the remaining five items. This is not surprising because when

scored according to both preplanned approaches in the protocol using a total score, there was no nominal difference between ataluren- and placebo-treated patients during the trial.

In such analyses, the results therefore depend on a number of details that are selected with data in hand. As you have heard earlier, the applicant has also presented the results of a post hoc pooled analysis of the ITT population from Study 007 and ITT population of Study 020.

This post hoc pooled analysis cannot negate the failure of two well-designed clinical trials. In addition, these two populations are not comparable with respect to steroid use, age, and baseline 6-minute walking distance. However, as with other exploratory analysis that have been presented by the applicant, we encourage its use to inform future clinical trial that would help support the efficacy of ataluren in nonsense mutation DMD.

Finally, we need to consider the development of ataluren for the treatment of nonsense mutation

cystic fibrosis. The applicant has asserted that ataluren should be able to read through all nonsense mutations, regardless of the disease.

In 2014, the applicant published the results of a large clinical trial conducted in nonsense mutation cystic fibrosis. Although that trial failed on its primary analysis, the applicant indicated that it was very encouraged by the results and stated that they were positive trends favoring ataluren on both primary and secondary analyses, as well as retrospective and subgroup analyses.

The applicant also proposed a seemingly very logical mechanistic explanation that aminoglycoside antibiotics interfered with the activity of ataluren and reported positive findings from a post hoc subgroup analysis that excluded patients on aminoglycoside antibiotics.

Based on these post hoc analyses, again, including a seemingly plausible subgroup, a second larger trial was then designed to enroll only patients with nonsense mutation cystic fibrosis who

were not taking aminoglycoside antibiotics. Earlier this year, the applicant unfortunately announced that the results of the primary and secondary endpoint from this trial were negative and that it was stopping the development of ataluren for this indication.

There are two important parallels from this development program that can be drawn to the development of ataluren for the treatment of nonsense mutation DMD. The failure of ataluren to demonstrate effectiveness in another disease, defined by nonsense mutations given its purported ubiquitous mechanism of action, lowers the prior expectation of efficacy in other conditions.

In addition, these results highlight the importance of the need to prospectively test even seemingly very logical theories from exploratory analysis of negative trials, in this case, the purported interference of aminoglycoside antibiotics.

Finally, as you have heard, the high dose of ataluren performed similarly to placebo and

numerically worse than the low dose in Study 007. The applicant has attributed this pattern of the results to what it refers to as an inverted U-shaped dose response for ataluren. This finding is extremely rare in practice when drugs are effective.

The applicant has used an exposure-response analysis from Study 007 in both in vitro dystrophin analysis from Study 004 and nonclinical data to support this contention.

As you will hear from the upcoming speakers, the FDA does not find the applicant's explanation to support this finding persuasive. Dr. Bhattaram from the Office of Clinical Pharmacology will first discuss the applicant's exposure-response analysis from Study 007. Thank you.

FDA Presentation - Venkatesh Atul Bhattaram

DR. BHATTARAM: Good morning. I'm Venkatesh Atul Bhattaram, a reviewer in the Division of Pharmacometrics, Office of Clinical Pharmacology. I will discuss an exposure-response analysis submitted in the NDA that is intended to explain

the inverted U-shaped exposure-response relationship.

As you heard earlier, the high dose of ataluren from Study 007 performed almost identical to placebo. As Drs. Dunn and Tandon have explained, this is a very rare pattern in the case of drugs that have been shown to be effective.

In the NDA, the applicant presented an exposure-response analysis that is intended to support this finding. Eventually they split the high-dose ataluren group into two groups based on the plasma drug concentrations above and below 19.3 microgram per mL.

The idea was to show that patients with lower concentrations in the high-dose group looked more like the low-dose group on trial endpoints, whereas, patients with higher concentrations in the high-dose group looked more like placebo, thereby supporting the presence of an inverted U-shaped dose response.

We reviewed this analysis and found that any differences in how the clinical endpoints were

found between these two exposure groups in the high-dose arm are likely predicted with baseline characteristics and not drug concentrations. In the following slides, I'll walk you through these results.

Before I go to the findings, I want to highlight that these figures only show the two concentration groups from the high-dose arm that were part of this analysis that is above and below 19.3 microgram per mL in placebo. The low dose is not shown at all.

On this slide, you see a bar chart showing the average 6-minute walk distance ability on the left Y-axis in placebo, which is shown in blue color, and the two concentration groups red and orange from the high dose in Study 007 at week 48.

Higher values for 6-minute walk distance mean better performance. The number of patients in each group is also shown in the graph. The applicant suggests that these results show that patients in the high concentration group actually have lower 6-minute walk distance than both placebo

and low concentration group at the end of the study. However, what this analysis does not consider is how these different groups looked at the baseline result.

We looked at the baseline performance to see if that could explain this observed difference. It turns out that these groups were not balanced at baseline. The differences you see at the end of the trial between these groups are also present at baseline visit. Hence, the differences in 6-minute walk distance in the two concentration groups at the end of the study are more likely due to differences in the baseline 6-minute walk distance than the threshold concentration of 19.3 microgram per mL.

Similar findings were observed for the timed function tests, including rise time, 4-stair climb, 4-stair descent, and 10 meter walk/run, which I will discuss in the next slides.

These next four slides will show that similar trends as discussed with 6-minute walk distance are observed with each of the timed

function tests in the trial. A shorter time to complete these tests means a better performance. Here also you see that any difference in the rise time at week 48 between the concentration groups are also likely explained by the fact that these groups had similar trends at baseline.

Similarly, you can see that the baseline 10 meter walk/run time is different among the concentration groups in the high dose, which resulted in similar trends at the end of the study.

You can see here that the baseline 4-stair climb time is different among the concentration groups, which result in similar trends at the end of the study, similar to the other endpoints that I've shown earlier.

Finally, you can see that the baseline 4-stair descent time is also different among the concentration group, which result in similar trends at the end of the study.

In conclusion, an inverted U-shaped dose-response relationship of clinical importance in Study 007 is not supported with applicant's

analysis that splits the high dose into high and low concentration groups. As I have shown you for each of the trials main efficacy endpoints, these differences are likely explained by similar trends between these groups at baseline, and not due to any difference in drug concentrations.

In relation to the explanation for lack of efficacy in the high-dose group from Study 007, the applicant also provided information on dystrophin measurements from early studies and in vitro model to support for the inverted U-shape dose response.

Now, Dr. Ashutosh Rao from Office of Biotechnology Products will discuss methodologies used to quantify dystrophin in clinical studies. Thank you.

FDA Presentation - Ashutosh Rao

DR. RAO: Good afternoon. My name is Ashutosh Rao. I'm chief of the laboratory of applied biochemistry in the Office of Biotechnology Products in CDER FDA.

In the NDA and during this morning's presentation, the applicant has drawn a parallel

between the lack of a dose response for ataluren to a bell-shaped dystrophin production by ataluren. My task here today is to provide you with a summary of our assessment of the dystrophin methods used by the applicant during the study of ataluren.

I will go over a brief description of the methods, followed by the significant limitations that we identified during our review that you should keep in mind as you consider the merits of the applicant's claims regarding dystrophin production.

From Study 004 and 007, the applicant provided dystrophin data using immunochemistry methods. The applicant previously showed you this data in their presentation this morning. It should be noted that immunochemistry is in general not a suitable method for quantitation of protein levels.

The first immunochemistry data was called in vitro analysis by the applicant and consisted of the applicant using patient-derived and subsequently cultured myotubes that were then exposed to ataluren. The second approach was

termed in vivo analysis by the applicant and consisted of data obtained from primary patient biopsies from EDB muscles before and after drug treatment.

In the first in vitro approach, the applicant exposed cultured myotubes for 9 days with ataluren followed by IHC analysis of the fluorescence intensity of dystrophin.

The fluorescence intensity of dystrophin was claimed to be normalized to spectrin, a cytoskeletal protein as the denominator. However, as seen in the representative images with the red staining, the spectrin staining was not consistent between untreated and treated pairs of samples, in many cases. This inconsistency precludes the applicant from reliably normalizing and presenting persuasive dystrophin measurements from their studies.

Additionally, other method validation deficiencies that lower the confidence in the data include the applicant's use of a different and user-defined threshold between samples and a

signal-to-noise ratio that was not optimized for consistency between samples. In general, the method was not prospectively validated prior to its application for the studies.

The second approach the applicant took involved testing pretreated and treated biopsies samples from patients who received ataluren. However, in addition to the analytical deficiencies identified in the previous slide, the applicant chose a cutoff threshold of greater than 30 percent of intensity to report their dystrophin findings in order to exclude revertant fibers.

As a reminder, revertant fibers in DMD patients have a background level of dystrophin based on spontaneous mutations that lead to dystrophin expression in some DMD fibers and patients. Importantly, it is simply not possible to visually distinguish revertant dystrophin from drug-induced dystrophin expression.

The applicant submitted to us that 39 percent of their samples had negative intensity, which could at least in part be explained by their

choice to exclude data with less than 30 percent intensity. In general, there was a high degree of variability in the intensity of the dystrophin between samples and the number of samples per group study.

Finally, a note about the applicant's methods used in Study 007. As acknowledged by the sponsor, the dystrophin methodology had significant limitations that preclude its serious consideration. We agree with the applicant that several serious problems with the dystrophin methods in 007 confound its interpretation.

These biopsy samples were taken from biceps of DMD patients. Only 21.6 of the samples did not have a freezing artifact, as noted by the applicant's expert pathologist in their study report.

About 36 percent had mild to moderate freezing artifacts, and 42 percent had severe artifacts that disqualified them from being used in the study. In addition, most of the samples had either suboptimal orientation for imaging,

considerable heterogeneity in fibrotic content, had ice crystals, were partially desiccated or observed, to have undergone proteolytic degradation.

In addition to the problems with immunohistochemistry, there was no Western blotting or RTPCR bioassay validation or data provided towards protein or mRNA levels in Study 004 or 007.

In summary, the dystrophin methods used by the applicant were not standardized, validated, or objectively performed to allow a reliable or a quantitative interpretation of dystrophin protein levels.

I will now turn this over to my colleague, Dr. Jim Weaver, to provide details on the non-clinical and in vitro dystrophin analysis. Thanks.

FDA Presentation - James Weaver

DR. WEAVER: Good afternoon. We're going to talk about four particular studies that were looked at to provide support for the inverted U-shaped dose curve. The first two are the in vitro and

in vivo studies from the Study 004 patients. We'll also look at the in vitro measurement of dystrophin in myotubes from the mdx mouse model, and finally, the measurements of production of iduronidase in the Hurler model.

As you've just heard, I won't repeat the study design, because you just heard it, this study used in vitro differentiated myotubes, which are biologically somewhat different from mature myoctyes. The dystrophin detection was only by immunofluorescence, and you've heard the issues with that. There were additionally multiple serious issues in the design and the conduct of the immunofluorescence assay.

In the in vivo study, as stated by the sponsor, there was no correlation between the ataluren exposure as measured by Cmax on day 27 and the reported in vivo dystrophin change measured in the day 28 biopsies. Again, the dystrophin detection was by the immunofluorescence method used in the in vitro study.

Analysis of individual patient data also

failed to show any relationship between the two measures. We also looked at examining C average, which is more of an average exposure measurement, but there was additionally no correlation there.

Our conclusion is that these two studies using samples from the same patients produced divergent results, and we conclude that these experiments did not produce interpretable data.

Next we'll turn to the in vitro measurement of dystrophin in myotubes from mdx mouse. This was again evaluated by immunofluorescence. There was a fully subjective measure with no objective quantitation. The dose response only shows a single data point per concentration and therefore lacks replicates enabling statistical evaluation.

Turning to the Hurler model, as illustrated by the ongoing and vigorous debate in the scientific literature, ataluren's mode of action and efficacy change greatly from one target to the next, and absence of some very considerable validation, the dose-response relationship from one target cannot reasonably be extrapolated to another

target.

So in summary, these studies have significant technical and design issues that result in data that we feel cannot be interpreted. Thus, we do not find any evidence to support the inverted U-shaped dose response for ataluren in this particular disease.

To reprise this, you've heard from Dr. Bhattaram that the patient imbalances may explain the differences in the high-dose group. In the high versus low drug concentrations, Dr. Rao has nicely detailed the major issues with the design, and conduct, and validation of the immunofluorescence assay. And I just talked about further additional issues with the experimental design.

I will now turn it over to Dr. Nick Kozauer for the FDA wrap-up.

FDA Presentation - Nick Kozauer

DR. KOZAUER: Thank you, Dr. Weaver.

I'm going to conclude the agency presentation by providing some final context.

We all want to see effective drugs approved. Recent approvals by the agency, including several by the Division of Neurology Products, highlight a strong willingness to be flexible, particularly in the case of rare diseases with unmet medical needs. However, substantial evidence of effectiveness must still be established.

A lot of data and analyses have been presented today. However, the agency's concerns about this application are very basic. They have to do with the persuasiveness of exploratory analyses from negative clinical trials. Such analyses are often used to generate hypotheses for further testing, an approach we actively support and encourage. However, they very rarely can establish that a drug is effective.

I will briefly summarize the agency's evaluation of the data that have been provided with this application.

The applicant, as you have heard, first conducted Study 007, which evaluated two doses of ataluren compared to placebo. This study was

negative. Notably, the high dose of ataluren performed similarly to placebo and numerically worse than the low dose. This inverted U-pattern of results is concerning as it is highly unusual in the case of drugs with proven efficacy. In addition, as Drs. Bhattaram, Rao, and Weaver have discussed, the data provided do not support a basis for this finding.

The applicant then conducted a number of post hoc analyses on the unblinded data from Study 007 that changed both the analysis methods and the populations. These post hoc analyses of negative clinical trials are well-known to be prone to may sources of bias. What they can do is help develop theories that need to be tested.

In 2011, the agency refused to file an NDA for ataluren based on these post hoc analyses of Study 007. The applicant went on to perform several additional post hoc analyses on the data from Study 007 to derive what it referred to as the ambulatory decline-phase or ADP population, where it believed there was an effect.

The applicant then conducted Study 020, which was empirically enriched, based on this population; an approach that the agency encourages sponsors to pursue. Unfortunately, Study 020 was also negative.

As the agency reviewers have noted, this study enrolled more than three times the number of patients as the ADP population from Study 007, which should have made it easier to show the effect the applicant expected, if it was present.

The applicant has stated that a higher mean baseline 6-minute walk distance in Study 020 was the reason that the study failed. However, as you have heard from Dr. Ling, this explanation was not supported by agency analyses. Ultimately, the post hoc findings from Study 007 were not supported and prospectively tested in Study 020.

As the primary analysis of Study 020 was negative, all other planned analyses can only be considered exploratory. The applicant conducted such exploratory analyses in a total of 9 subgroups, 5 of which were based on 6-minute walk

distance at baseline. There was no control for multiple comparisons for the analyses of any of these groups in the protocol.

One of these nine subgroups, patients with a baseline 6-minute walk distance between 300 and 400 meters, nominally favored ataluren, although results in some of the other adjacent subgroups, numerically favored placebo.

As Dr. Temple has emphasized, the nature of these sorts of subgroup analyses of negative trials, even when they appear very logical, can be misleading and need to be prospectively tested. Additionally, as Dr. Tandon has discussed, baseline 6-minute walk distance alone is an unreliable predictor of disease progression over 48 weeks. Other factors that are known, like rise time, age, and corticosteroid use, and unknown, also play important, and perhaps ultimately more important, roles with a sizable degree of progression still unexplained.

Therefore, it is very difficult to know if the results in any specific subgroup based on a

variety of prognostic factors, including 6-minute walk distance, from a negative clinical trial in DMD are due to drug. These findings can also be explained by disease variability or chance.

As Dr. Tandon has also mentioned, the applicant has further refined the primary analysis population for its ongoing efficacy study to also include a minimum rise time, which speaks to the evolving understanding of how best to enrich clinical trials in DMD.

The applicant then attempted to support the exploratory 6-minute walk distance subgroup findings from Study 020 by going back and looking at these new post hoc 6-minute walk distance subgroups in Study 007. These data were already known, which creates significant bias in any such analysis.

Importantly, as with the primary analysis of Study 007, the high dose also performed similarly to placebo and numerically worse than the low dose in this subgroup. Further, as Dr. Ling observed, there were several important inconsistencies

between how the various 6-minute walk distance subgroups behaved between the two trials. Therefore, these new post hoc subgroup analyses from Study 007 cannot provide support to the exploratory results from Study 020.

Finally, the applicant presents the results of pooled analyses that were only designed when the unblinded data from Study 007 and 020 were known. Such pooled analyses that are only proposed with the data from both trials in hand are not capable of overcoming negative results from two well-designed trials. However, as with the other exploratory analyses that have been presented today, they can provide additional support for hypotheses for further testing.

To conclude, this application presents the results of a number of exploratory analyses from two negative clinical trials that are intended to support the effectiveness of ataluren for the treatment of nonsense mutation DMD. Unfortunately, as Dr. Temple has also discussed, there are many examples in drug development where seemingly very

logical exploratory theories turn out to be unsupported.

The development of ataluren itself provides two very relevant cautionary tales. The first is that, as Drs. Dunn and Tandon have mentioned, the applicant has also developed ataluren for the treatment of nonsense mutation cystic fibrosis, based on the theory that it should read through all nonsense mutations regardless of disease.

The first large efficacy trial in nonsense mutation cystic fibrosis was negative. The applicant then identified a subgroup based on unblinded data, patients not taking aminoglycoside antibiotics, where it believed there was a benefit based on a theory that these drugs interfere with the mechanism of action of ataluren.

A second larger trial was then also conducted to test that theory. The results were unfortunately negative, and the applicant is no longer developing ataluren for that indication.

The failure of ataluren in another nonsense mutation disease decreases the prior expectation of

efficacy in the current indication, given the reported ubiquitous ability of ataluren to read through all nonsense mutations. In addition, these results emphasize the need to prospectively test exploratory hypotheses from negative trials, even when they appear very logical.

Most relevant is that the applicant identified a post hoc subgroup from Study 007, where it believed ataluren was effective. It then designed Study 020 to enroll three times more patients meeting those criteria.

Again, this sort of empiric enrichment to prospectively test theories that are based on post hoc analyses is a good thing. Unfortunately, Study 020 did not support the post hoc findings from Study 007.

There may be exploratory findings from Study 020 that merit further study. However, as these and many other examples demonstrate, they also have the potential to be misleading and need to be prospectively tested.

Finally, it is important to note that the

applicant is already evaluating the exploratory findings from Study 020 in an ongoing clinical trial that is enrolling patients who are now defined by criteria that include a baseline 6-minute walk distance greater than 300 meters and a rise time greater than 5 seconds.

We support this approach and hope the results from this trial can help support the effectiveness of ataluren for the treatment of nonsense mutation DMD. We thank you for your attention, and the review team can now take any clarifying questions on the agency's presentation.

Clarifying Questions

DR. ALEXANDER: Thank you. We'll take a few minutes for questions for the FDA. Dr. Ovbiagele?

DR. OVBIAGELE: Thank you. My question is actually for Dr. Kozauer. If you look at the context, I don't think there's any argument at all, right? So it's obviously a huge unmet medical need for a rare disease; no argument there.

If you look at the issue of scientific methodology, even there you see that even for PTC,

there's a note to the fact that this is probably less than ideal in terms of scientific methodology. Obviously, from the FDA presentation, and obviously from experts and the protoscientific community, this is less than ideal.

But I think the issue I wanted to learn more about is the issue of precedent because that was alluded to in the PTC presentation, that the FDA has been flexible in the past regarding exploratory results. So I wanted to hear, if I may, a little bit more about that to see if there have been situations like this where the FDA has been flexible.

DR. KOZAUER: Sure. I can start off the answer, and if Dr. Dunn or Temple might want to -- someone else might want to jump in as well.

Certainly, specific situations require consideration in the context of the data that are provided for a given application. For example, you can have a situation where a drug may have a high prior expectation of efficacy, approved in a number of different indications already, or different

mutations for one disease that you conduct a study, and for some reason it misses closely on the primary analysis, but there's a high prior.

There are situations where the primary analysis may just barely positivity, but there was a preplanned pooled analyses that was designed before knowing the data from any of these trials. There are considerations that are unique for every application, and I think that's how you have to consider that.

DR. TEMPLE: I spent some time trying to think of examples of that sort of thing, and there certainly are some where a study didn't win on its primary endpoint, and we eventually approved it, usually though based on other highly supportive data from controlled trials.

There are very few such examples. There are a couple with post-infarction beta blockade, where a study didn't win on the combined endpoint of death plus hospitalization, but won on death. Well, it's easier to get excited about death, but it's extremely unusual for all the reasons I gave.

Everybody worries about even a very plausible endpoint that wasn't selected prior to the fact, and then emerged later.

So there really are not very many examples. I can't think of any in neurology at all, or psyche for that matter. You never say never, but it's very unusual, for all the reasons we gave. There are too many opportunities for error.

MR. SOUZA: Dr. Alexander, may we address that question as well?

DR. ALEXANDER: Sure. Briefly, please.

DR. McINTOSH: In terms of the question of flexibility, there are other examples, and we do understand every case is unique. For us, this is a big question in terms of how do we apply flexibility in the light of our data? FDA has presented their view and we have presented ours.

There are specific examples, and I'll show if I can put my slide up, of flexibility.

DR. ALEXANDER: I want to focus this time primarily on questions specifically for the FDA, as we did previously for the sponsor.

DR. McINTOSH: Sure.

DR. ALEXANDER: So if you have a very brief comment, that would be fine.

DR. McINTOSH: Yes. I mean the examples that we have is Kalydeco, as an example, where there was a failed study. They saw that there was an effect in younger kids; there was effect in adults. There was a clear understanding from the natural history. They approved that. Remodulin was another example, two failed studies.

We just to understand the view on the FDA in terms of flexibility and how it can be applied.

DR. ALEXANDER: Thank you. Dr. Mielke?

DR. MIELKE: I have two questions. One was giving back in terms of the mechanism of the drug and understanding the CF data in light of the current data. Am I correct in interpreting that there should generally be -- or the mechanism is the same in both of the missense mutations, and that there should be an effect for both the CF as well as DMD? Because it's come up a couple times, and I think the sponsor had mentioned also that

there are two mutations, but I'm just trying to figure out what the CF data mean in light of the current indication.

DR. KOZAUER: I'm not sure if Dr. Weaver wants to add to this. Our understanding is that the mechanism of ataluren is that it should be able to read through all nonsense mutations, which seems like it would be relevant for these different diseases.

DR. TEMPLE: Can I comment there? There are two issues here. One is, does it make you worry about the whole mechanistic explanation here? That's one point. The other is it's living, breathing example of how a subset analysis that looked plausible didn't work out. That's a separate and distinct question.

DR. DUNN: I completely agree on similar points. Those are the two main issues. Biological plausibility. There may be subtle differences, of course, in the difference, but the main approach to how it works raises the issue of biological plausibility, and its inability to do so. At least

at some level, a similar mechanism is crucial. Then again, the lessons learned from the very, strikingly similar path that that took, we think are quite relevant.

DR. MIELKE: Okay. And --

DR. ALEXANDER: Thank you. Dr. Kesselheim?

DR. MIELKE: Can I ask another question?

DR. ALEXANDER: I'm sorry. Go ahead, Dr. Mielke.

DR. McINTOSH: First, let's hear the question, because I'd just like to -- I think it's a very important point. Cystic fibrosis is an entirely different disease. With cystic fibrosis, you have a CFTR protein, and it has to be trafficked and then activated in the membrane in order to be functional.

There are two competing nonsense mutations, so it's very different from DMD. And I don't think you draw parallels. We did show in phase 2 that we did replace CFTR. The question is, can you replace enough to reverse the trajectory of the disease? Thank you.

DR. ALEXANDER: Thank you. Dr. Mielke, a brief follow-up question?

DR. MIELKE: Dr. Temple originally presented some data suggesting that ataluren was not effective for the most recent trial for FEV1, and I was wondering where that came from because that wasn't Study 007. Was it a follow-up with Study 020, or is that a completely different study?

DR. TEMPLE: No, I didn't present data on FEV1, except for the study we just were talking about.

DR. MIELKE: It was slide 10.

DR. TEMPLE: But that's from the cystic fibrosis trial.

DR. MIELKE: Oh, that's cystic fibrosis. Okay. Thank you.

DR. TEMPLE: Yes, and that came from their press release. Again, the point that I was making there is that a perfectly sensible, plausible subset -- the subset they chose to study in the second study was very reasonable because the drug they dropped out and took away was interfering with

the whole effect of ataluren. So it was very sensible to do that study, and it didn't show anything.

DR. ALEXANDER: Thank you for that clarification.

Dr. Kesselheim and then Dr. Perlmutter.

DR. KESSELHEIM: Hi. Dr. Kesselheim here. Two questions. The first is whether, from the FDA's point of view, accelerated approval was considered in the context of the drug's effect on dystrophin? And then a more technical question, on Study 007, a point was made that there were 50 secondary endpoints tested, but it appears that a much smaller number of secondary endpoints was tested in Study 020, more like 3 or 4. I guess I was wondering if the FDA knew why there were much fewer secondary endpoints in that and if in fact I'm interpreting that correctly.

DR. UNGER: This is Ellis Unger, FDA. The first question was about accelerated approval, whether we considered it. As I think people around the table know, accelerated approval is when you

have substantial evidence of an effect on a surrogate endpoint that you believe is reasonably likely to predict clinical benefit. The company didn't ask for that. The surrogate endpoint here would be dystrophin, as you heard.

As you heard from our review staff, the immunohistochemistry is not a quantitative method. Although people have tried to make it out to be quantitative, it's not. We had a number of issues with the quality of the data. So we have a problem with that.

But aside from that, and maybe more importantly, is when you have clinical data, you have data on a surrogate endpoint that seems reasonably likely to predict clinical benefit, and you have clinical benefit that doesn't bear out the effect that you're hoping to see, then you really are stuck. You really have no way to move forward with accelerated approval on the surrogate when in fact the clinical data are negative. That's the problem.

In terms of the numbers of secondary

endpoints, I think that might be something you would want to ask the company this afternoon, in terms of why they had certain numbers of secondary endpoints. The point we were making, I think many times, is that you can have as many secondary endpoints as you want, and you can have as many subgroup analyses as you want. But if you don't control for the type 1 error rate, it's meaningless.

MR. SOUZA: I just want to clarify the question asked five different times for the conversion to accelerated approval, and they were never considered by the FDA, so that assertion is not correct. There was, nevertheless, offer to a prior application in the base of the 6-minute walking distance as an intermediate outcome, as it could be, since subpart H is not only a surrogate likely to predict.

So in both cases, we believe it would qualify, and we have a request included in the briefing materials in the dispute resolution that we provided to this committee.

DR. ALEXANDER: Okay. I'm still interested in the answer to Dr. Kesselheim's second question. Do you want to discuss the accelerated approval?

DR. TEMPLE: Accelerated approval does not represent a lower standard of evidence, okay? Whether it's a surrogate, there needs to be good evidence on the surrogate. We wouldn't consider it unless there was. For an intermediate endpoint, that's more complicated. That means an endpoint we don't think quite makes the clinical benefit apparent, but you'd still have to show that it was real.

We consider increased walking distance a perfectly valid endpoint for full approval, and if they had shown that to our satisfaction, the drug would have been approved. But data that you don't trust is not a basis for accelerated approval.

DR. ALEXANDER: Thank you. We have several more questions, but we will end shortly, but I want to give the sponsor an opportunity to answer the question why there were so many fewer secondary endpoints selected in study -- or proposed for

Study 020 than 070 [sic].

DR. McINTOSH: Thank you very much. When 007 was designed, it was the first placebo-controlled study in nonsense DMD, and at the time the evolution of endpoints for DMD was quite primitive. In fact, this was the first study to ever use the 6-minute walk test.

In that study, we added the standard measures associated with clinical practice, which are the timed function tests, all four of them, as well as 6-minute walk test. We did add a series of other exploratory assessments to try and get a better understanding of whether these endpoints had utility in DMD. We had digital finger span, we had heart rate assessments, et cetera.

So what we're trying to do is further science and understand how these endpoints performed. Based on that, we selected endpoints that we know are better. We know the 6-minute walk test, despite its ceiling and floor effect and the problems with it, can be used as long as you select your patient population, and the TFTs have real

relevance to the clinic, because they are used in the clinic. And those are the endpoints we presented today.

DR. ALEXANDER: Great. Thank you. Dr. Perlmutter, and then we'll do Mr. Watkins and Dr. Fountain, and then we'll conclude.

DR. PERLMUTTER: Joel Perlmutter. I have two statistical questions. First for Dr. Bhattaram, you mentioned that potentially you could explain the inverted U clinical finding between the low and the high level of drug. Based upon that baseline 6-minute walk finding or data, did you do a correlation to see if that actually related to the outcome?

DR. BHATTARAM: I mean we did think about when we saw this invert, these differences in the baseline, how to address them in the analysis. But as Dr. Tandon had mentioned, there are multiple factors that need to be accounted for which describe the progression as reflected in 6-minute walk distance, and that requires a combination of several prognostic factors. We're

not sure how to do that, so that's why we just presented the findings as you see there.

DR. McINTOSH: We can address that because we were very aware of those prognostic imbalances, and that was an analysis to try and understand the dose response. So what we did was built a PK/PD model. And the beauty about the PK/PD model is that it adjusts for these imbalances in baseline.

So that was just a preliminary analysis. We built a full model to explore the dose. We've got our PK/PD modeler who can discuss the dose because I feel that that analysis is a little misleading if you don't adjust for those baseline covariants. If you allow our PK/PD modeler, he'll take you through our dose response.

DR. ALEXANDER: Why don't we after lunch, time permitting, have an opportunity for you if you want to have a brief comment to address some of the remaining questions for the FDA in this last few minutes, please?

DR. PERLMUTTER: Then my follow-up question is, we keep hearing about going back and looking at

forest plots, where you see a bunch of things on the right side and not on the left. And what I haven't heard is, sure, if you flip a coin a whole bunch of times, you may average it, but if those different measures are not independent, you're flipping the same coin, or you're biasing your other coin flips.

Is there any thoughts about that or should we address that?

DR. ALEXANDER: Does the FDA want to address that?

DR. TEMPLE: You can tell me if I understand the question right. There's no question that when a trial wins on its primary endpoint, we are very interested in looking at various subsets and being informed by that. That's not the same as losing overall, and then finding a subset on your forest plot that looks like it's pretty good. That is very, very unusual or never. It's hardly ever done.

I just want to make it clear. We are very interested in possible differences, demographic,

etiologic, all those things, once you've shown that the drug works. And that's the point here. We don't object to looking at subgroups and trying to figure out how various baseline characteristics might influence the result. That's very important. It's very important to look at those things. But we have not believed that you can save a failed study that way.

DR. ALEXANDER: Mr. Watkins and then Dr. Fountain briefly.

I'm sorry. Dr. Bastings?

DR. BASTINGS: Yes. To expand on what Dr. Temple said, I think it's a fair point that these various endpoints are not completely independent. They measure related domains, so there is some expectation that if you identify a group of patients who did overall better in the study, that you may expect to see some related movements in various endpoints that measure similar domains. I think that's certainly a consideration that can be made.

DR. ALEXANDER: Thank you. Mr. Watkins?

MR. WATKINS: Yes. Jeff Watkins. I'm trying to get a better understanding of the first bullet point in slide 69 where you say both doses negative when compared to placebo. I understood that the high dose basically was very similar, if not worse, to the placebo, so I know you're talking about statistical negativity here.

My question is how negative, or how close, was the low dose to being statistically significant? Because I don't understand the numbers. It was a long time ago when I took that class.

DR. ALEXANDER: Okay. I'm sure you're not the only one thinking the same thing. Can the FDA address how close was the low dose in Study 007 to statistical significance, or how does one interpret the assessments that were done of the statistical significance of the low dose in that study?

DR. KOZAUER: Sure. Our statistician may want to comment more as well. But the adjusted p-value for the low dose was 0.3, where significance would be 0.05. So we wouldn't

consider that really close to being significant.

DR. DUNN: And actually it was it 0.025 or 0.05.

DR. ALEXANDER: Finally, Dr. Fountain?

DR. FOUNTAIN: It's a little bit of a related question, but might also have a brief answer. It has to do with the FDA analysis on slides 29, 30, and 31. And the question is, is this the same population that was analyzed in the sponsor's analysis, or is this a refined or different population or group? This may not be the case, but it seems like there was a lot of p-values to keep track of. It seems like sometimes some are close and some are not.

So my question is about, for instance, if we went to slide 29, 30, or 31, is this a group that's different from that analyzed by the sponsor or is it the same group?

DR. LING: For slides 29, that's for the secondary endpoints. That's for ITT population. Can you repeat your question?

DR. FOUNTAIN: Yes. This says ANCOVA with

multiple imputations. So that's corrected for multiple analyses or not?

DR. LING: Multiple imputation is for imputing the missing data.

DR. FOUNTAIN: Okay. So this doesn't account for the multiple imputations.

DR. LING: No.

DR. FOUNTAIN: Okay. Thank you. I just wanted to clarify that.

DR. ALEXANDER: Okay. Thank you very much. That concludes this morning session and early afternoon session. We'll adjourn for lunch. We'll reconvene again promptly at 1:45. Please take any personal belongings with you that you may want at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:52 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:20 p.m.)

Open Public Hearing

DR. ALEXANDER: Thank you. We'll reconvene the meeting at this time, and this is the beginning of the open public hearing session.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes it's important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comment provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will the first speaker step to the podium and introduce yourself? Please state your name and any organization you're representing, for the

record.

MS. WOOD: Good afternoon and thank you for taking the time to listen to us. My name is Teresa Wood, and this is my son, Matthew Harrison. Our travel and hotel have been provided by PTC.

Matthew is 15 years old and was diagnosed with Duchenne at the age of 7. At the time of diagnosis, we were told that Matthew would stop walking between the ages of 10 to 12, he would lose the ability to feed himself and breathe on his own, and would eventually succumb to the disease by the age of 20.

At the time, the only therapy for the disease was corticosteroids like prednisone. While this slowed down the progression and stopped the random falls, we were always looking for a meaningful and long-term solution. After searching the internet and speaking with his doctors, we learned about a clinical trial of a mutation-specific drug named PTC124 or later, ataluren. However, I learned that Matthew would be unable to join the study as it was not currently

open to new patients.

Knowing the progression of the disease, as each year passed I wondered what the next year would bring. When would he start falling again? Would he wake up one morning and be unable to feel his legs? Would his heart or lungs begin to fail? We were forced to watch and wait.

Eventually, the ataluren trial did reopen. He was eligible to participate, and was enrolled in the phase 3 efficacy and study in February 2014. He moved to the phase 3 extension study in January 2015, and finally the phase 3 open label in May 2017.

We have continued in the trial because we believe in what we are seeing. Matthew hasn't had any side effects to the drug, and he has maintained every physical ability he had prior to the trial. Not only is Matthew able to walk and run, but he can perform activities of daily living like dressing himself and brushing his teeth. Prior to the trial, he couldn't get into the car without assistance, and just recently I noticed that he

does it without assistance with ease.

Matthew's providers are continually impressed by his strength. Recently, I had back surgery, and when I drop things, he can bend over and pick them up for me. This year he has joined Future Farmers of America and is raising a goat.

I know that there are some who would simply call him an outlier, but I don't agree. Our neurologist, Dr. Brenda Wong, a leading expert in Duchenne, told us at his last visit that he should continue walking into his twenties.

Saying he is an outlier is insinuating that his achievements are pure luck. However, I say that the only difference between him and the boys that are not walking, not on this trial, is ataluren. My hope is that other boys are given the same opportunity to be an outlier.

DR. ALEXANDER: Thank you very much. Will speaker number 2 please step to the podium and introduce yourself? Please state your name and any organization you're representing, for the record.

MS. MILLER: Hello. My name is Debra

Miller. I'm the CEO and founder of CureDuchenne, who has paid for my travel here. Thank you to the FDA and to this committee for giving me, and all these families here, the opportunity to speak today.

We're so thankful the FDA convened this meeting so that all the data surrounding ataluren can be carefully reviewed by this panel of outside experts. The whole community appreciates your effort to take a fresh look, and a fair look, at all the data, and the real-world experience with this drug. CureDuchenne believes that the totality of the data supports ataluren's approval.

It is our hope that the data presented today in the briefing materials, in this morning's presentations, and Q&A sessions, and what is being reported by families and by healthcare professionals during this open public hearing, will provide this committee the information it needs to guide FDA towards a path forward in making sure ataluren remains available to boys in the U.S.

There is no denying this is hard disease to

study, and as science advances, we've learned more, especially how the disease does advance. So what do we now know that we didn't know before PTC started studying Duchenne?

We know that once muscle is gone, it's gone forever. We know that studying the so-called transition phase is helpful in providing evidence of treatment effect in a one-year study. We know that the boys in this room today, and those not strong enough to travel here today, do not have time for the FDA and the drug companies to design the perfect trial to definitively prove ataluren's benefits.

The FDA has acknowledged that accidental falls were reduced in the ataluren-treated group. Many Duchenne boys stop walking forever because of fractures due to accidental falls. The incidence of fat embolism syndrome also increases with these fractures, and both of these consequences are serious and can be helped with ataluren.

If we wait to approve drugs now, we lose this generation of boys. Patients know this is not

a cure, but slowing down the progression of this horrible disease, buying boys time, preserving function, it's important to us. Every added year, every month, every added day is priceless to the families in this room. Every added moment is another hug, an additional smile with our sons.

My son, Hawken, is 20 years old with Duchenne, and I can tell you each moment is truly priceless. I ask you to look at all the data, including the case studies and patient experience described during this open public hearing, and then work with the FDA to make sure our boys can continue with their ataluren treatment. Thank you very much.

DR. ALEXANDER: Thank you. Will speaker number 3 please step to the podium and introduce yourself? Please state your name and any organization you're representing, for the record.

MS. GUNVALSON: My name is Cheri Gunvalson. I'm a clinical assistant professor of nursing, and I'm here today with our son, Jacob, who will be 26 next week. Our travel was supported by PTC.

Two years after losing his ability to walk, Jacob began in the non-ambulatory, open-label arm of the ataluren trial. I urge you to look at Jacob's real life experience and data on this drug, as Dr. Gottlieb recently said the FDA needs to do.

Dr. Brenda Wong, the lead pediatric neurologist at one of the world's largest Duchenne centers, finds Jacob relatively stable. His pulmonary function tests are great with an FEC of 75. He's never had pneumonia. He hasn't had an antibiotic in 10 years. When the trial was stopped for 10 months, Jacob experienced drastic decline. He's had zero side effects from the drug.

Since starting on the ataluren eight years ago, Jacob has experienced the benefit of stability. Keep in mind, he started on this drug two years after he lost ambulation, and he has been wheelchair bound for 10 years. We know the natural history of Duchenne, that once patients are non-ambulatory, they experience drastic decline in pulmonary function, which leads to pneumonia, a ventilator, and death.

As a patient representative on the previous advisory panels, during my FDA training, we were urged to weigh the risk-benefit analysis. There's no question the efficacy and benefits of this drug far outweigh the risks. We know what the future holds without this drug. Most of Jacob's friends from MDA camp his age are dead.

MR. GUNVALSON: [Inaudible - off mic] efficacy. I have reached many of the goals in my life, I add, that I would not have been able to reach without it. I can work, live independently and be a productive member of society as a social worker.

Throughout college, I never had to use a notetaker or an aid. When I interned for the Minnesota governor, and at an institute for mental diseases, I did so without an aid. I'm able to type for long hours and don't have to rely on others to use my urinal, cell phone, feed myself, or reach out to hold a woman's hand.

My successes are not supposed to be possible with Duchenne, but I'm sitting here today showing

you what is possible with ataluren. Sadly, for those not on the drug, the future is death. A young man in my area, several years younger than me, with the same mutation, is not on ataluren. He is now bed bound, totally dependent on a ventilator. He does not have time for another clinical trial. He needs ataluren now.

Twenty-five other countries have already approved this drug. The ball is now in your court. Approve this drug to save our lives and allow me to keep working and thriving, or deny it and allow us to continue to die.

MS. GUNVALSON: Thank you.

DR. ALEXANDER: Thank you. Will speaker number 4 please step to the podium and introduce yourself? Please state your name and any organization you're representing, for the record.

MS. JOHNSON: My name is Joanna Johnson. I'm here with my husband, Paul, and my two sons, Elliot, and Henry. Our travel and hotel were paid for by PTC.

Elliot is nearly 14 and was in Study 007,

and is now in the extension program. Henry is 11, and was in Study 020, and also is now in the extension program. My sons experience real, meaningful benefits from ataluren and it merits FDA approval.

During one study visit about a year into treatment in 2009, Dr. Richard Finkel was so surprised to see that Elliot no longer showed a Gowers maneuver, that he brought two PTs over to watch Elliot get up from the floor to confirm what he was seeing.

A school PT report stated, "In the beginning of 2009, Elliot ascended stairs two feet per step holding the railing." Five months later, it stated that he could ascend a flight of stairs alternating feet without the railing.

These are the kind of functional benefits that were noted in the North Star Ambulatory Assessment results from Study 020. These things mean more independence for a longer period of time, keeping up with peers, or even being able to go to a friend's house; truly meaningful benefits.

In March 2010, PTC terminated the trial because of a dosing issue, and the benefits that we were seeing began to disappear. Elliot went back to a spider crawl up the stairs, back to feeling fatigued easily, back to showing a typical Gowers maneuver. We fought to get him back on the drug, and we were finally provided access 14 months later.

Henry was eligible to be screened for Study 020 in January of 2014, but walked too far and too fast, and was excluded. He declined significantly enough over the next nine months to be included in the study, and started in the trial in September of 2014.

Henry's decline before ataluren highlights that boys with Duchenne cannot wait to get access to this drug. Despite the fact that I have seen firsthand that ataluren is slowing their progression, they will never get back what ability they lost while not on drug.

However, at almost age 14, Elliot is watching his friends with Duchenne transition to

wheelchairs, yet he is still ambulatory. His brother, Henry, still has the ability to play soccer with his friends. At this age, we should be seeing a more steady, rapid decline, but thankfully we are not.

There is still so much we do not understand about this disease. It may be impossible to design the perfect trial that demonstrates statistical significance within the time constraints and other limitations of clinical trials. Furthermore, not all drugs work the same for all people. Different options and classes of drugs exist for many diseases. We cannot wait for the perfect study. Ataluren can change the trajectory of this disease and we can continue to build upon its success. Thank you.

DR. ALEXANDER: Thank you. Will speaker number 5 please step to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MS. LOPEZ DE NAVA: Hello everybody. My name is Azucena Lopez de Nava. Our son, Romero,

has been the ataluren Study 020 in UCLA. He went to an extension and continued extension. He has been in the trial for almost three years. My travel and hotel were covered by PTC.

Let me tell you about my son, Romero. He was diagnosed six years ago with DMD. So the first day, it was no hope for my son, until his doctor told us about this trial called ataluren. So we decided to participate.

As I mentioned before, our son has been in the trial for almost three years, and since the beginning, he was very stable. All the time, he finished the 6-minute walk without any problem and conclude very well other tests. He continues swimming and do other things by himself.

Until this year that the trial has to stop in UCLA, he was off of the medicine, like about six weeks, and we can see immediately the difference. He felt very insecure walking around the house. He asked for help and assistance more often than before. He started using his scooter inside the home for moving around, which before he only uses

for long distance or at school.

Now he's back on the trial, and he's getting more energy and better stability. He's still able to walk around in the house. He's 12 years old, and his doctor said he's very lucky to be in the trial. Not to mention he had never felt any side effect on the ataluren.

To conclude, I really believe ataluren deserves to be approved. It will be a help for thousands of children with DMD if they start younger with this medicine. Thank you very much.

DR. ALEXANDER: Thank you. Will speaker number 6 please step to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MR. PIACENTINO: Hello. My name is Jonathan Piacentino, and I'd like to speak on behalf of the adult and adolescent patients who have been on ataluren by sharing my personal experience with taking this drug. PTC Therapeutics has covered my travel and lodging expenses.

First, I would like to state that my

diagnosis is that of a true Duchenne MD patient diagnosed in 1997. Thus far, I've participated in Study 004 in 2006, Study 007 in 2009, which was then truncated in early 2010, and then continued active participation within the extension study since November of 2010.

Now I would like for someone to start a short clip of myself receiving my high school diploma in June of 2011, as well as my Eagle Scout ceremony two months prior. I was 17 at this time.

In both segments, you can see that I'm able to walk unhindered. During this time, I could traverse my entire high school campus with the aid of a double decker shopping cart, commonly found in most grocery stores. This served to stabilize my body and conserve energy each day. My backpack of school material as well was also unloaded into said cart. As you can expect, I wasn't just walking, but pushing weight simultaneously.

The majority of Duchenne MD patients unfortunately become permanently wheelchair bound prior to this age, and thus don't have to deal with

the complications of constantly maintaining balance while they walk, let alone adding any form of weight to this daily routine.

During this time, I also fractured my back and suffered fractures to my feet as well, and was still able to walk while these injuries healed, and continue to walk thereafter. To emphasize, I walked an additional four years afterward, throughout college. It wasn't until late August of 2015 when I became permanently wheelchair bound at the age of 22.

While I have lost the ability to walk, I suffer no severe side effects from taking drug, and I currently do not suffer any cardiac or pulmonary complications either, that plague most Duchenne's patients my age. Just as well, I do not require oxygen therapy or the use of breathing aid during night hours.

To put this into perspective, my FEV1 over FEC score is 96 percent. Compare this to the normal pulmonary function of individuals without muscular dystrophy, anything 80 percent or higher

is considered healthy.

I attribute my success to the use of ataluren in these past 11 years, and would like to be able to receive drug in the years to come. I don't have the time to wait for the perfect trial's results in order to successfully attain this drug. Thank you for your time.

DR. ALEXANDER: Thank you very much, and we'll either return to you or we're still working on presenting the video that I think you had submitted as part of your testimony, so thank you very much. We'll return to try to include that video. Thank you for your comments.

We'll now turn to speaker number 7. Please step to the podium and introduce yourself. Please state your name and any organization you're representing, for the record.

MR. WAGNER: Hi. My name is Josh Wagner, and my hotel and travel here today were paid for by PTC Therapeutics. I participated in the 007 study, and I'm in the extension study. With the exception of 2010 suspension and one other interruption, I've

been on ataluren for 10 years.

I am now 24 and was diagnosed with muscular dystrophy just before my first birthday. Throughout my childhood, this illness shaped my daily reality. I couldn't run and jump with my classmates, and by the end of grade school, I was navigating much of my world with the use of a motorized scooter.

Night splints, orthotics, PT and OT were part of my life ever since I can remember. After walking or standing for more than 10 minutes, my muscles would get so tight that I'd collapse into a chair with my legs straight, unable to bend. By sixth grade, I was crawling up the stairs to my bedroom, and my parents made a new room for me on the first floor of our house, and rendered a ground floor bathroom wheelchair accessible.

When I was in ninth grade, I was accepted into the ataluren 007 study. My life has not been the same since. Halfway through high school, I stopped using my motorized scooter. I began getting strength and endurance, and by my senior

year, I had learned to drive and could walk from the school parking lot to classes.

That same year, I recall taking a mile long hike with my family; a feat that had been unimaginable in the past. During college I rebelled briefly by taking ataluren erratically, if at all. I definitely fatigued more quickly and my school bag felt heavier. Not surprisingly, it was a short lived rebellion.

In the last few years, I've started exercising regularly, eventually losing 35 pounds. I still experience fatigue if I walk very long distances, but the feeling is nothing like how it was prior to ataluren. My scooter sits in my parent's garage as, for now, I am completely ambulatory.

When I was little I lived with the understanding that I would lose strength. Recently, I've experienced something I had never dreamt. I've grown stronger rather than weaker. With ataluren's help, I have overcome obstacles that used to seem insurmountable, and I now live

independently.

I've experienced no negative side effects. I see no reason why this drug should not be approved to help other boys and young men like me. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker number 8 come to the podium and introduce yourself? Please state your name and any organization you're representing, for the record.

MR. ELNABARAWY: Good afternoon. My name is Tamir Elnabarawy, and I'm a legislative assistant in Congressman Peterson's office. I do not have a financial relationship with the sponsor. Although the congressman is unable to join us, he has asked me to deliver the following remarks on his behalf.

"Thank you for the opportunity to speak on behalf of Minnesota's 7th District regarding ataluren's application for approval. The timely delivery of this treatment is of the utmost importance to the Duchenne community.

"One of my constituents, Jacob Gunvalson, spoke earlier to share his experience with

Duchenne. Jacob was not expected to live past his teenage years, but access to ataluren has allowed him to live and thrive well into his twenties with no side effects. Jacob recently completed a very successful internship in Governor Dayton's office in Minnesota.

"During my time in Congress, I've consistently supported several measures to ensure that my constituents can benefit from the lifesaving therapies the way that Jacob has.

"The 2012 Food and Drug Administration Safety and Innovation Act, or FDASIA, enhanced the FDA's ability to speed patient access to safe and effective products. In particular, the legislation helped develop and implement accelerated approval programs to provide patients with therapies if they suffer from rare, debilitating, and/or 100 percent fatal diseases.

"Under FDASIA, treatments that benefit Duchenne patients warrant consideration for full approval. Such an approach is consistent with the FDA's balanced review of eteplirsen, another

Duchenne therapy that was granted accelerated approval in September 2016.

"More recently, Congress passed the 21st Century Cures Act, which recognized the essential role that patient advocates play in the development of drugs and medical devices. It is my hope that in keeping with this legislation, the FDA will enhance its efforts to incorporate patient experience into its regulatory evaluations and decision making.

"As there are no alternative therapies for this particular form of Duchenne eligible for purchase or approval in the United States, patients are left unable to mitigate the effects of the deadly disease. The full consideration of ataluren not only fulfills the congressional intent of FDASIA and the 21st Century Cures Act, but also the potential to save lives across the nation."

Thank you.

DR. ALEXANDER: Okay. We're going to show the video associated with speaker number 6, Mr. Piacentino. And Mr. Piacentino, if you want to

come briefly to the microphone, and again tell us what we're watching here, I'd welcome you to do so.

MR. PIACENTINO: Okay. To reiterate, both of these segments in the video are from my high school graduation in June of 2011 --

DR. ALEXANDER: Oh, I'm sorry. Let's wait and just be sure we have it up successfully.

MR. PIACENTINO: I apologize.

DR. ALEXANDER: No, no. That's fine. I appreciate your coming back, and we'll give it another try. Go ahead, please.

MR. PIACENTINO: So to reiterate, both of these segments are from my high school graduation in June of 2011, as well as my Eagle Scout ceremony from two months prior. I was 17 at this time, and if we can be able to see the video, you can clearly see that I'm walking unhindered. There we go.

(Video played.)

MR. PIACENTINO: By this age, at the age of 17, most individuals with Duchenne muscular dystrophy are permanently wheelchair bound. And the photo at the end is a photo of me from my

college graduation in the year of 2015, where I was permanently wheelchair bound and had to take the stage within my power chair.

DR. ALEXANDER: Okay. Thank you very much for sharing that.

Will speaker number 9 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MR. RODRIGUEZ: Good afternoon. My name is Chris Rodriguez. My wife, Diane, and I are from Davenport, Florida, and our travel today was sponsored by PTC Therapeutics.

We're today to discuss our 5-year-old son, Benjamin, and his experience with ataluren. Benjamin has completed the pediatric study and is now enrolled in the extension study. Prior to takin ataluren, Benjamin showed the typical symptoms that we see in the early stages of Duchenne. He had difficulty walking up stairs. He was unsteady on his feet. He couldn't step up or down from a curb without assistance. He couldn't

run or jump, and he was actually diagnosed with mild osteoporosis because of his steroid treatment.

But when Benjamin began taking ataluren, we started to witness a number of physical improvements within just one month. He started walking up stairs more easily. His walking and overall balance became much more stable. He could step up or down a curb, or a small step, without any assistance at all. And for the first time, he could elevate his feet off the ground to run and jump.

But the most surprising change that we discovered was that his bone density measured in the normal range, and he no longer had mild osteoporosis after eight months of treatment on ataluren.

This type of finding is undocumented in ataluren studies, but it is an extremely relevant example of what benefit the drug can have, based on empirical data. These improvements provide qualitative and quantitative evidence of ataluren's efficacy, and Benjamin has sustained each of the

improvements during the 15 months that he has been on the drug. And besides all these improvements that I have mentioned to you today, Benjamin has also had zero side effects while taking ataluren.

In our minds, this drug provides significant benefit with no downside.

MS. RODRIGUEZ: When Benjamin was first diagnosed at 16 months old, we were told go home and give him the best life you can, because in four years, he will start to decline. November 26, 2017, will be exactly four years since those words were spoken to us, and the complete opposite is happening in his life.

Instead of decline and struggle, like most boys his age with Duchenne, he is achieving independence and catching up to his peers. Instead of fear and heartache, our family now has hope.

Benjamin looks up to his older, 8-year-old brother, and like most younger brothers, tries to imitate every single thing he does. Without ataluren, Benjamin will become a bystander, watching his brother achieve physically what was

taken from him at such an early age.

Benjamin is just 5 years old, and he has a whole life in front of him. The approval of ataluren will, quite simply, change this. Thank you.

DR. ALEXANDER: Thank you. Would speaker 10 come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MS. VERTIN: My name is Betty Vertin. My husband, Jason, and our children stand with me. Our travel and hotel were covered by PTC.

My family knows Duchenne. Half of our children, three of our sons, have Duchenne. Max was in Study 020, beginning February 2014, now in the extension. Rowan [ph] and Charlie in PTC's sibling access program, beginning July 2015, now in the extension.

My family has experience with ataluren at three different starting ages, and at three different beginning strength and fatigue levels. Ataluren is helping them all. It has been well

tolerated. Each of them maintain stable heart and lung function.

Max is 11. His stamina lasts all day in middle school on a campus of more than one building. He also participates in extracurricular activities. Max's progression of DMD has slowed. Prior to starting ataluren, he was not able to complete an entire Lego set without a break. At 11, he can put a 750-piece Lego set together without a break. He can still ride a bike without training wheels.

Max's neurologist at Cincinnati Children's Hospital has commented, "I do think ataluren is working," several times as she notes that as an 11-year-old he can still jump and have both feet clear the floor, and get up from a seated position without using hands.

Rowan is 8 and has high functioning autism spectrum disorder in addition to DMD. The physical symptoms of autism, like hypotonia and decreased upper body strength, affect him. Rowan is the weakest of my sons.

I have met other boys with DMD that at Rowan's age are similar to Rowan in strength and fatigue level. Those boys have not been on ataluren. In comparison, Rowan's gait is better. He waddles less than the other boys who's severely affected. His lordosis is not as severe.

In anticipation of Rowan's ability to stop using stairs, we built a ramp at home. I thought he would lose the ability months ago, and yet he can still manage 4 to 5 stairs. It's not pretty, but he can do it independently. He needs ataluren to maintain the function level that currently exists. To lose access to this drug would be detrimental to Rowan's quality of life and independence.

Charlie is 6. He was able to start ataluren when he was 4 and is stronger than either of his brothers were at age 6. Starting ataluren at a younger age has benefited him.

Charlie uses a motorized scooter for long distances. Recently, it was in the shop. We went to a high school football game and he ran around

with his friends. He did not tire. This was after a full day of school. His stamina is like that of a healthy peer.

Riding a bike without training wheels is a feat for a child with Duchenne. Charlie started at age 6, two years earlier than his brother with Duchenne. The natural progression of Duchenne is different in each of my sons, yet ataluren is helping each of my children. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker number 11 please come to the podium and introduce yourself? Please state your name and any organization that you're representing, for the record.

MR. M. SILVERMAN: Good afternoon. My name is Mark Silverman, and I've travelled from London with my son, Thomas, who was diagnosed with Duchenne in 2007. I'm also national vice-chair of Action Duchenne in the United Kingdom. PTC has covered the cost of our travel and accommodation.

We're here on behalf of the many families in the U.K. affected by the condition, including all

of those who are receiving ataluren, and have submitted such compelling written testimonies to you. It's fantastic to have Naomi Litchfield here today. Naomi was a nurse working with families on the PTC124 trials at Great Ormond Street Hospital in London.

Thomas' diagnosis 10 years ago hit us very hard. It took several months to get back on the horse, but as the fog began to lift, we read about PTC124. We read about the 007 trial, which our son was just too young to enroll in. Progress seemed glacially slow, and in 2011, I collected testimonies from families across Europe to show PTC Therapeutics how important it was that they continued with these clinical trials.

We retained hope, and it was an immense relief for Thomas to be able to enroll on the 020 trial in late 2013. We now know that in summer 2014, Thomas was on the placebo arm of the trial. He rarely played soccer in the backyard then. Twelve months later in 2015, he was out there playing soccer throughout the summer. We now know

that Thomas was receiving the drug then. For us, that was a statistically significant and meaningful outcome measure.

He's been receiving ataluren for three years now, along with many others across the UK. The drugs have no side effects and it has been easy for him to take. It has made a huge difference to Thomas, who is nearly 13, ambulant, and attending a mainstream school. He's looking forward to his soccer-themed bar mitzvah in December.

We'd now like to show you a short video from 16 months ago where Thomas is playing soccer at home. Thomas will then introduce another video we made in our backyard last weekend. You'll still see he loves to play.

MR. T. SILVERMAN: Here is a video of me playing soccer, or football, as we like to call it. Ataluren helps me play soccer, and I want the boys over here to have ataluren drug. We all deserve it. Thank you.

(Video played.)

(Laughing.)

DR. ALEXANDER: Thank you very much for your testimony. Will speaker number 12 please come to the podium? Please state your name, introduce yourself and any organization you are representing, for the record.

MS. CASTLE: My name is Jill Castle, and this is Joanne Wechsler. Our travel has been reimbursed by PTC. Our sons, Anthony and Adam, began on the ataluren during the 004 trial. Between trial 007, the extension trials, and the unexpected suspension in 2010, they went on and off the drug five times.

When on the drug, Anthony and Adam had an increase of energy and improved cognitive function. Anthony reduced his scooter use, saw an improved, 3- to 4-second Gowers from the floor to standing, and was able to jump off the floor using both feet for the first time in his life. Adam was busy during those years playing wall ball, drums, pursuing National Honor Society, and becoming an Eagle Scout.

When taken off the drug each time, Adam and

Anthony saw dramatic declines. Anthony experienced a crash which included exhaustion, legs buckling from underneath him, dropping in a heap 3 to 4 times a week, and going from his reliable 3-to 4-second Gowers, to being unable to get off the floor without assistance. When the drug resumed the final time, his independent Gowers also resumed at 8 seconds.

Anthony walked until a month before his 15th birthday. He is now 18 and has minimal heart involvement. He has plenty of energy to engage in adventure sports, rock concerts, dating, and traveling to Mexico to volunteer. After 11 years of experience with this drug, there have been no negative side effects. However, it does appear ataluren has helped curve the negative side effects of Duchenne.

We ask you to remember our obligation, "first do no harm." And if you were to withhold a non-harmful, life-enhancing drug, harm is exactly what you may do.

MS. WECHSLER: The previous photo was Adam

when he was 14 years old walking all around Disneyland in Florida. Adam walked until he was 16, only stopping due to a broken femur. He's 21 now. His heart and lungs are strong. Just two weeks ago, his neurologist compared pulmonary function testing from the last four years, noting a very minimal decline; quote. "My impression over time is that Adam has remained quite stable with the pulmonary data to support this opinion."

Adam is now a senior at the University of Vermont, living independently in the dorms with assistance limited to bed and morning routines. He can manage his meals, bathroom, and a full course load while working on his honors college thesis. In his free time, he is an editor for a student magazine, organized a collegiate competitive race to zero team, and maintains an active social life.

Eleven years in a trial is a long time and a lot to sacrifice. I can only imagine how well he would be doing had he been on drug continuously starting at a prime age of 5, rather than 10, with all the stops.

Please consider approval so that our sacrifice may spare future generations the devastating outcomes of this disease. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker 13 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

DR. NELSON: Hi. I'm Stanley Nelson. I'm professor of human genetics at UCLA and co-director of the Center for Duchenne Muscular Dystrophy. I'm a physician and also care for approximately a hundred children and serve as the director of the UCLA Certified Duchenne Care Center. My travel here was paid today by PTC.

Ataluren demonstrated a small increase in dystrophin protein in young boys' muscles. The small amount of dystrophin is unlikely to stop or reverse the disease process as we'd all hope. However, much available data indicates that a small amount of dystrophin can be therapeutically relevant over a boy's lifetime.

As you've heard, PTC performed two large,

well-run, multisite, double-blind, placebo-controlled trials over a one-year period, and both failed to meet their primary endpoints. It's thus the intellectually easiest route to deny approval.

FDA reviewed, dissected each individual study, but the core question which I'd like you to consider is, is there sufficient data in aggregate that this drug has a positive benefit and is sufficiently safe to give to these children?

Trials in Duchenne, as you've learned and will continue to learn, are often too short and sometimes subject to issues around the subgroup analyses, which were part of this discussion as well. Meta-analyses help us deal with some of these issues.

One way to deal with a relatively short-term trial date is to compare subjects who have received ataluren long term within open-label portions of clinical trials with matched contemporary external controls. You've actually had the privilege of meeting some of those children who are long term

ataluren therapy, and some of them are shocking outliers, possibly because of the drug exposure.

To determine if there's any substantive evidence of efficacy of ataluren from across the multiple studies, my laboratory recently compared loss of ambulation data, a hard endpoint, from 809 subjects with Duchenne Connect, the largest repository of Duchenne data.

I retrieved this data in October 2016, and we could compare this data by mutation type, steward usage, and other controlling variables, with data provided by PTC on a 101 subjects -- some of those we just saw -- retrieved in January of 2017, who on average have had over 3 and a half years exposure to ataluren.

Similar to the data that was shown from Dr. McDonald, comparing this to synergy, there was a 3-year delay in age at loss of ambulation, purely on the variable of exposure to ataluren. So this hard endpoint for Duchenne is relevant and I think highly significant. The p-value of that Kaplan-Meier plot has actually a p-value of less

than 10 to the minus 8, and survives any multiple comparison that we're doing within that set.

This type of analysis fairly aggregates most of the company data generated and is a way to go forward to aggregate the data in a mindful, thoughtful, intellectually satisfying, manner. This supports a therapeutic effect of ataluren strongly, certainly in the ambulatory population.

A comment as well that a family approached me last year to prescribe ataluren. They were not able to be on any of the trials, but it was worth my time and effort, and their time and effort, to go through many days to get the requisite single-person IND in our approvals to make this possible.

At age 6, he's having modest gains. At this point, subtle improvements with no side effects. As was mentioned early, any one patient is not sufficient to determine efficacy, but the aggregate data actually convinces me that I'd very much like to keep this patient on study drug, and I'd like to be able to prescribe it to other patients. Thank

you.

DR. ALEXANDER: Thank you. Will speaker 14 please come to the podium and introduce yourself? Please state your name and the organization you are representing, if there is one, for the record.

MS. MICELI: I'm Carrie Miceli, professor and co-director of the Center for Duchenne Muscular Dystrophy at UCLA. PTC paid for my travel.

My laboratory is focused on dystrophin replacement strategies. I chair the scientific advisory board for imaging DMD, one of the most comprehensive ongoing assessments of natural history in Duchenne, and I sit on advisories for planning DMD trials. Therefore, I'm well equipped to comment on the strength of the data presented in support of ataluren.

PTC was a pioneer in DMD trials, performing the largest multisite, placebo-controlled Duchenne trial at the time of Study 007. While missing their primary endpoint, subset analysis revealed a possible drug effect in boys with defined entry criteria and dosing.

PTC performed a second placebo-controlled trial. Meta-analysis of subjects fulfilling the predefined criteria from both studies indicates a positive treatment effect when analyzed in aggregate.

Loss of ambulation and pulmonary function data support a treatment effect, bolstering the trial findings. Additional support for efficacy comes from the dystrophin results presented. While there are limitations regarding the ability of immunofluorescence to precisely quantitate dystrophin protein, this method did clearly demonstrate dystrophin introduction in response to ataluren, establishing the mechanism of action, and providing a plausible explanation for the bell-shaped curve.

There is no well-established lower threshold of dystrophin production under which expression is clearly predicted to be insufficient for inducing some functional gain. Rather, there are compelling data from mouse models, Becker patients, and patients amenable to exon 44 skipping, that

expression of very low levels of dystrophin can result in increased functionality.

The study findings predict that ataluren likely produces dystrophin at levels compatible with the effect size observed. Together, in my opinion, the data represent substantial evidence of efficacy.

Admittedly, the package presented may not fulfill the conventional strict criteria for full approval. However, since the inception of the original PTC study, scientists, clinicians, and regulatory bodies have realized that the strict adherence to conventional trial design is neither optimal or appropriate for rare disease approval, encouraging flexibility in approvals. Such flexibility is appropriate in considering full approval for ataluren.

Further, Congress has enabled accelerated approvals for drugs treating serious disease with unmet need, based on the criteria of reasonably likely to predict clinical benefit. In the event that the FDA cannot apply such flexibility for full

approval, I suggest the ataluren package be considered for an accelerated approval as the data clearly fulfill those stated criteria.

It does not seem appropriate or ethical to deny boys access to a safe drug that's likely to be effective, while there are regulatory paths and pace enabling approval and continued patient access to ataluren based on existing data.

In light of the large number of boys exposed to ataluren now, worldwide, it's anticipated that confirmatory data relating to the efficacy of ataluren, or lack thereof, should be forthcoming from ongoing studies and continued patient exposure.

Failure to apply flexibility in considering ataluren approval unnecessarily puts procedure ahead of patient wellbeing, an outcome we hope you as an advisory committee can help prevent.

DR. ALEXANDER: Thank you. Will speaker 15 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MS. FURLONG: Thank you. My name is Pat Furlong. I'm president and CEO of Parent Project Muscular Dystrophy, and I have nothing to disclose.

In good faith, we've all come together today to discuss the data that's been collected from Study 004, 007, and 020. We're deeply grateful to the committee for your willingness to review the data that's been collected and to listen to these families in an effort to understand the data that was not collected, that was not part of the studies.

As parents, we participate in clinical trials. We sign the informed consent, and our sons sign the assent, with the understanding that there will be requirements of us and our sons: blood, urine, tissue, and functional measures, such as the North Star 6-minute walk time test, and others.

We cooperate because that is the current methodology for clinical trials, and then we go home. We watch as we go through the motions of our lives and we notice subtle things, subtle things that make a difference in our sons' lives, and by

default, our own.

Energy, the ability to engage in activities without fatigue; sleep, sleeping through the night without the need to be turned, without the need for comfort measures by another member of the family; breathing, no signs of CO2 toxicity, no need for non-invasive ventilation, a step toward progress in breathing on your own for a very long time; small things, soft data, not measured in numbers, and not analyzed, but measures that we see in how our son feels and functions.

Please consider these measures, those done in the context of our lives that preserve the quality of our sons' lives and our lives. But there's more. Please consider those who are not represented here today in the Duchenne community. Those individuals that didn't meet the criteria, that sit and wait, and wait, and wait, they have not had this opportunity to try to preserve the quality of their lives, and they will need access and deserve access.

Please think of all those standing in line

waiting, and don't let them wait the rest of their lives. Thank you.

DR. ALEXANDER: Thank you. Will speaker 16 please come to the podium and introduce yourself? Please state your name and the organization you are representing, for the record, if there is one.

DR. MCFARLAND: Good afternoon, advisory board. I am Dr. Robert McFarland, a diagnostic radiologist. My son, Ross, has Duchenne's dystrophy. I'm here with the Motts family, and Brandon, who also has Duchenne's dystrophy. My only financial disclosure is my travel arrangements were paid by PTC. Ross has been on ataluren for about 11 years. He was on beginning with the Study 004 and presently on 007. Brandon also has been on the drug for 10 years and was involved with Study 007.

Both my son, Ross, who is 22, and Brandon, 19, were both diagnosed at the age of 4. At the time of diagnosis, both families, both got the same horrendous prognosis. No viable treatment, basically love your child, and expect an early

demise. What is really disheartening, it is the same prognosis I heard in 1984 as a second-year medical student, but thank god things have improved.

Ross and Brandon have outlived their diagnosis. Ataluren has given these kids a good quality of life, and they are very good about participating in their community. My son, Ross, is a Shocker at Wichita State, and is working part time. Brandon has been very active in the community of Jackson, Michigan doing a lot of volunteer work. Both boys are making a positive impact in their community, but I must say that both boys experienced major setback in the interruption when the drug was on hiatus.

Ross' ability to ambulate was lost during that hiatus, and there was some noticeable truncal loss of strength. Being very active in Ironman community myself, my son was an avid swimmer. He was swimming about 350, 400 yards, prior to termination of the drug. I noticed the deterioration. I've seen deterioration in people

with multiple sclerosis and other degenerative diseases. Ross' decline was apparent and visible, and it was during this drug interruption.

Upon reinstatement, he did not return to 500 yards, but he went back from 150, back to 400 yards. For us, the endpoint to validate ataluren on just ambulation and muscles of movement, probably needs to be of some question.

Since being back on the drug, the slope of his deterioration has flattened. I am lucky that I can do echoes; his ejection fraction stays above 55 percent. His FEV is still well-maintained. There have been no signs of any deterioration of his neck muscles, and there's been no need for utilization of any BIPAP.

I can say, with great conviction, that the detrimental effects of termination of ataluren are real. I can see that with the positive clinical trials, that my son has benefited directly. I ask this board to listen to the positive statements that are made throughout this room, and the benefits that was presented today, and at least

give time to better establish the medical and clinical upside of this medication. We owe it to the field of science. We owe it to people suffering from muscular neurological diseases. But for most of all, we owe it to humanity. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker number 17 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MR. BUCCELLA: I am Filippo Buccella from Parent Project, Italy. My travel was supported by PTC, and I represent the boys of many Italian parents. They have meaningful experiences that we strongly believe should be considered in your decision to make ataluren available to American Duchenne's children.

Forty-three Italian boys have access to ataluren now. Seven are older than 14 years, and 17 older than 10, and they're still all able to walk, just as stated for the 019 study.

Today, ataluren is available for patients in Europe, thanks to the conditional approval granted

by EMA. In Italy, our agency the AIFA has agreed for fully reimbursed access to the treatment. This is a big milestone for our entire community. Many of our children are receiving the treatment, which will delay the progression of their disease. However, we feel this is an opportunity that cannot be restricted to just a few, but should be extended to every Duchenne boy all over the world.

We parents have the clear perception of the many improvements in our kids and daily activities and tasks. We interviewed three families during our last meeting and here's what they say.

Andrea is 14 years old, and he's able to run and ride his bike. This is what was said by his father, Fabio. "Six years ago, we were included in the trial with ataluren, and it allowed my son to maintain his strength and give us all more time. In the last six years, there was no degeneration. We were at the swimming pool a few days ago, and I was impressed," continues Fabio. "Before taking Translarna, Andrea could swim for just a few meters. Now he doubled. Even the results of his

lungs and heart tests show no loss functionality and most of all, he never had any side effects."

"The teacher noticed that something was not okay with Marcos," says Carla [ph], his mother. "My husband and I had just seen our pediatrician. It was the day when the long journey to reach a diagnosis of Duchenne muscular dystrophy had just begun. That day I was feeling dizzy and confused. Everything seemed unreal to me.

"Today Marcos is 12 years old, and he should be bound to his wheelchair, but he's still standing and is able to walk to his school by himself. When his first teacher saw him a few years later, she was very surprised, and we had to explain to her that Marcos was taking Translarna," adds Carla.

"Daniele [ph] started taking Translarna one year ago," says Maria [ph], mother of Daniele. "At the time, it was also available in Italy, thanks to the 648 law that is promoted and expanded an early access. We just have one-year experience, but Daniele could not lift his feet from the ground, and today he can make a little jump. His balance

has also improved and his stamina has, too."

We are really confident Translarna is giving our kids the opportunity to gain time, a time to discover the world by themselves, a time to live. Thank you for considering these patients real-world experience in your recommendation whether to make Translarna also available to United States patients.

DR. ALEXANDER: Thank you very much. Will speaker 18 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MR. MITCHELL: Good afternoon, and thank you for the opportunity to speak today. I am Jack Mitchell, director of health policy for the National Center for Health Research. Our non-profit organization analyzes medical data and provides objective health information to patients, providers, and policy makers. We do not accept funding from drug companies, so I have no conflicts of interest to report. I'm not a clinician or MD, but I'm presenting these views on behalf of our

team of PhD researchers and analysts.

I'd like to acknowledge the patients, children, and families who've come as far away as Europe today to express their views to the FDA panel. Patients with rare diseases urgently need safe and effective treatments, and we appreciate the companies diligent efforts to provide such treatments. That means we need persuasive data based on soundly reviewed science.

We agree with FDA that substantial evidence of effectiveness must be provided to support approval of a new drug. FDA has been flexible in approval criteria for treatments for some devastating rare diseases. In some cases, however, that has resulted in insurance companies refusing to pay for FDA-approved treatments that the insurance companies deem experimental rather than proven.

This disconnect adversely affects patients who otherwise would have free access to the drugs in clinical trials when the trials are either stopped or limited. Patients and their families

cannot afford to pay for treatments that insurance companies maintain have not been proven to work.

We agree with FDA scientists that the data presented today do not indicate significant benefit in randomized, double-blind, placebo-controlled trials such as Study 007. Only after making many post hoc changes did ataluren show it was effective for patients, but this was not replicated in Study 020. As you know, these post hoc manipulations do not provide clear evidence of efficacy.

For both studies, 79 percent of patients were white, but the CDC reports that Hispanic males are disproportionately likely to have these conditions. It is essential that an adequate number of Hispanic males be analyzed to determine if they can benefit from a treatment such as ataluren.

Finally, we have concerns regarding safety. Elevated blood lipids and blood pressure are not benign side effects, particularly in children. These risks are substantially increased in children

taking chronic corticosteroids. In addition, the effects of ataluren on kidney function blood tests are also a matter of concern, especially in children taking many other drugs that could be harmful to the kidneys.

We agree with the FDA that no study conducted as planned has sufficiently positive results. A possible signal of treatment effectiveness for patients deserves further study certainly, but the current data, in our opinion, are not sufficient to warrant FDA approval.

Patients and their loved ones deserve the benefits and most rigorous research. We urge the committee to decide that the data suggest that ataluren has not yet proven sufficiently effective.

I respectfully recognize that the families and their children here today do not share that viewpoint. Their stories are both moving and meaningful. We're a patient advocacy group, among other things, so this is not an easy position to take, but we believe further research is necessary. Thank you for allowing to share our viewpoints.

DR. ALEXANDER: Thank you very much. Will speaker 19 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

DR. CAMPBELL: Thank you. My name is Craig Campbell, and I'm a pediatric neuromuscular specialist at Western University in Canada. By way of disclosure, I've been a site investigator and a voluntary advisor for PTC, including travel costs that include getting to this meeting today. I've also been involved in many other clinical trials for various childhood neuromuscular disorders.

While I have equally positive experience in my study patients on ataluren, as many that you've heard today, I would like to take a bit more of a broad evidence-based perspective on why the DMD community should be compelled to be using ataluren for nonsense mutation DMD.

It's a well-established evidence-based principle that a meta-analysis of two or more well-designed, congruent RCTs is a high level of evidence, perhaps the highest, even, and maybe

especially, when results are statistically negative, but consistently favoring treatment.

I'm showing here in the panels on the slide, the definitive meta-analysis data that we have for this drug, taken from a combination of the 020 and 007 trials of ataluren. In addition, and by extension, the grade guidelines that inform clinical adoption of evidence calls us to match consistent quality evidence with the benefit-risk balance and place the decision to treat in a clinical context.

Of course, in the case of DMD, we know that we are dealing with a consistent phenotype of certain progressive, life-limiting muscle weakness, with no definitive treatment at present. Needless to say, this is a very difficult scenario for patients, families, and clinicians, and I would welcome any safe intervention that has any degree of effectiveness that could slow the progression of the disease.

Let's look at the evidence, and all this evidence is available in the peer-reviewed public

realm. On the slide that you can see in front of you -- I apologize, it may be a bit difficult to see at that granularity, but I've shown the results of meta-analysis of the 020 and the 007 trials for ataluren.

On the left panel, you'll see primary clinical trial outcome of 6-minute walk test, and on the right, timed functional tests such as 10 meter walk run, and the stair climb, which are secondary outcomes.

The meta-analysis results is the top green line in all figures, and in all cases it points to the point estimate and confidence interval line to the right of the no effect line, thus showing a statistically significant result favoring ataluren. There are some sub-analysis broken down into three conditions on the slide as well, but in the interest of time, I will not go into those, although they do show a significant effect.

Perhaps, though, the strongest evidence, in my opinion, is the recent data we have, not shown on this slide, that's simply taking all subjects

data; so a true ITT population from both trials. The meta-analytic approach shows a statistically significant result favoring ataluren, and this is a result that we have confirmed in our own analysis, although the results above are taken from PTC data.

Combining this clinically statistically significant evidence for effectiveness, and the positive safety record of ataluren, and the context of DMD, I think this makes a compelling case to all of us in the DMD community that ataluren should be made available. And it's critical that patients are not exposed unnecessarily to further clinical trials, or even worse, denied beneficial drug entirely. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker 20 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MR. J. KIRLEY: Hello. My name is Jack Kirley, and this is my family; Terry, my wife, and Maxx, my son who is now 16 and has Duchenne muscular dystrophy.

Maxx was in Study 007 starting at age 7 and has been on ataluren, except for a several-month period when the study was stopped, ever since. He is currently in the extension. Our travel and hotel were covered by PTC.

We'd like to thank the advisory committee for taking the time to review the data. Most of all, we'd like to thank the heroes, like Maxx, that participate in clinical trials.

Ataluren is an effective and beneficial drug that has given Maxx strength and endurance. Because of ataluren, Maxx is ambulatory at 16, and he keeps on going. He's taking a college course and so much more.

Soon after, and over the course of taking ataluren, we saw significant improvements in all areas of his life. Here are a few of the observations by us, by teachers, by peers, by PTs, by OTs, doctors, friends, and family members, most not knowing he was in a trial.

His 6-minute walk increased 56 meters by the end of trial. Please note his baseline was between

300 and 400 meters. His walking pattern changed from toe walking to a heel-to-toe stride. He had increased stamina and better coordination. He was able to jump into bed. He was able to throw balls further, with more accuracy. He started using his wheelchair less. He started climbing large hills. His hand strength improved. He was able to write as much as his peers. He's never had pneumonia.

Before ataluren, and during the months he was off ataluren, we saw notable declines and falls were more frequent. Please consider this in your decision.

Ataluren has improved our son's life significantly. Maxx feels better. He has improved energy and function, and in over 9 years on drug, Maxx has had no adverse side effects. While some here may be uncertain of the benefit, we as parents are not.

Please don't risk the potential of a type 2 error. We've seen the benefits of taking this drug and the danger and risks without the drug. Once function is lost, it's lost. Please do no harm.

Maxx would like to say a few works.

MR. M. KIRLEY: We don't have time. Please approve ataluren now so that all will have access. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker 21 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MS. MONSON: Good afternoon. My name is Carolyn Monson. My son, Grant, who is now 24, was in the original safety study and is now on the extension study since the age of 15. I and my husband, Tim, are representing our family. Our expenses have been covered by PTC.

Grant has been involved with ataluren for 12 years. Right before the extension trial started, Grant fractured his left femur. He rehabilitated enough to complete the 6-minute walk and start the trial November of 2008. On ataluren, he gained strength and stamina, and returned to walking in school in spite of the traumatic femur break. He gained speed as the months went on.

During the latter part of his junior year, the trial was suspended. We, his peers, and teachers, noticed his decline. He had numerous falls at school and became increasingly fatigued. When the trial was reinstated, we noticed Grant steadily returned to his former state. A few months after he resumed ataluren, he walked up the stairs and across the podium to gather his high school diploma.

During his college years, Grant continued to ambulate to his classes. He graduated with hardly missing a day due to illness or fatigue. He stopped walking at the age of 22 and a half, a remarkable feat that few with Duchenne are able to do.

He currently uses a manual wheelchair to push himself around his home and his office. He is employed working 30 hours a week. He has no incidences of pneumonia, and his respiratory function is excellent. He is able to transfer himself from his bed and can transfer himself on and off the toilet.

He gets himself ready for the day with little assistance. He can stand for several minutes when helped to his feet and given support for balance. His overall quality of life with Duchenne far exceeds the outlook we were given when he was diagnosed at age 4.

We understand, firsthand, how difficult Duchenne and other rare diseases are to study, but we have also witnessed firsthand the impact that ataluren has had on Grant. Slowing the progression of the disease has given him time to grow up, graduate college, and join the working world of adulthood. For this reason, Grant remains in the study, even after 12 years.

He remains a highly functioning individual in spite of the trial measure outcomes documented in your records. His experience with ataluren convinces us it is working. So many doors have been opened to Grant because of ataluren. Please don't shut the door on him. Time is running out. Thank you.

DR. ALEXANDER: Thank you. Will speaker 22

please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MR. FARWELL: My name is Charles Farwell, and thanks to the FDA for giving us this opportunity. My travel and accommodation for the trip have been provided for by PTC. I'm the father of Ryan Farwell, who is now 24 and living with muscular dystrophy.

At nine months of age, Ryan was diagnosed with MD. Today, he is 24. Throughout his life, we have searched for medications with the hopes of maintaining his strength, as well as possibly increasing it. Ataluren is one medication that we can state definitively has shown a beneficial effect. Ryan has been on this treatment since 2007 with zero side effects.

Our first indication of benefit came with the increase in overall energy we noticed with Ryan after starting on the drug. We believe that throughout his high school years, he maintained strength largely due to ataluren. Ryan was proudly

able to navigate the crowded and noisy hallways of high school and was ambulatory until just a couple of years ago.

The obvious question one might ask is how do you know how the disease would have progressed without ataluren? Well, in an odd or ironic way, we are fortunate that Ryan lost access to the drug for much of 2010, when PTC halted the trial. That experience cemented in our minds just how effective the drug had been.

Up to the point the trial was stopped, Ryan never had a history of falls. That summer, prior to his college departure, and after Ryan had been off ataluren for about three months, he took a very bad fall. We absolutely feel this had everything to do with discontinuing his ataluren treatment.

Because of this fall, we were forced to reassess his dream of attending college without the appropriate physical support structures in place. As further confirmation of the treatment impacts, we again saw improvement in Ryan's energy when he was restarted on the trial, but it is not clear if

he ever regained what had been lost.

In closing, please see the slide which illustrates Ryan's specific mutation. This slide is just a snippet of the dystrophin gene, and you'll have to imagine a deck of almost 20 slides that would be required to show the entire gene.

Mutations that cause MD can occur in thousands of different places along this gene, resulting in a virtually endless set of disease variations. For this reason, it seemed clear that our kids are going to need a broad variety of treatment options, and I urge you to consider that ataluren deserves to be one of them.

DR. ALEXANDER: Thank you very much. Will speaker 23 please come to the podium? Please state your name and any organization you are representing, for the record.

MS. WAGNER: Hello. My name is Ellen Wagner. Mine and Maria McDonnell's travel and hotel have been provided by PTC Therapeutics.

My son, Tim, was one of the first 12 boys to try PTC in the safety trial. My husband and I made

the decision to allow our little boy to try a drug that would alter his DNA, knowing that to do nothing was a fatal choice. Sometimes to do nothing is to cause harm.

We saw significant improvement all those years ago. He was able to climb stairs, jump, and play tag. We saw a precipitous drop when the trial ended, a drop in not just physical ability, but in his academic performance. As sad as we were to see this drop, we were ecstatic that the drug worked. We were so anxious to put Tim back into the extension trial as soon as it became available.

We did enroll Tim in the extension trial. He remained stable during this period; able to climb stairs in his non-accessible school and generally not show very many signs of DMD. His clinic physician commented he would be one of the lucky ones, walking to his late teens with a strong gait.

In 2010, the trial was stopped. Unfortunately for Tim, the time off drug was devastating. We saw him rapidly come off his feet

and begin the decline typical of DMD. After a lengthy delay, Tim was able to go back on drug, but it was too late for him. We did not see the immediate gains of the first two experiences, but we strongly believe the little ability Tim has left is due to ataluren.

To take Tim off this drug again, could be catastrophic. It's very hard to show improvement in a progressive disease. We cannot afford to take a chance with Tim. To do no harm would be to approve ataluren for Tim and all the boys. This is their only chance. There is no other therapy.

We do not want to take the risk of losing this drug and the benefits that allow our 19-year-old to enjoy his life. His siblings, friends, and family need him to stay around. Remember, to do no harm would be to allow these boys to continue a drug therapy that Tim has been on for 12 years, most of his life.

MS. MCDONNELL: Hello. My 17-year-old son, Aidan [ph] was in the ataluren Study 007 and is now in the extension study. Aidan is not here with me

today because he hates to miss school. He's a pretty serious student with a 4.0 GPA who has his eye on college acceptances.

Aidan maintains good grades and good attendance in part because of good respiratory function. At nearly 18, Aidan's respiratory health is excellent. He does not require BIPAP assistance, although the majority of boys his age do use non-invasive ventilation. He has never had pneumonia or even a chest cold. His pulmonologist always remarks on his well above average PFT results.

I strongly feel that Aidan's respiratory function has been preserved by his years of taking ataluren, and I fear what may happen if the drug is discontinued as Aidan nears the college years he has been looking forward to.

My son deserves the bright future he has been working for, and I urge to make ataluren available to Aidan and all of the patients who will benefit from this medication. Thank you.

DR. ALEXANDER: Thank you very much. Could

speaker 24 please come to the podium? Please state your name and any organization you are representing, for the record.

DR. HAGERTY: My name is Dr. Laura Hagerty, and I work in the research department at Muscular Dystrophy Association. By way of disclosure, MDA has been leading the funding of Duchenne therapies for more than 65 years, including providing support for the development of ataluren, and many other potential therapies in development.

Thank you for the opportunity to be with you today. I'm pleased to speak on behalf of MDA and the thousands of Duchenne families we support and represent. At the outset, I'd like to share MDA's optimism about the robust Duchenne therapy development pipeline, and that for the first time ever, there are treatment options to change the course of Duchenne muscular dystrophy.

As a scientific program officer focused on Duchenne muscular dystrophy at MDA, I'm aware of the serious impact and lethal nature of DMD. MDA has led the search for treatments and cures for

Duchenne for more than half a century and will continue to do so until there is a cure.

Beginning over 15 years ago, we have funded the development of stop codon readthrough therapies, including ataluren. While there is still no cure for DMD, it is essential for this body to appreciate that the DMD community needs safe and effective therapies, even if not cures, as slowing the progression of the disease is a significant and positive development for those living with DMD.

What has long been known about the disease and confirmed by MDA's data in conjunction with published studies, is that individuals with DMD are affected early in life, even at birth, and that disease manifestation resulting in clinical signs and symptoms are obvious prior to age 5 years in virtually all individuals with DMD.

While a cure for DMD is the goal we're all working tirelessly to achieve, the slowing in disease progression and symptom manifestation is of great value. To extend the ability to walk, to eat

independently, and to breathe is of value.

There are many abilities that are critical to having the best possible quality of life that fall short of being cures. In reality, being able to fasten a button without assistance, to independently adjust yourself into a more comfortable position, to be able to operate a joystick on an electric wheelchair, and simply to be able to hug the people you love, these are important things to maintain for as long as possible.

While some of these milestones may be consistent with clinical trial endpoints, many may not be captured as outcome measures, but the absence from being measured in clinical trial outcomes does not diminish their importance.

Slowing progression of the disease is critical, particularly because we know that if we can slow the progression of the disease to early milestones, we can delay progression to later milestones as well, as we set out in our written comment.

All of us at MDA, as well as our sister organization, scientific community, families, and supporters have been working tirelessly to see a time like the present, a time when therapies could be more than just a hope for the future. We are all here for those living with Duchenne and the people who love them. Thank you.

DR. ALEXANDER: Thank you very much. Speaker 25, if you could come to the podium and state your name and organization you're representing, if there is one, for the record.

DR. SALAZAR: Good afternoon. My name is Rachel Salazar. I'm a doctor of physical therapy at Columbia University's Pediatric Neuromuscular Center. We treat over 200 boys and men with Duchenne muscular dystrophy, 20 of which with nonsense mutations.

I truly appreciate this opportunity to address the advisory board and share my experience with the efficacy of ataluren. I received travel assistance from PTC to attend this meeting.

Eight patients are enrolled and followed in

the PTC extension study at Dr. Darryl De Vivo site at Columbia University. All patients remain free of any drug-related side effects. Six of our eight treated patients are now able or are predicted to walk beyond age 14. Three of the patients suffered lower extremity fractures due to falls and osteopenia related to ongoing corticosteroid treatment. All three patients regained the ability to walk.

Even with extensive physical therapy, regaining the ability to walk after a fracture is unlikely, based on our experience with the natural history of this disease. Boys who walk between 300 to 400 meters on their 6-minute walk test are in a transition phase and are at risk of rapid decline in walking ability. However, those treated with ataluren showed statistically less decline than those on placebo.

At our site, we followed two brothers who at baseline walked between 275 and 300 meters on their walk test. Over the years, their walking ability continued to improve, and at their last visit at

ages 12 and 13, they walked nearly 500 meters. These improvements mean that these boys are able to walk to school, six city blocks away, without resting and without falling.

I'm reminded of a former patient who would have been 21 years old today. At age 6, he was diagnosed with muscular dystrophy. At 9, he fractured his femur and never regained the ability to walk. By 18, he was severely disabled and completely dependent on his mother. Sadly, last year, at 20, he passed away in his sleep.

He had a disease-causing mutation that would have been amenable to treatment with ataluren. If treated, his lung function may have been preserved, as was showed in non-ambulant ataluren-treated patients, and he likely would have been here today to speak to you.

We should not deny treatment to anyone with this fatal disease who may benefit from ataluren, and the earlier the better. If treated at a young age, we will likely facilitate early muscle growth and development, maintain the strength to walk

longer, breathe better, and preserve clinically meaningful function.

I truly hope we can seize this therapeutic opportunity. Our patients certainly deserve it. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker 26 please come to the podium and state your name and identify any organization you may be representing, for the record?

MS. PARZYMIESO: My name is Susan Parzymieso. I'm speaking on behalf of those children who have been unable to access ataluren. Standing with me today are Joseph and El'Freda Agboka and their son, Omari, Michelle Barshay, and Deb Jenssen. Our group has received travel assistance from PTC.

My son, Thomas, now 9 years old, was diagnosed in 2010 at the age of 2, with his nonsense mutation. At that time we were told we were lucky. It was only a matter of time before we would have access to ataluren. More than 7 years have now passed and we are still waiting.

In 2013, we were excited when PTC announced the opening of a new clinical trial for boys age 7 to 10, but enrollment closed when Tommy was still 6. Then PTC opened another trial for the younger boys. We were hopeful until we found out it only included boys up to age 5. We couldn't qualify for sibling access when that became available, and we even explored compassionate use, but that too was a dead end.

The wait for our son's turn has been excruciating. My son has fallen through the cracks and we have no other options unless ataluren is approved.

Michelle Barshay's son, Connor [ph], is now 10. He loves to cook and hopes to become a chef when he grows up. He, too, has been unable to gain access to ataluren through the clinical trials.

Joseph and El'Freda's son Omari is 14. Omari did not meet the inclusion criteria to gain access to ataluren because he was not yet on steroids. He has waited 10 years to be added to the waiting list for ataluren's long-term outcome

trial.

Finally, Deb Jenssen is here on behalf of two of her three daughters. Giving birth to triplet girls, she thought her family was safe from the Duchenne that had stolen her brother and her cousin. However, it wasn't long before she received the seemingly impossible diagnosis that two of her girls were, in fact, manifesting carriers and clinically have Duchenne, just like our sons.

No clinical trial in Duchenne, including ataluren, has ever had female as part of its inclusion criteria. If ataluren is not approved, her children will have nothing.

In the over 10 years that ataluren has been involved in clinical trials in over a thousand boys, this drug has proven to be safe. We have been waiting years for just the chance to have access to ataluren. We have been relegated to the sidelines, knowing that our children could benefit from ataluren, while we watch hundreds of others get their chance.

Time means everything to us. Every day that passes without access to ataluren is another day where muscle is wasted and function is lost forever. Today, by the grace of God, our children can still walk, but time is not on our side. The incremental benefits of ataluren are worth it to us.

Give our children a chance with ataluren, a chance to slow the progression with a known safe drug. Please vote in favor of access to ataluren for our children that have no other options. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker 27 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MS. KNIGHT: Hi, and thank you. I'm Angela Knight, and I'm here with my husband, Darryl [ph], and our 17-year-old son, Jack. Our entire group has received travel assistance from PTC.

Jack started in the 004 study in 2006, and as you've heard from others, we can't possibly

imagine what would happen if he came off ataluren. But today really what I want to talk about is the life of a 17-year-old high school student living it to the fullest because of the added energy, physical stability, respiratory function, and cognitive improvement that he has experienced through the ataluren experience.

We watch other kids with DMD in high school that have adjusted their schedules and cut back time because of weakness and loss of function, while Jack participates in the STEM and AP programs at school, as a member of the National Honor Society, and performs and travels with his concert and marching bands.

Jack plans to go to the University of Colorado and study engineering. Outside of school, Jack advocates for himself and others affected by Duchenne. He enjoys weekly horseback riding, adaptive snow skiing, swimming, traveling, Broncos games, theater, and music events.

As we're busy with Jack's high school life, we're especially grateful for his normal pulmonary

function, and that helps support his normal cardiac function, and that gives us hope for a long and successful life for Jack because of ataluren.

MR. MUELLER: I'm Ron Mueller. I'm here for my son, Ian. He started ataluren with Trial 007. He has cognitive difficulties. Prior to his DMD diagnosis, he was thought to be on the autism spectrum. When he started the trial, we and his teachers noticed an increase in his focus and communication. This is not well-measured with the 6-minute walk test.

Ian went off drug for several months when 007 was shut down and had a precipitous drop in ejection fraction. We'll never know if that would have been his natural history. He's not been harmed being on this drug. He didn't grow a tail from skipping a stop codon.

But what happens when he goes off drug? A little over two years ago, his heart started failing. In June 2016, he received a heart transplant. I don't think he would have been well enough to be approved for it if he wasn't on

ataluren. Ian's maintained strength far beyond the prognosis we were given when he was diagnosed at 3. He's never been on steroids. He's still ambulatory at 20 years. He has no pulmonary issues.

First do no harm. Let's not see what happens next time he's forced off ataluren. We need continued access, even as you collect more data.

MS. DURAN: Hi. I'm Carissa [ph] Duran. I'm a music educator, and I have the privilege of teaching Ian and Jack. I'm not a medical expert. My expertise is music and its value in the lives of kids. I give kids a place to explore who they are and make meaning in an unfair world.

I know it takes courage to stand up at a concert and play a ruckus bass drum like Ian, or actively participate in marching band like Jack. I know that every moment in their lives is precious, and I owe them every tool I've got to help them be successful. I believe you owe them that too.

As an outside observer, I know that without the intervention of this medication, these

wonderful boys would not be able to move with more freedom, experience the joy of not just listening to music, but making it, or just live a relatively normal day.

Think back to your own high school days. Maybe you were a clarinet player, maybe an oboe player, and in the band. Something made it meaningful for you. I ask that you approve ataluren to help the boys of the Duchenne community have that same chance. They need it now.

DR. ALEXANDER: Thank you very much. Will speaker 28 please come to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MR. KARPEKIN: Hi. My name is Daniel Karpekin, and I'm 12 years old. I would thank PTC for my travel and lodging to D.C. from the capital of California.

I've been on ataluren since 2012. I would like you to consider the approval of ataluren. I had no negative side effects from this drug. Before I started taking ataluren, I had occasional

back spasms. Since taking the study medication my back spasms have ceased. I have maintained my walking ability due to ataluren, and my fine motor skills have improved dramatically, and I believe that I'm able to play piano because I was on this drug. I also have no respiratory or cardiac abnormalities so far.

I wish I had a chance to start this medication when I was much younger; the improvements might have been better. Now that the extension study I was on ended a few weeks ago, I now have a harder time and it takes me longer to stand up off the ground, and I get tired as the day is progressing.

I ask you to allow me to continue receiving ataluren. Please give a chance to boys with Duchenne muscular dystrophy to receive the benefits from ataluren. Thank you.

Clarifying Questions (continued)

DR. ALEXANDER: Thank you very much. So this concludes the open public hearing portion of this meeting, and we'll no longer take comments

from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We have just one voting question, but before we consider that question, I would like, if it's possible, to offer the committee members an opportunity to ask further clarifying questions of the FDA or of the sponsor.

Do any of the panelists have clarifying questions that they would like to ask of either the FDA or the sponsor?

DR. GORDON: This is Mark Gordon. I have a question for the sponsor, please. We've heard many testimonies that during washout, the patients who were in the study got worse. Then when they reinstituted the drug, that they improved to some extent or stabilized.

So my question to you is, is there any quantification of this? Have you analyzed this? And if so, could you tell us about it, please?

DR. ALEXANDER: I'd like for the sponsor to

address that question, which is about whether there's any quantification of the effects of washout that we heard remarked upon by some of the speakers.

DR. McINTOSH: Yes, thank you. I'd like to invite Dr. Marcio Souza to answer that question. Thank you.

MR. SOUZA: Marcio Souza, PTC Therapeutics. During the brief period of time between Study 007 and the other studies, we had to stop treatment in different parts of the world. So the restarting happened between months, and in some case, years, depending on IRB approvals and contracting, and so on and so forth, as you all know.

So there is no controlled data in that period that we could legally or actively collect, so there's no way to control. So the only information we really have is the evidence we provided to the panel this morning on the study that was controlled before that, Studies 004 and 007, and Study 020.

On the extension, or most of these patients

mentioned, there are studies either 019, outside of the U.S., or a safety study in the United States, that is Study 016, where most are in. I hope it answered your question.

DR. ALEXANDER: Thank you. Dr. Fountain?

DR. FOUNTAIN: My question is about the nature of the long-term follow-up. What we've heard is such compelling stories --

DR. ALEXANDER: Is your question for the FDA or the sponsor?

DR. FOUNTAIN: Sorry. The sponsor. We've heard some compelling stories about the long-term effects, and often in other disease areas, we see evidence of what seems like continued efficacy from long-term studies. And I'm really just asking the question I asked before, although maybe I'll come around to ask it differently is, we saw the pulmonary evidence of improvement. We saw fleeting other evidence, but the question is why is there not -- or do you have evidence of some longer term or sustained effect? Because what we're talking about are other kinds of complex issues and

statistical analysis. If those bring certain things into question, then certainly looking at long-term data would be at least that good, even if it's open label.

DR. McINTOSH: Thank you very much. I think the core of the problem with studying Duchenne is the duration that you can run a placebo-controlled study. If you look longitudinally, the average boy loses ambulation over an 11-year period.

DR. FOUNTAIN: But my question's not about the placebo-controlled studies. My question is about the long-term follow up studies. Over time, do you continue to measure it and did they change? Because we have a natural history control to some degree, but if you don't have that, that's okay.

DR. McINTOSH: Correct. The best long-term data we have is Study 019. This study is an open-label extension study, which enrolled patients previously enrolled in PTC studies and has an exposure of 3.5 years. In that study, we have done a natural history comparison, which was the lung function data that we presented, as well as loss of

ambulation assessments. Those are hard outcome assessments. I'd like to invite Dr. Craig McDonald who did those natural history comparisons to speak to this data.

DR. McDONALD: Again, data presented earlier to the panel, I think was really very consistent with what you're hearing with the open label from the open public hearing.

The data on the left really shows the loss of ambulation in 330 patients with Duchenne. The median age is 13.4 years. The 95 percent confidence interval for that median value was, again, 12.5 to 14 years. The patients studied long term in Study 019, a median age of loss of ambulation was 16.3 years, so again, a 2.3 year prolongation.

I think that, in addition, if we look at the FVC, the forced vital capacity data, which we show here actually from Study 019, long-term follow-up. Again, when patients progress below one liter, that puts them at increased risk of death by four-fold.

You can see from this data that in the late

teenage years, patients with ataluren are not progressing to that critical threshold, in relation to our synergy natural history data. Again, that was really, I find, very compelling. In addition, these groups were well-matched in terms of baseline characteristics, proportions on steroids, and age at entry.

Then finally, with the North Star data, when we look at loss of function, that's really what matters to patients is the loss of function data. In fact, when we look at the North Star, which is a new endpoint in Duchenne's dystrophy, the PTC trial was one of the first trials to use this endpoint.

When we look at the hard endpoint of a transition to a zero score, which is clinically meaningful to a patient, loss of function, we see a 31 percent reduction --

DR. ALEXANDER: Thank you. I think Dr. Fountain feels your question was answered.

Is that the case, Dr. Fountain?

DR. FOUNTAIN: Yes.

DR. ALEXANDER: Okay. Thank you.

Dr. Mielke?

DR. MIELKE: Thank you. Really building off the last question as well, it did sound that the longer term effect on the drug was most beneficial. It also sounded that people were on one study, and then transitioned to -- maybe it was off and then on another study.

So I was wondering if anybody had done any analyses, based on those people that were on previous studies versus those individuals who were receiving the drug for the first time?

DR. ALEXANDER: Before we get to that, I want to give Dr. Bastings and Dr. Kozauer a chance to respond also.

DR. BASTINGS: Just a couple of comments. The first one is that these data on long-term preliminary outcome have not been submitted to the NDA. So these are not data that we have independently reviewed and analyzed.

The second comment is that these historical controlled studies are generally a lot more difficult to interpret than randomized controlled

studies. So the quality of evidence coming from these studies is generally much higher, and they tend to be more interpretable than the historical control studies.

DR. ALEXANDER: So you're referring to example, I think it was slide 79 that showed a comparison with the CINRG study or controls?

DR. BASTINGS: Right, among others, yes.

DR. ALEXANDER: Dr. Kozauer?

DR. KOZAUER: Yes. I was going to essentially say the same thing that, it sounds like the CINRG data potentially wasn't matched to mutation type, which might be important. But the bigger issues is all of these were described very briefly in the NDA. We haven't been provided efficacy data, like the FEV data from Study 019 or the CINRG data to review.

MR. SOUZA: Can I respond, Dr. Caleb?

DR. ALEXANDER: I'd like to hear Dr. Mielke's question first, and then I'll give you a chance to respond.

Can you restate your question, please?

DR. MIELKE: Yes. My question was, we've been talking about more potential efficacy for long-term use, although it's not shown actually in the clinical trials right now. But based on observations and patient reports, and the suggestion that people were on multiple clinical trials, I was wondering if there was any analysis that was done, only looking at those people that were new to drug, as opposed to those who were on previous clinical trials. For example, with Study 020, if you separated those that were in Study 007 versus those that weren't.

Just trying to get a little bit at the long-term effectiveness and get a better idea, even though there isn't a specific clinical trial for it.

DR. ALEXANDER: Okay. Does the sponsor have any data on drug-naïve patients, essentially patients that were naïve to having received the drug in the past, or was that considered in any of the analyses that were performed?

DR. McINTOSH: Yes. Let me answer that

question. Study 007, all patients were the first randomized, placebo-controlled study. All patients were naïve to the drug. All those patients went to the open-label extension studies. Study 020 again, all naïve patients. So the randomized controlled studies were naïve patients. The open-label extension study is obviously where patients had been previously exposed to drug.

DR. ALEXANDER: Okay. Great. Thank you. I just want to try to summarize what I heard from the prior exchange, which was based on a question from Dr. Fountain about whether there was evidence of long-term efficacy. And I think if I understood your question, you were raising the question of, in addition to any data that we saw about pulmonary improvements, whether there was more evidence of long-term or sustained effects.

If I understood the data that the sponsor provided, it included some examples of comparisons of the study population, for example, with the CINRG cohort or group. Then if I understood the FDA's comments following that, there were two. One

was that long-term primary outcome data haven't been submitted to the FDA as part of this application, and then the second was just cautioning with respect to the use of historical or asynchronous controls and in interpreting data.

Are there other questions for clarification? I guess I have one more that I wasn't totally clear on. This is for the FDA, and it has to do with this correction for multiple comparisons.

So I'll again say on the record that I'm not a biostatistician, but we've heard so many times that there were lots of secondary analyses, that these weren't prespecified endpoints. In some cases, it sounds like in many cases they weren't positive, but in some cases they were. Then we're heard a lot about nominal statistical significance.

So for Xiang Ling or someone from the FDA, is it not possible to adjust for multiple comparisons? I think at one point you briefly said that had adjustments been made, even fewer of the analyses would have been statistically significant, but it seems to me that -- are those very difficult

to pull off or to know how to do, or why wouldn't one just do those adjustments?

DR. LING: As a primary analysis for Study 007, as a type 1 error control was not prespecified for secondary endpoints, there's no way for us to really to compute or adjust the p-value for the secondary endpoints.

If we were going to adjust for the multiplicity of only testing the 2 doses, we can do that, but we cannot adjust for multiple doses and multiple endpoints.

DR. ALEXANDER: Okay. Thank you.

Are there further clarifying questions for either the FDA or --

MR. SOUZA: May I comment on that?

DR. ALEXANDER: No, my question was for the FDA. Thank you.

MR. SOUZA: There was a question before the break that we asked to comment on.

DR. ALEXANDER: Yes, I understand that, but I'm sure that there may be more that you wish to say, and also probably more that the FDA wishes to

say, and this period is really reserved for discussion among the panel, as well as specific questions that we have for either you or the FDA.

Are there other questions that the panelists have either specifically for the sponsor or for the FDA? If not, I think we'll go to the voting portion of the meeting.

Dr. Gordon?

DR. GORDON: We heard during the course of the proceedings today that there is an additional study underway, and I'm curious to clarify if this is a double-blind, randomized, control study, and if so, perhaps we can hear a little bit more about it to understand what data might be forthcoming.

DR. ALEXANDER: Okay. Thank you. That's a question for the sponsor, I presume?

DR. GORDON: Yes, it is.

DR. ALEXANDER: Okay.

DR. McINTOSH: Thank you very much. Yes. I will put the slide up here. The current study, which we refer to as Study 041 by number, is a double-blind, placebo-controlled study. The

double-blind, placebo-controlled period is 72 weeks, followed by additional 72 weeks of open-label therapy, so it's a three-year study.

This study is essentially part of our postmarketing commitment in Europe and to provide additional evidence of effectiveness. The expected results will be '20, '21, '22, with any filing based on that to be 2023.

Questions to the Committee and Discussion

DR. ALEXANDER: Thank you very much. We'll now proceed with the questions to the committee and panel discussions, and I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the request of the panel.

For voting questions, we'll be using an electronic system. When we begin the vote, the buttons on your microphone will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote, or you wish to change your vote, you may

press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The designated federal officer will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want. I think that's very helpful qualitative information for the agency sometimes; perhaps even more helpful than the quantitative vote. We will continue in the same manner until all questions have been answered or discussed.

The question that we've been asked to vote on is the best interpretation of the information presented today regarding the use of ataluren for the treatment of dystrophinopathies resulting from nonsense mutations in the dystrophin gene is that: a) the data suggests that ataluren is not

effective; b) although it is possible that ataluren may be effective, the data are inconclusive, and more work would be needed to establish whether ataluren is effective; or c) the data are sufficient to conclude that ataluren is effective.

Are there any issues or questions about the wording of the question itself? Yes, Mr. Watkins?

MR. WATKINS: Yes. When you say the data, do you incorporate the testimony from the public comments, from physicians, and clinicians that have studied populations under the drug, is that part of the data set that we're asked to comment on or vote on?

DR. ALEXANDER: Yes. You should consider the totality of information that was submitted in the briefing packets that have been provided to you, as well as the proceedings of the discussion today.

Are there other clarifying questions?

(No audible response.)

DR. ALEXANDER: If not, I'll once again read the question and the options. The best

interpretation of the information presented today regarding the use of ataluren for the treatment of dystrophinopathies resulting from nonsense mutations in the dystrophin gene is that: a) the data suggests that ataluren is not effective; b) although it is possible that ataluren may be effective, the data are inconclusive, and more work would be needed to establish whether ataluren is effective; or c) the data are sufficient to conclude that ataluren is effective. Please enter your note now.

(Voting.)

DR. CHOI: Everyone has voted. The vote is now complete.

DR. ALEXANDER: Okay.

DR. CHOI: For the record, we have zero votes for A, 10 votes for B, and 1 vote for C.

DR. ALEXANDER: Thank you. We'll now go around the room, and please state your name and your vote into the record, and I think just a very brief qualitative discussion about why you voted the way you did would be of assistance as well.

Why don't we start over here with the first voting member, which would be Dr. Onyike?

DR. ONYIKE: Yes. I --

DR. ALEXANDER: Please state your name, again, and your vote for the record.

DR. ONYIKE: My name is Chiad Onyike. I voted that the data are inconclusive. We've heard the testimony from the FDA, I won't repeat it. We've heard as well the testimony from the sponsor. But the reality is that, firstly, the dispute is about the signal in a very narrow group, whereas approval will apply to everyone.

The quality of that signal is still disputed and is, in fact, under investigation in the new study. So it would be premature to call a verdict while that study is in progress.

What I'm also curious about is what the experience is and what the data is from the market, basically, in areas where this drug is already available, and we heard nothing about that.

As for the testimony from the families, it is compelling on its face, but it's usually the

case that advocacy testimony is compelling. It's also the case that not every person who was in the trial, or who has been in the trial, so who's been exposed to the medication, has testified. So it's very difficult to understand how to think about that that quantitatively.

I think on balance, when you hear compelling experience and you hear inconclusive data, and you understand that there's a study in progress that might resolve the question, it seems to me best to wait.

DR. ALEXANDER: Thank you. Dr. Kesselheim?

DR. KESSELHEIM: Hi. My name is Aaron Kesselheim. I voted for B. I think that I came back to the question of whether there was substantial evidence in this case. And it seemed like the evidence that kept coming out was mostly from post hoc re-examinations of existing trials after the data had been revealed.

I'm concerned about the possibility for whether, consciously or sub-consciously, there are ways that reanalysis of data in that way can be

misleading.

I'm not one to be fixed on any particular p-value. I think that for me the critical issue here was that in a lot of the studies that we saw, when the studies were set up and evaluated prospectively, that there was not a clear effect. Retrospectively, it looked like there were certain areas where there were clear effects, and that kind of reanalysis can be misleading.

I feel like there is still a lot to know about whether or in what circumstances this drug might be effective, and it seems like that data is underway. But for me, right now, it did not appear that there was evidence of effectiveness of the drug.

DR. ALEXANDER: Thank you. Dr. Green?

DR. GREEN: Okay, I'm Mark Green. I voted B as well. I found the public testimony compelling. I found the data disappointing. I understand that defining an acceptable significance level in a study is a bit of sliding scale, a bit of a value judgment, and I think it's reasonable to alter it

based on the penalty of being wrong.

I hope as we go forward -- and hope we will go forward with this drug development -- that we predefine these significance levels before the data is broken, so it becomes more definable to us when it's evaluated in the future.

DR. ALEXANDER: I'm Caleb Alexander, and I voted B, as well, inconclusive. I think the FDA does often exercise flexibility, but there is some statutory threshold of evidence of efficacy and safety required for approval. I guess when I was looking at the question about whether or not there was evidence of effectiveness, I felt that the data were inconclusive.

The dystrophin analyses are of interest, but we heard a number of reasons that those are difficult to interpret. The U-shaped dose-response association was also of interest, but there were alternative explanations for those. The subgroup analyses, as has already been mentioned by others, were post hoc, and even those weren't necessarily always consistent.

I'm someone that lives doing observational analyses, but even the meta-analysis wasn't as convincing as it might have been because of its being based on subgroups. So I'm not sure any number of post hoc analyses can replace the confidence that's provided by a well-controlled, randomized trial that meets its primary, prespecified endpoints.

DR. PERLMUTTER: I'm Joel Perlmutter, and I voted B as well. I was impressed by the heart-wrenching testimony of many of the people in the public, and I thought that was very compelling. But I'm also reminded if that kind of response had occurred in all these people that were treated with this in the study, we wouldn't have had a failure to find statistically significant results. So although it's compelling and it's emotional, it wasn't really supported by the data that we had at hand to review.

The post hoc analysis, I find that there are multiple questions in my mind about its validity. I think there's a lot of interesting potential with

this. I think a way forward is clear.

I take care of a lot of people who have neurodegenerative diseases, and I know the harm of going off on a treatment that turns out not to be useful down the road. So there's risk in that as well. This could be great, but I don't think we have the data, yet, to approve that.

DR. FOUNTAIN: Nathan Fountain. I voted B, inconclusive, and I agree with everything that's been said so far, that the data is just not sufficiently compelling. But I think we need to congratulate PTC and thank them for this tireless effort, because if companies, sponsors, people don't pursue rare and uncommon diseases, which is a relatively narrow group -- and especially I thank the participants in the clinical trials. They are the heroes that do it, so it's a really heavy burden we have to decide that.

I hope this encourages you to move forward, particularly with the ongoing clinical trial that deals with many of the things. I think that the next trial sounds like it'll really be

groundbreaking.

But as to the data we have before us, I also think that it's inconclusive for all those reasons, but I would have a little difficult perspective. I think all of the data is going in the right direction. Each one, at face value, I think provides evidence, but the problem is the evidence of each one is not very strong, so when all considered together, is not quite strong enough. But I think we have to encourage that continued pursuit for this specific condition, but the general philosophy as well.

DR. MIELKE: Michelle Mielke. I also voted B, and I fully agree with the previous comments. There is clearly an unmet need in DMD. It would be wonderful to have something that was a little bit more effective.

The discussions today were very compelling. There appears to be a trend in the data, but at this point, I don't think there's enough evidence there right now to say that the drug is effective. I strongly encourage PTC to continue working on

this with their additional trials.

DR. KRYSCIO: It's Richard Kryscio. I voted B as well. I found that we do need a definitive trial. I certainly want to thank all the participants, especially the company for pursuing this topic and actually providing very good data. I thank the young men who came here this afternoon to tell us their experience in being the clinical trials.

MR. LISON: Wyatt Lison. I voted B as well. I am not a medical doctor. I am not a PhD. I'm a lawyer. I came here as a consumer representative to look at whether or not there was data sufficient to say from the consumer angle that this should be marketed.

Based solely on the language in the question, my inclination would suggest that the data shows it's not effective because it didn't meet its primary endpoints. But based on the company's vigilance, their continued study, the additional clinical trial, and the testimony of the people who came here today, I really hope it works.

I really hope they can show it's effective and they can get it to market.

MR. WATKINS: Jeff Watkins, and I'm the guy that voted C.

(Applause.)

MR. WATKINS: As the father of a son who had Duchenne muscular dystrophy, and I experienced all phases of the disease with him, I came in here today -- I did my homework. I read everything. I read all the comments. I read the testimonies from the FDA. I have somewhat of a scientific background, so I was very impressed with the criticism the FDA had and the lack of statistical validity, and I was prepared to vote B coming in.

I changed my vote for two reasons. One, I read all the hundred and some odd comments online, and I did a little analysis. And of those hundred and some comments, 19 were from clinicians who had observed positive impact of the drug on their patients, and some were stronger than others.

Those 19 clinicians had a total of 74 patients, all over the world, under their care,

some here in the U.S., but in Italy and the U.K. So I put a lot of validity to their observations. They're not data from the trial necessarily, but they're valid observations, because I know, I saw my son progress through the stages, and anything that would stop or even reverse, I would have considered a miracle. He wasn't on any kind of drug trial.

Then the second powerful evidence that I heard today was the reversal or the deleterious effect of stopping the drug. Patients would reverse symptoms; when they get back on, they would see improvement.

So I interpreted that, there's sufficient data to conclude it's effective. It's not effective in everybody. It's not a cure, but it's certainly effective, I believe, in some people.

DR. OVBIAGELE: Bruce Ovbiagele. I voted B. Going last, I don't have much to add to my other colleagues who also voted B. I will say that I am cautiously optimistic about ataluren. I was highly inspired by the public testimony. However, I think

the data are encouraging, but there are lots of concerns, lots of concerns in terms of the interpretation of data, so much that it was hard for me to vote anything else apart B. But I'm very, very optimistic, and I laud PTC for all they have done.

DR. ALEXANDER: Thank you. I'd like to try to summarize what I heard. First, congratulating PTC for their tireless effort to bring this product to market and their vigilance and undertaking, all of the scientific work that we've seen.

To patients that participated in clinical trials, several panelists noted thanks to those patients and their families, high levels of unmet need. With respect to those people that we heard from in the room, very compelling testimony; once again, thanking individuals for sharing their experiences and their experiences with the product and living with Duchenne's.

One panelist also noted, however, that if the same sort of response that was expressed by the panelists here were to be consistently demonstrated

by the product, then we wouldn't have had as hard a time. The drug would have been more likely to have met primary, prespecified, statistical significance tests.

On balance, globally, there were many panelists expressing that the data felt inconclusive. One said disappointing, not sufficiently compelling. It's going in the right direction, but not sufficiently strong, a trend in the data, but not sufficiently strong; need a definitive trial.

We heard from a panelist that voted in support of adequate demonstration of effectiveness, who noted that it does appear to be effective in some people, and that anything that could help, it would be valuable to have that treatment available. Also, the panelist noted powerful anecdotes from patients and family members about reversal, when the product was stopped, that people's symptoms worsened.

There were several comments about post hoc analyses that were performed and that the evidence

that was provided was mainly from post hoc analyses, and there was concern about the possibility of conscious or subconscious bias. There was a comment made about statistical significance, that one need not be fixated on a specific p-value, but the prospective studies didn't have a clear effect.

There was an emphasis on the importance of future research and an interest in that, lots more to know about whether and in what circumstances this drug might be effective. One panelist said the way forward is clear; lots of interest and lots of possibility.

Finally, a panelist noted that there is a concern also about treatments that turn out not to be useful and that there are risks in pursuing treatments that turn out not to be useful clinically as well.

That concludes my summary of the comments, and I just would like to thank all of you, especially patients and family members, and loved ones, clinicians, and the others that have

participated in these trials, and participated in making today possible.

Also, there's an enormous amount of work that we don't appreciate, even having read all of the briefings that the sponsors and the FDA have done to synthesize everything that we've deliberated over today. So it's really just an incredible undertaking and a very important part of our commercial development, so I'd like to thank the sponsors and FDA.

Finally, I'd like to give the FDA an opportunity for any final comment before we adjourn.

DR. DUNN: Thank you, Dr. Alexander. Comments I would like to make are a few that would echo some that we've heard. First, I'd like to thank the committee for their careful considerations and your input. You probably see us over here scribbling furiously. We take the input very seriously. That's why we convened the committee, and we'll be sure to take this all under careful advisement.

I would like to thank all of the -- I already did this this morning, but I want to reiterate my thanks to the patients, the families, and the invested parties who came here to testify on behalf of ataluren, or in reference to ataluren, I should say, given the spectrum of opinions that were provided.

We listened very hard. I echo the feelings of the committee and that we find the testimony highly compelling. We're very interested in this, and we are very interested in working carefully and proactively with our sponsors to gather these data, as best we can because these stories -- as one of the committee members pointed out -- they're there. We tend to hear them at these committees, and we want to make sure that we're capturing them and we understand them.

It's very challenging, as I think Dr. Perlmutter pointed out, to see a disconnect between what we hear and what the data from the trial show, so we are going to be paying an awful lot of attention to that.

The other thing that I wanted to mention is I want to reiterate, with great sincerity, our commitment to continue to work with PTC. I heard a number of committee members mention the trends, which are the same things that we had identified. I think we tried to take great pains to distinguish our concerns about the conclusiveness of the data, and not allow that to be interpreted as a rejection of the signs of effectiveness that we see in the low dose, but to discuss the issues that call that into question for us, in terms of the degree of its reliability at this time.

So I want to reiterate our commitment to work with PTC on efficient paths forward for you so that we can continue to try to get the answers that we need and that the committee has suggested are necessary. Thank you very much.

Adjournment

DR. ALEXANDER: Thank you to all. We will now adjourn the meeting. Panel members, please take all personal belongings with you, as the room is cleaned out at the end of the meeting day. All

materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so that they may be recycled. Thank you again.

(Whereupon, at 3:54 p.m., the meeting was adjourned.)