Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)

74th Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC)

Zoom Video Conference

May 12, 2023

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

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Participants

Members:			
Chair (Acting)	Tabassum (Taby) Ahsan, Ph.D.	Vice-President, Cell Therapy Operations, City of Hope	Los Angeles, CA
Industry Representative	Eric Crombez, M.D.	Chief Medical Officer, Ultragenyx Gene Therapy	Cambridge, MA
Consumer Representative	Kathleen O'Sullivan-Fortin, Esq.	Founder, ALD Connect, Inc.	Middleton, MA
	Donald B. Kohn, M.D.	Distinguished Professor, David Geffen School of Medicine at UCLA	Los Angeles, CA
	Nirali N. Shah M.D., M.H.Sc.	Head, Hematologic Malignancies Section, National Cancer Institute	Bethesda, MD
Temporary Voting Members:			
Patient Representative	Christopher "Buddy" Cassidy, M.A.	Ph.D. Student, Muscular Dystrophy Patient	Irvine, CA
	G. Caleb Alexander, M.D., M.S	Professor, Bloomberg School of Public Health, Johns Hopkins University	Baltimore, MD
	Anthony Amato, M.D.	Chief, Neuromuscular Division, Brigham and Women's Hospital	Boston, MA
	John (Jay) Chiorini, Ph.D.	Associate Scientific Director, National Institute of Dental and Craniofacial Research, NIH	Bethesda, MD
	Susan Ellenberg, Ph.D.	Professor Emerita, Perelman School of Medicine, University of Pennsylvania	Philadelphia, PA
	Richard Kryscio, Ph.D.	Professor, University of Kentucky	Lexington, KY
	Lisa Lee, Ph.D.	Research Professor, Associate Vice President for Research and Innovation, Virginia Tech	Blacksburg, VA
	Steven Pavlakis, M.D.	Professor, SUNY Health Sciences University	Brooklyn, NY
	Rajiv R. Ratan, M.D., Ph.D.	CEO, Burke Neurological Institute; Professor, Weill Cornell Medicine	White Plains, NY
	Raymond Roos, M.D.	Professor, University of Chicago Medical Center	Chicago, IL
FDA Participants:			
Speaker	Peter W. Marks, M.D., Ph.D.	Director, CBER, FDA	Silver Spring, MD
Speaker	Celia Witten, Ph.D., M.D.	Acting Director, Office of Therapeutic Products (OTP); Deputy Director, CBER, FDA	Silver Spring, MD

	Leila P. Hann	Associate Director for Policy, OTP, CBER, FDA	Silver Spring, MD
Speaker	Emmanuel Adu-Gyamfi, Ph.D.	Chemistry Manufacturing and Controls (CMC) Reviewer, Office of Gene Therapy, Division of Gene Therapy, OTP, CBER, FDA	Silver Spring, MD
Speaker	Theresa Chen, Ph.D.	Pharmacology/Toxicology Reviewer, Office of Pharmacology and Toxicology, Division of Pharmacology and Toxicology, OTP, CBER, FDA	Silver Spring, MD
Speaker	Xiaofei Wang, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Evaluation, Division of Clinical Evaluation and General Evaluation and General Medicine, OTP, CBER, FDA	Silver Spring, MD
Speaker	Mike Singer, M.D., Ph.D.	Clinical Reviewer, Office of Clinical Evaluation, Division of Clinical Evaluation and General Medicine, OTP, CBER, FDA	Silver Spring, MD
Speaker	Rosa Sherafat-Kazemzadeh, M.D.	Clinical Team Lead, Office of Clinical Evaluation, Division of Clinical Evaluation and General Medicine, OTP, CBER, FDA	Silver Spring, MD
Designated Federal Officer (DFO)	Marie DeGregorio	Division of Scientific Advisors and Consultants (DSAC), CBER, FDA	Silver Spring, MD
Alternate DFO	Christina Vert, M.S.	DSAC, CBER, FDA	Silver Spring, MD
Committee Management Specialist	Tonica Burke, B.S.	DSAC, CBER, FDA	Silver Spring, MD
Committee Management Officer	Joanne Lipkind, M.S.	DSAC, CBER, FDA	Silver Spring, MD
Director	Prabhakara Atreya, Ph.D.	DSAC, CBER, FDA	Silver Spring, MD
Open Public Hearing Speakers:			
Daniel Flessner			
Mr. Brent Furbee			
Mrs. Melanie Hennick			
Dr. Linda Lowes			
Ms. Kelly Maynard			
Debra Miller			
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Marit Sivertson
Sheila Ungerer
Dr. Michael Abrams
Mr. Mohamed Ali
Dr. John Brandsema
Dr. Anne Connolly
Mr. Paul Melmeyer
Mr. Nathan Plasman
Dr. John Porter
Dr. Aravindhan Veerapandiyan
Dr. Diana Zuckerman

Contents

Call to Order & Welcome

Dr. Ahsan: Good morning, everyone. I'd like to welcome you to the 74th Meeting of the Cellular Tissue and Gene Therapies Advisory Committee on May 12th, 2023. I am Taby Ahsan. I'll be chairing today's meeting. And the topic is: we will be discussing in an open session the Biologics License Application 125781 from Sarepta Therapeutics for delandistrogene moxeparvovec, SRP-9001. The applicant has requested an indication for the treatment of ambulatory patients with Duchenne Muscular Dystrophy with a confirmed mutation in the DMD gene.

I'd like to remind all the committee members to use the raise your hand feature to turn your camera on when you have a question or comment to make, and then I can call upon you to speak. So right now I would like to start with introducing Marie DeGregorio, the Designated Federal Officer for today's meeting. She'll be making some administrative announcements, taking roll call, and reading the conflict-of-interest statement.

Ms. DeGregorio: Great. Thank you, Dr. Ahsan. Good morning, everyone. This is Marie DeGregorio, and it is my great honor to serve as the Designated Federal Officer, i.e., DFO, for today's 74th Cellular Tissue and Gene Therapies Advisory Committee meeting. On behalf of the FDA Center for Biologics Evaluation and Research and the committee, I'm happy to welcome everyone for today's virtual meeting. Today, the committee will meet in open session to discuss the Biologics License Application, BLA, 125781 from Sarepta Therapeutics, Incorporated. Today's meeting and the topic were announced in the Federal Register Notice that was published on April 11th, 2023. Next slide.

At this time, I would like to acknowledge and thank my Division Director in the Division of Scientific Advisors and Consultants, DSAC, Dr. Prabhakara Atreya, for her excellent

leadership, and my team, whose contributions have been critical for preparing today's meeting. This includes Ms. Christina Vert, who is backup DFO for this meeting, and who will be conducting the committee voting later today. I would also like to thank Ms. Tonica Burke and Ms. Joanne Lipkind, who have provided excellent administrative support in preparing for this meeting. Next slide please.

I would now like to acknowledge CBER leadership, including Dr. Peter Marks, Director of CBER, and Dr. Celia Witten, Deputy Director for CBER, as well as Acting Director in the Office of Therapeutic Products, OTP and many other OTP staff who will be serving as speakers and presenters during the course of the day, as indicated on the agenda. On behalf of DSAC, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes working to ensure that today's virtual meeting will also be a successful one. I also thank all other FDA staff contributing to today's meeting discussion, some of whom are present at the moment, and others who may be joining the meeting at other times. Next slide, please.

Please direct any press or media questions for today's meeting to FDA's Office of Media Affairs at fdaoma@fda.hhs.gov. I would also like to thank the audio-visual team, Christopher Swett, Devonte Stephenson, and Derek Bonner in facilitating the meeting today. The transcriptionists for today's meeting are Ms. Debbie Dellacroce and Ms. Catherine Diaz. Next slide please.

We will begin today's meeting by taking a formal roll call for the committee members and temporary voting members. When it is your turn, please make sure your video camera is on and you are unmuted. Then state your first and last name, organization, expertise, or role. And when finished, you can turn your camera off so we may proceed to the next person.

Okay. So please see the member roster or slides, in which we'll begin with the chair. Dr. Ahsan, please go ahead and introduce yourself.

Committee Introductions

Dr. Ahsan: Good morning. I'm Taby Ahsan. I am at City of Hope. I am the VP of Cell and Gene Therapy Operations. My expertise has long been in stem cells and regenerative medicine, as well as tissue engineering. And the last five or so years have been focused on immunotherapies for CAR T and rNK.

Ms. DeGregorio: Thank you, Dr. Ahsan. We have a standing member of the committee, who is a non-voting member, Dr. Eric Crombez.

Dr. Crombez: Thank you. And good morning. I'm Eric Crombez. I'm Chief Medical Officer at Ultragenyx. Biochemical geneticist by training. Been working in the field of gene therapy for the past nine years, and I'll be serving as the industry representative for today's meeting.

Ms. DeGregorio: Okay. Thank you, Dr. Crombez. Dr. Donald Kohn.

Dr. Kohn: Hello. I'm a pediatric bone marrow transplant physician and a gene therapy investigator for 35 years at University of California Los Angeles.

Ms. DeGregorio: Great. Thank you, Dr. Cohn. Ms. Kathleen O'Sullivan-Fortin. Next slide, please.

Ms. O'Sullivan-Fortin: Hi, I'm Kathleen O'Sullivan-Fortin. I'm a co-founder and patient advocate at ALD Connect, a rare disease organization, and I am the acting consumer representative.

Ms. DeGregorio: Great. Thank you, Ms. O'Sullivan-Fortin. Next, we have Dr. Nirali Shah.

Dr. Shah: Hi, everybody. I'm Nirali Shah. I lead the hematologic malignancies program in the pediatric oncology branch of the intramural program of the NCI. My primary expertise is in

immune-based therapies that are genetically modified, including CAR T-cell based therapies, and in the care of children and young adults.

Ms. DeGregorio: Okay. Thank you, Dr. Shah. Next, we will do roll call of our temporary voting members. Starting with Dr. Anthony Amato.

Dr. Amato: Thank you very much. I am Anthony Amato. I am Professor of Neurology at Harvard Medical School and the Chief of the Neuromuscular Division at the Brigham Women's Hospital.

Ms. DeGregorio: Okay, thank you, Dr. Amato. Dr. Caleb Alexander.

Dr. Alexander:Good morning. Caleb Alexander, Professor of Medicine and Epidemiology at Hopkins. I'm a pharmacoepidemiologist. I lead an FDA-funded Center of Excellence in Regulatory Science and Innovation at Johns Hopkins. And former chair and member of the Peripheral and Central Nervous System Advisory Committee.

Ms. DeGregorio: Okay, great. Thank you, Dr. Alexander. Next, Mr. Christopher "Buddy" Cassidy.

Mr. Cassidy: Hi, Christopher Cassidy. Buddy, please. I am 33 years old. I have Duchenne Muscular Dystrophy, and I am the patient representative today. My normal area of expertise, I'm working on a PhD at UC Irvine, albeit in English literature. Thank you.

Ms. DeGregorio: Great. Thank you, Mr. Cassidy. Next, Dr. John "Jay" Chiorini.

Dr. Chiorini: Hi, I'm Jay Chiorini. I'm a senior investigator and associate clinical, or scientific, director at NIDCR at NIH. My expertise is in AV biology and its use in gene therapy applications.

Ms. DeGregorio: Great. Thank you Dr. Chiorini. Dr. Susan Ellenberg.

Dr. Ellenberg: Good morning. I am a professor emerita of biostatistics, epidemiology and informatics at the University of Pennsylvania Pearlman School of Medicine. And my main area of expertise and interest is the design and analysis of clinical trials.

Ms. DeGregorio: Okay. Thank you Dr. Ellenberg. Dr. Richard Kryscio.

Dr. Kryscio: Good morning. It's Richard Kryscio at the University of Kentucky. I'm a professor of statistics and biostatistics and do a lot of work in the area of neurodegenerative diseases.

Ms. DeGregorio: Okay. Thank you Dr. Kryscio. Dr. Lisa Lee.

Dr. Lee: Good morning. I'm Lisa M. Lee. I serve currently as Associate Vice President for Research Integrity and compliance at Virginia Tech. I'm formerly the executive director of the Presidential Bioethics Commission, and I am a professor of public health. I'm an epidemiologist and a bioethicist by training, and I am here as the Bioethicist Temporary Voting Member.

Ms. DeGregorio: Okay, great. Thank you, Dr. Lee. Dr. Steven Pavlakis.

Dr. Pavlakis: Hi, this is Steve Pavlakis. I'm calling from Brooklyn, and I'm a professor of neurology and a pediatric neurologist. And it's nice to be here.

Ms. DeGregorio: Great. Thank you, Dr. Pavlakis. Dr. Rajiv R. Ratan.

Dr. Ratan: Good morning, everyone. I'm Raj Ratan. I'm a professor of neurology and neuroscience at Weill Cornell Medicine. My clinical specialty is neurorehabilitation. I also direct the Burke Neurological Institute. We're focused on brain repair. And I have a scientific interest in the transcriptional regulation of survival and repair and neurons.

Ms. DeGregorio: Thank you, Dr. Ratan. Dr. Raymond Roos.

Dr. Roos: I'm Raymond Roos. I'm professor in the Department of Neurology at the University of Chicago, and also appointments in microbiology and immunology. I have an expertise in Coronaviruses and also some experience in gene therapy. Thank you.

Ms. DeGregorio: Thank you, Dr. Roos. Okay. Great. Thank you everyone. There are a total of 15 participants, 14 voting members, and one non-voting member. Thank you again for your introductions. Before I begin with reading the conflict-of-interest statement, I would just like to briefly mention a few housekeeping items related to today's virtual meeting format for members, speakers, FDA staff, and anyone else joining us in the Zoom room. Please keep yourself on mute unless you are speaking to minimize feedback. If you have raised your hand using the raised your hand feature and are called upon to speak by the chair, Dr. Ahsan, please turn on your camera, unmute, state your name, and speak slowly and clearly so that your comments are accurately recorded for transcription and captioning.

Conflict-of-Interest Statement

Ms. DeGregorio: I'll now proceed with reading of the conflict-of-interest statement for the public record. Thank you. The Food and Drug Administration, FDA, is convening virtually May 12th, 2023, for the 74th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Tabassum, Taby, Ahsan is serving as the acting chair for today's meeting.

The CTGTAC committee will meet in open session to discuss the Biologics License Application B12581 from Sarepta Therapeutics, Incorporated, for delandistrogene moxeparvovec, SRP-9001. The applicant has requested an indication for the treatment of ambulatory patients with muscular Duchenne Muscular Dystrophy, DMD, with a confirmed mutation in the DMD gene. The topic is determined to be a particular matter involving a specific party, PMISP.

With the exception of the industry representative member, all standing and temporary voting members of CTGTAC are appointed as special government employees or

regular government 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 include, but are not limited to, 18 US Section 208, which is being provided to participants in today's meeting and to the public.

Related to the discussions at this meeting, all members, regular government employee and special government employee consultants 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 spouse or minor children, and for the purposes of 18 US Code Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research, and development agreements, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation.

FDA has determined that all members of this advisory committee, both regular and temporary members, are in compliance with federal ethics and conflict-of-interest laws. Under 18 US Code Section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflict of interests when it is determined that the agency's need for a special government employee's services outweighs the potential for a conflict-of-interest created by the financial interest involved, or when the interest of a regular government 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.

Based on today's agenda and all financial interest reported by committee members and consultants, no conflict-of-interest waivers were issued under 18 US Code Section 208 in connection with this meeting. We have the following consultants serving as temporary voting

members: Dr. Caleb Alexander, Dr. Anthony Amato, Dr. John "Jay" Chiorini, Dr. Susan Ellenberg, Dr. Richard Kryscio, Dr. Lisa Lee, Dr. Steven Pavlakis, Dr. Rajiv Ratan, and Dr. Raymond Roos.

We have one patient representative, Mr. Christopher "Buddy" Cassidy, who is serving in the meeting as a temporary voting member and also as a patient representative to bring patient's perspective to the committee's attention due to his personal experience with Duchenne Muscular Dystrophy. Ms. Kathleen O'Sullivan-Fortin is serving as the consumer representative for this committee meeting. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee. Dr. Eric Crombez of Ultragenyx Gene Therapy will serve as the industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Industry representatives act on behalf of all related industry and bring general industry perspective to the committee. Industry representatives on this committee are not screened, do not participate in any closed sessions, if held, and do not have voting privileges.

FDA encourages all meeting participants, including Open Public Hearing speakers, to advise the committee of any financial relationships that they may have with any affected firms, its products, and, if known, its direct competitors. We would like to remind members, consultants, and participants 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 inform the DFO and exclude themselves from such involvement, and their exclusion will be noted for the record.

This concludes my reading of the conflict-of-interest statement for the public record. At this time, I would like to hand over the meeting to tab Dr. Taby Ahsan. Thank you.

Dr. Ahsan: Great. Thank you, Marie, for guiding us through those administrative activities. I want to reiterate my thanks to the committee and all the participants for taking their time out to discuss this important topic today. So we're now going to pivot to the presentation portion of this meeting. We're going to start with the FDA opening remarks, and so I'd like to introduce Dr. Celia Witten, who's the. Deputy Director of CBER and Acting Director of the Office of Therapeutic Products. So, Dr. Witten, if you could unmute yourself and go on camera, please.

FDA Opening Remarks — Dr. Celia Witten

Dr. Witten: Thank you. Good morning and welcome on behalf of FDA, the Center for Biologics Evaluation and Research, and the Office of Therapeutic Products, or OTP. During this meeting today, the committee will be asked to consider the Biologics License Application from Sarepta for accelerated approval for treatment of ambulatory patients with Duchenne Muscular Dystrophy with a confirmed mutation in the DMD gene. We are asking this committee to consider critical questions related to safety and effectiveness. These questions relate to the adequacy of the surrogate endpoint of expression of Sarepta's micro-dystrophin to predict clinical benefit, your clinical interpretation of the data as it relates to the appropriate target population for the product, and your assessment of risk benefit. The completion of a confirmatory study is of importance for clinicians and patients as well as for FDA. And we're asking for your comments in that area, as well.

Muscular dystrophy is a serious condition with an urgent medical need. We appreciate the efforts of the sponsor and the scientists and others who have brought the product to this stage of development. We're grateful for the efforts of patients and caregivers who participated in the

clinical trials that will be discussed today. We'd like to thank the participants in today's Open Public Hearing, both those who were able to participate today and those who have submitted comments to the docket. We will carefully consider the written comments we receive as well as the comments from those presenting today. I'd like to particularly thank the FDA review team and the advisory committee staff who've worked hard to prepare for today's meeting and to thank the advisory committee members for your willingness to participate.

Because this application is for accelerated approval, before we hear the presentation from FDA introducing the day's agenda, I would like to briefly review our regulations on accelerated approval. Next slide. I'm going to review the standards for accelerated approval and then talk briefly about confirmatory trials. Next slide. So in order for a drug to be approved, the sponsor needs to provide substantial evidence of effectiveness, which I will talk about in a moment. The sponsor also must provide a demonstration that the benefit of the drug outweighs the risk for the intended use. This standard applies to biologic products as well, such as the product we're discussing today. It's important to note the definition of substantial evidence of effectiveness. And I highlight the requirement for adequate and well controlled investigations, on the basis of which it could fairly and responsibly be concluded by experts that the drug will have the effective reports or is represented to have under the conditions of use, recommended, or suggested in labeling. Next slide.

So the use of accelerated approval to support product approval was codified under FDASIA. Accelerated approval is for a serious or life-threatening disease or condition on the basis of an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. The Act also provides the potential for accelerated approval based on

intermediate clinical endpoints. But for the purpose of today's discussion, we'll focus on surrogate endpoints. Next slide.

Most of you probably know what a surrogate endpoint is. It can be a laboratory measurement, a radiographic image, physical sign, or other measure that is not itself a direct measure of clinical benefit but is expected to predict clinical benefit. The data supporting a conclusion that a surrogate endpoint is able to predict a clinical benefit may be based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence. The strength of the evidence distinguishes a validated surrogate from a reasonably likely surrogate. A validated surrogate is a marker that is known to predict clinical benefit, while a reasonably likely surrogate is a marker that is reasonably likely to predict clinical benefit. In this case, you'll be asked whether, based on the strength of the evidence provided by the sponsor, the surrogate endpoint proposed is reasonably likely to predict a benefit. Next slide.

To complete the discussion of validated surrogate versus reasonably likely surrogate, this slide shows the two pathways for approval. Any approval requires substantial evidence of effectiveness, as defined in the earlier slide I showed. If a clinical endpoint or a validated surrogate were measured in the trials, that approval would be a traditional approval. If the approval is based on measurement of a reasonably likely surrogate or intermediate clinical endpoint, approval would be via the accelerated approval pathway. Next slide.

Why is accelerated approval a valuable option? For serious and life-threatening diseases without adequate therapies, there's an urgency to get effective and safe therapeutics to patients. In some cases, there may be enough understanding of the disease that a surrogate marker, a surrogate endpoint, can be identified. This could create an opportunity for a more streamlined development program by enabling trials that may be shorter and, in certain cases,

smaller, and the result for patients can be greater and earlier access as the study is being conducted to confirm the benefit. There's a tradeoff between smarter, faster drug development and greater uncertainty as to whether the reasonably likely surrogate does indeed predict clinical benefit. Next slide.

The main challenge is to identify a surrogate for which there is sufficient evidence that it's reasonably likely to predict a clinical benefit. This requires a sufficient understanding of disease pathogenesis. Many animal models have limitations in the ability to support use of a surrogate marker. Epidemiologic data may demonstrate a relationship between a surrogate and disease outcome, but evidence is needed that the change in the surrogate correlates with the change in clinical status. Next slide.

Lastly, I want to say a few words about confirmatory trials. If a product is approved under accelerated approval, post-market trials are routinely required to verify and describe the drug's clinical benefit. The goal of the clinical trial is to address the uncertainty of the surrogate endpoint’s relation to clinical benefit. The expectation is that some trials will not confirm clinical benefit. Once a drug is on the market, if confirmatory trials are not ongoing at the time of approval, there can be challenges in conducting the trials needed to confirm clinical benefit. Although I'll just mention that in the case of Sarepta, there is an ongoing trial at this time and a discussion question on this topic. Next slide.

I just want to acknowledge all the people who contributed to this presentation. And last slide. I'd like to thank you for your attention. We have a few minutes for questions from the advisory committee and then I'll turn it over to Marie DeGregorio. Thank you.

Q & A

Dr. Ahsan: Great. Thank you, Dr. Witten, for your explanation of the accelerated approval process and requirements. Are there any questions from the committee members regarding this aspect and this presentation? Trying to see the hands. Dr. Steven Pavlakis, would you like to unmute yourself and go on camera?

Dr. Pavlakis: Yeah. I just wanted to ask one question. If it's approved and there's a trial going on, what happens if the trial, the clinical trial, fails, and we've approved the medication or the whatever it is? Is it back, is there a re-review?

Dr. Witten: Well, certainly the results of such trial would get re-reviewed, or would get reviewed by the staff here. If you mean re-reviewed by an advisory committee, not necessarily. It would depend on whether we had questions. And as to what would happen after that, I think that'd be a matter for discussion with the sponsor. We do have the authority to remove products from the market. I mean, there's been considerable discussion about that in the public, but. Also sometimes the sponsors will withdraw the product. So the goal would be if a product, if a trial fails, we would look at it and see what our interpretation would mean, but we'd expect to remove it from the market.

Dr. Ahsan: Great. Thank you for that explanation, Dr. Witten. Are there any other questions from the committee on this topic? Please indicate so by raising your hand through the Zoom mechanism. Dr. Raymond Roos, would you like to unmute yourself and go on camera please?

Dr. Roos: Yes, thanks. I just wondered when the other study was going to be available. And maybe just to clarify what the other study is as far as treatment versus controls, the number of individuals.

Dr. Witten: That's a great question, Dr. Roos, but I think that's a question to ask the sponsor following their presentation. This discussion that we have right now is not specifically about the application under review, just accelerated approval in general. But that's a very good question, and hopefully it'll get clarified during the course of the morning's discussions.

Dr. Ahsan: Dr. Roos, we'll make sure that we get to that bit when, when the sponsor is presenting. Thank you. Any other questions? Oh Dr. Anthony Amato, please.

Dr. Amato: Yeah, I'm just going to be interested, again, in the confirmatory trial, but how you're going to be able to do a confirmatory trial if the drug is approved. And so I'm going to want to hear. Because from the ethics point of view, is it's not how you're going to recruit patients to the trial if they're able to get the drug, but the subjects who are already participating, What's, you're going to have to, from an ethics point of view on, I'm speaking of this being on the ethics board at Harvard for 17 years, you're going to have to inform them that it's approved. And so are you, are they going to allow, are they going to notify the subjects? And allow them to be un-randomized so they can get the drug that's approved? So I'm just putting this forward that I'm going to want to hear about this. Because what's going to happen if it's approved and there is not going to be a confirmatory trial because no one's going to want to participate, and the subjects that are already participating and are getting placebo are going to be want to be unblinded to get the drug if it's available.

Dr. Witten: So again, that is certainly, you know, important questions that you're asking, but I think those would be better addressed during the sponsors or during the committee discussion. So thank you for that comment.

Dr. Ahsan: Again, Dr. Amato, we'll make sure that we get to that that bit of information to inform your question. I think at this point, the questions are really about the mechanism of

accelerated approval in general and not this particular BLA. Are there any other questions for Dr. Witten about the concepts, the standards, the expectations for accelerated approval? Okay. I think with that, thank you very much, Dr. Witten, for clarifying that route of approval so that we can better understand the matter at hand today.

Dr. Witten: Thank you.

Dr. Ahsan: So I think we'll move on. Then we have, now the FDA will present an overview of the BLA that's being submitted. And this will be done by Dr. Rosa Sherafat-Kazemzadeh, who's the Clinical Team Lead in the Office of Clinical Evaluation, Division of Clinical Evaluation and General Medicine at OTP, CBER. If you could unmute yourself and get on camera, that would be much appreciated.

FDA Overview of BLA 125781, Application for Accelerated Approval of delandistrogene moxeparvovec (SRP-9001) — Dr. Rosa Sherafat

Dr. Sherafat: Thank you, Dr. A. Good morning. I'm Rosa Sherafat, Clinical Team Lead in the Office of Therapeutic Products in FDA's CBER, Center for Biologics Evaluation and Research. On behalf of the BLA review team, I would like to thank the advisory committee members and the Sarepta Therapeutics team and all the public attendees tuning in for today's advisory committee discussions, especially the patients with Duchenne Muscular Dystrophy and their caregivers and the clinicians who have provided written comments and who will be participating in the Open Public Hearing this afternoon. Next slide, please.

This morning, I will present an introductory overview of the BLA on their discussion today, starting with some brief background on Duchenne Muscular Dystrophy, or DMD, and the unmet medical need for this condition. I will then discuss FDA's regulatory standards and regulatory flexibility regarding approval of safe and effective treatments for rare

and serious diseases with unmet medical need such as DMD. Then, I will briefly describe the product SRP-9001 and give a short summary of the clinical studies to support this biologic license application. I will end with an overview of today's agenda and the discussion topics and voting question for the advisory committee. Next slide, please.

The proposed indication for this product is treatment of ambulatory patients with Duchenne muscular dystrophy with a confirmed mutation in the DMD gene. DMD is a serious, progressive, and life-threatening genetic disorder for which there is a profound unmet medical need. Mutations in the DMD gene affect the dystrophin protein, which is critical for the structure and function of muscle cells. Without dystrophin the muscle cell membrane is easily damaged by normal day-to-day activity, which creates micro tears in the membrane, leading to muscle degeneration, inflammation, and fibrosis. The DMD gene is located on the X chromosome, and the disease affects approximately 1 in 3,300 boys. It often presents in early childhood with increasing muscle weakness in the legs, followed by weakness of the arms as well as the respiratory and cardiac muscles. Patients experience worsening movement, orthopedic complications, and ultimately respiratory and cardiac failure. Although disease progression varies in individual patients, patients typically lose the ability to walk by approximately 12 years of age. Sadly, DMD still leads to loss of life by early adulthood, often due to respiratory com complications and cardiomyopathy. Next slide, please.

Despite incremental advances in the standard of care which have added nearly 10 years to the average lifespan of the affected patients, there is an urgent need for better treatments for DMD patients. The current standard of care involves long-term treatment with corticosteroids, which provides only a modest benefit on slowing disease progression and has deleterious effects on these children's growth, bone density, and other aspects of their general health. In recent

years, four exon-skipping drugs have been approved under the accelerated approval pathway to treat patients with certain types of DMD gene mutations. However, the clinical benefits of these exon-skipping drugs still remains to be verified by confirmatory clinical trials. It is estimated that each year for every 1,000 patients with DMD who are in their early twenties, approximately 86 patients will lose their lives annually. Unfortunately, the mortality rate further increases with age, such that the average life expectancy of affected individuals is significantly shortened. It is critical to pursue novel therapies such as safe and effective gene therapy for these patients. Next slide, please.

We would like to emphasize that all of us in the Office of Therapeutic Products recognize and are committed to FDA's mission of protecting and promoting public health by ensuring the safety, efficacy, and security of human biological products. Through our thorough evidence-based review of all data and information, we must determine that each to-be-marketed product is safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling. Next slide please.

As Dr. Witten pointed out in her presentation, the regulatory requirements for approval of all new drugs and biologics are substantial evidence of effectiveness and sufficient evidence of safety, which should be obtained from adequate and well-controlled clinical studies. However, we understand that in certain circumstances, such as in drug development for rare diseases, some aspects of drug development that are feasible for common diseases may not be feasible for rare disease. Therefore, FDA regulations allow flexibility for such situation as development of products that treat rare and serious disorders such as DMD. Next slide, please.

Now I will provide a brief description of SRP-9001, the product in this BLA submission. SRP-9001 is an adeno-associated viral vector-based gene therapy that encodes an

engineered protein, which will be we will be referring to as Sarepta's micro-dystrophin. SRP-9001 is prepared as a suspension containing 1.33 times 10 to the 13 vector genomes per mL. It is administered as a single intravenous infusion. The proposed dose is 1.33 times 10 to the 14 vector genomes per kilogram of body weight. Patients weighing 70 kilograms or more would receive a dose of 9.31 times 10 to the 15 vector genomes. The applicant has proposed that expression of Sarepta's Micro-dystrophin protein serves as a surrogate endpoint, reasonably likely to predict clinical benefit of SRP-9001 for the proposed indication. Next slide, please.

It is important to note that dystrophin is the largest known gene in the human genome, with a coded sequence of approximately 14 kilobase pairs, so it cannot be packaged into AV vector, which has a carrying capacity of approximately 4.7 kilobase pairs. To fit in the AV vector, the transgene in SRP-9001 has been engineered to express selected parts of the normal dystrophin gene which are considered important. The transgene in SRP-9001 is about a third of the size of the coded sequence in the dystrophin gene. As illustrated in this slide, the dystrophin protein expressed by SRP-9001 is a shortened version of the normal dystrophin protein. My colleagues will provide further details regarding Sarepta's microdystrophin in the presentation in the afternoon session. Next slide please.

Throughout the product's life cycle and during the IND review, the FDA review team has had numerous interactions with the applicant. The product has been granted orphan disease designation, as well as rare pediatric disease designation and fast track designation. The BLA was submitted on September 28th, 2022, and was granted an eight-month priority review designation. Next slide please.

This slide provides an overview of the three clinical studies described in this BLA. The two earlier studies shown on the left and middle of the slide in blue, Study 101 and

Study 102 used SRP-9001 manufactured by process A. The later study, Study 103, shown in purple, used SRP-9001 manufactured by process B, which is the process intended for producing SRP-9001 for marketing. The transgene is the same for process A SRP-9001 and process B, but as my colleagues will discuss this afternoon, process B SRP-9001 is of lower purity.

Study 101 was the first in human tests of SRP-9001. It had an open label design and enrolled four patients, aged four to seven years, and the primary objective of the study was assessment of safety of the product. Preliminary efficacy was evaluated by measuring change in expression of Sarepta's microdystrophin from baseline to day 90, and also by measuring functional endpoints such as the 100-meter walk test. So far, follow up data for approximately five years post treatment have been collected for these four boys.

Study 102 was a crossover, three-part study involving 41 patients, aged 4 to 7 years old. Only the first two parts of this study are shown on this slide. In part one, patients were randomized one-to-one in a double-blind and placebo-controlled design to receive either SRP-9001 or placebo. Randomization was stratified by age at baseline into two groups, four to five years old versus six to seven years old. Efficacy was assessed using a functional assessment scale called the NorthStar Ambulatory Assessment, or NSAA, which is a multi-scale clinical outcome measure of lower limb function and is widely used in DMD clinical trials. Change in the NSAA total score evaluated from baseline to about one year, or 48 weeks. Efficacy was also assessed by expression of Sarepta's microdystrophin at 12 weeks after infusion. Notably at the start of part two of this study, following crossover do crossover of the SRP-9001 and placebo arms, the patients, caregivers, and evaluators were aware that by that point, all the patients had received SRP-9001. So part two of Study 102 essentially had an open label design. Data from parts one

and two of the study have been submitted in this BLA. Part three of Study 102 is an ongoing open label follow up of the study participants.

Study 103 was intended as a bridging study. It used process B SRP-9001 and had an open label design. The primary objective was measuring expression of Sarepta's microdystrophin at week 12. Four cohorts of boys were enrolled based on their age and ambulatory status. Data from cohort one, consisting of 20 ambulatory patients aged four to seven years, were submitted in this BLA in support of effectiveness of SRP-9001. Data from all four cohorts as well as from study 101 and 102 contributed to the exposure analysis set for evaluation of safety of SRP-9001. Those data will be discussed in the FDA presentation this afternoon. Next slide please.

As outlined in Dr. Witten's presentation the review team has identified several challenging issues and concerns during review of this BLA. Therefore, we look forward to the presentations, the Open Public Hearing session, and the discussions by the members of the advisory committee. In the afternoon session after FDA's presentation, we will seek the advisory committee's input on the following topics and questions. Next slide. Please, please discuss the strengths and limitations of the available data in support of the use of Sarepta's Microdystrophin as a surrogate endpoint reasonably likely to predict clinical benefit in this patient population. Next slide please.

Part one of Study 102 was the only randomized double-blind, placebo-controlled clinical study for which data currently are available. This study did not demonstrate a statistically significant effect of treatment with SRP-9001 versus placebo on the primary clinical outcome measure change in the NSAA total score from baseline to year one. Exploratory subgroup analyses suggests that the SRP-9001 group may have had a better NSAA outcome compared to

the placebo group among ambulatory patients between four to less than six years of age, but not among ambulatory patients between six to less than 8 years of age. The clinical significance of these findings.

Question three focuses on the potential benefits, risks, and uncertainties associated with SRP-9001 for the proposed patient population. Next slide, please.

The applicant is conducting Study 301, a phase three randomized, double-blind, placebo-controlled 52-week study. Part one of this study is currently underway. Discussion topic four is about the potential impact of accelerated approval of 9001 on completion of part one of the applicant's phase three study. Please note that the last patient's last clinical visit for part one, is expected to be completed by the end of September of this year, and the top line data is expected to be available by late in the fourth quarter of 2023. Next slide please.

Lastly, please discuss and vote on the overall benefit risk considerations of accelerated approval of SRP-9001 for the treatment of ambulatory patients with DMD. Next slide please.

So this concludes my presentation. Thank you for your time and attention, and we are looking forward to an insightful discussion today. I will now turn it over to Dr. Ahsan. Thank you.

Q & A

Dr. Ahsan: Great. Thank you so much, Dr. Sherafat. So just so that everyone is familiar, now we have opportunity to ask questions of Dr. Sherafat, but I do want to bring to everyone's attention that each discussion question or point that she mentioned will have its opportunity to be discussed in an isolated fashion in the afternoon. So right now what we're looking for are questions for Dr. Sherafat about the overview of the BLA application. And if you could indicate

that you have questions by raising your hand, that would be much appreciated. Great. Dr. Alexander, could you unmute yourself and go on camera please?

Dr. Alexander:Yeah. I'm Caleb Alexander, Hopkins. Tell me if these are better. held off 'till later. So one has to do with the regulatory history, and we got a nice table summarizing interactions between the company and FDA. And the NIH have a second about the manufacturing processes. I know we have a 75-minute presentation by the FDA this afternoon, so are either of both of those fair game now, or should I pick one, or should I hold off on both of them until the afternoon presentation?

Dr. Ahsan: You know, we have a bit of time, so why don't you go ahead and state your questions specifically, and then Dr. Sherafat can either punt it for later in the afternoon or address it now.

Dr. Alexander:Okay, so the first is the manufacturing processes, and you mentioned this, and I'm wondering that agree to which the FDA is confident or concerned regarding pooled analyses across the two different manufacturing processes. You know, on the one hand in figure five of the FDA briefing, which doesn't have a y axis, you know, it suggests that there could be important differences in these processes. But in fact Figure 10 suggests only modest differences in expression, I think, across the groups. And, you know, some of the adverse effects like hepatotoxicity, I believe, were similar across the groups. So I'm just wondering if you can speak to the degree to which we should be you know concerned or reassured and regarding the fact that there are these two different processes taking place. Thank you.

Dr. Witten: I wonder if I can comment here. This is Celia Witten.

Dr. Ahsan: Please go ahead, Dr. Witten.

Dr. Witten: Yeah, I think these kind of questions — thanks for asking that. That's a very good question, and I think it's good insight that may asking us when these should be addressed, but I think these questions about specific review issues and what, you know, what the evidence is, and what the sponsor, you know, might be presenting and discussing, or questions for FDA would be better in those two sessions and just if there's some specific questions about the agenda now. But I encourage these questions for later. They're very good questions.

Dr. Alexander:All right. Well, I have them written down and I'll hold my time, but I'll hold on off on the other one as well. Thank you.

Dr. Witten: Thank you.

Dr. Alexander:Perfect. We'll get to those for sure. Thank you, Dr. Witten, for clarifying the Q and A purpose at this point. So, any other questions? I guess the topic is really about the agenda for today and if there are any questions about the agenda. So I don't see any, any raised hands, just verifying — nope, there is one. Oh yes, I see one. Although I cannot see the name. I'm sorry. It's Buddy Cassidy. Okay, great. Buddy Cassidy, if you would like to unmute yourself and go on camera to ask your question, that would be wonderful. Buddy, did you want to go ahead? Okay, great.

Mr. Cassidy: Sorry. Okay, my apologies. It takes me a minute to move my hands. But I did have a question about the advisory committee meeting itself today. So I was wondering that, in November 22 the FDA accepted Sarepta's Biologics License Application seeking accelerated approval, and they did a review related to this process as it already had occurred, the mid-cycle review. And the FDA did not flag any significant safety issues between November and as of the end of February. So after the mid-cycle review in February, there wasn't going to be an advisory committee meeting. But then about two weeks later, mid-March, the FDA had reversed cores.

And so I'm just curious as to what happened in those two weeks that led to this reevaluation and reversal of the decision on the Ad Com. Did a new piece of information emerge, or is there a particular reason for concern? I'm just curious.

Dr. Marks: This is Peter Marks. I'm happy to take this one. So in the process of this review, it's not so much that anything new developed with the application, but that when management review took place, it became apparent that this would benefit from an open public discussion. So I don't think there was anything substantial that changed internally. It was that a management decision was made that this would benefit from public discussion as an important gene therapy for an indication under development.

Mr. Cassidy: Thank you.

Dr. Ahsan: Great. Thank you, Dr. Marks, for clarifying that position. Any other questions? And thank you, Buddy, for that question. Any other questions at this point in time? Double checking for any raised hands. I don't see any. So Marie, I think we should head to our break a little bit early. I think that's next on the agenda. Would you suggest that we keep the duration 10 minutes, or that we return at 10:15?

Ms. DeGregorio: That is a good question. I think we could keep it at 10:15 for now.

Dr. Ahsan: Great. So that would be wonderful. We have a little break now. If everyone can return back to their computers in time for 10:15, that would be when we move forward with the sponsor presentation.

Dr. Ahsan: Thank you everyone for returning from the break. We have a lot to cover today, so let's keep moving on. Next are the presentations from Sarepta Therapeutics. There'll be several speakers, so I will introduce the first speaker who will then pass it along. So first we'll be Mr.

Patrick O'Malley, who is the Vice President of Regulatory Affairs at Sarepta Therapeutics. Mr. O'Malley, if you can turn on your camera and go on off mute.

Sponsor Presentation — Sarepta Therapeutics, Inc.

Introduction — Patrick O'Malley

Mr. O'Malley: Good morning. I'm Patrick O'Malley, Vice President of Regulatory Affairs at Sarepta Therapeutics. We want to thank the FDA, the chair, and members of the committee for the opportunity to discuss our new gene therapy, SRP-9001, for the treatment of Duchenne Muscular Dystrophy. We also want to give a special thank you to the patients who are participating in our clinical trials and their families, and to all those in the DMD community watching today. You, more than any of us, know the devastation of DMD and the urgent need for treatments, and you are the reason we are here today.

The proposed indication is for the treatment of ambulatory patients with DMD with a current confirmed mutation in the DMD gene, and a contraindication in patients with any deletion fully includes exons nine through thirteen. Our presentation will include supporting that an age-based limitation to this therapy is not recommended. 9001 is administered intravenously as a one-time infusion, the dose of 1.33 times 10 to the 14 vector genomes per kilogram of body weight. It is not recommended in patients with preexisting antibodies to the AAV RH 74 vector at titers greater than or equal to one to 400.

Our BLA was submitted using the accelerated approval pathway. Let me briefly walk through how 9001 meets each of the criteria for accelerated approval. There is broad alignment with FDA that the first two criteria are met. DMD is a devastating condition with high unmet need. Available therapies and standard of care have recognized limitations. The third criterion is the most important to today's discussion. Does 9001 demonstrate an effect on an

endpoint reasonably likely to predict clinical benefit? Throughout this presentation, we will show you how the 9001 dystrophin protein meets this criteria based on a rational product design, nonclinical and clinical empirical data, and preliminary clinical functional effect data.

Finally, although not an official criterion for accelerated approval, we have a confirmatory study already underway that is fully enrolled. Study 301 is a global, double blind, randomized, placebo controlled confirmatory trial powered with 125 patients, ages four to seven years old. The data from previous studies were critical to informing the design of study 301. The primary endpoint is the change from baseline in North Star ambulatory assessment at 52 weeks. A well-recognized clinical endpoint for DMD supported by FDA guidance. The part one study report is expected early next year.

FDA has asked whether there is any risk to completion of this confirmatory trial if accelerated approval is granted. The answer is no. The study was fully enrolled in September of 2022, which was purposely timed to support the accelerated approval criteria. Approximately four months post-approval, all US patients will complete study part one and all will be treated. Patients in this study are guaranteed treatment. It is highly unlikely that any patient would drop out after approval to seek uncertain access to commercial product.

As described an FDA guidance, determining whether a biomarker is reasonably likely to predict clinical benefit is ultimately a matter of judgment based on the biological plausibility of the relationship between the disease, the endpoint, the desired effect, and the empirical evidence to support that relationship. With 9001, there is strong biological plausibility since DMD is a monogenic disease where low levels of residual or restored dystrophin have been shown to confer significant benefit. Functional, shortened dystrophin that conserve key protein

domains are observed in nature. A 9001 dystrophin is rationally designed based on these observations and decades of research.

The empirical evidence supporting the surrogacy of the expressed 9001 dystrophin is the effect data, which demonstrates transduction expression, localization, biological function, and a relationship with clinical functional effect. These two surrogacy pillars of biological plausibility and supporting empirical evidence will be the focus of this presentation. It's important to highlight that in the case of 9001, the express protein is the surrogate endpoint, but it is also the therapeutic agent, therefore, the foundational question for accelerated approval is whether 9001 dystrophin is adequately expressed and exhibits the biological function of endogenous dystrophin.

The clinical data that support accelerated approval BLA is from three ongoing studies. Study 101 is a four-patient open label safety and proof of concept study in ambulatory boys four to seven years old and is currently in its fifth year post-dosing. Study. 102 is a 41. Patient double-blind, randomized, placebo-controlled study in ambulatory boys, four to seven years old and is currently in the open label study part three. Study 103 is a 40 patient multi cohort open-label study in ambulatory and non-ambulatory patients with the primary data for the BLA coming from the 24- to seven-year-old ambulatory boys in cohort one.

We will also introduce use of external controls. These are propensity score weighted comparator pools established according to a pre-specified analysis plan. We understand that well-designed placebo controlled trials are the gold standard for con confirmation of efficacy. But in many cases, external controlled data can help contextualize and interpret preliminary study results. Here is our agenda for today's presentation. We also have a number of external experts with us today to help address your questions. All outside experts have been

compensated for their time and travel. Thank you, and I will now turn the presentation over to Dr. Jerry Mendell.

Disease Background and Unmet Need — Dr. Jerry Mendell

Dr. Mendell: Good morning. I'm Dr. Jerry Mendell, professor of pediatrics and neurology, and the current Peter's chair of research at Nationwide Children's Hospital. I've been working to improve the lives of boys with Duchenne muscular dystrophy for my entire career, beginning with my post-doctoral fellowship at NIH in 1969. I was the PI on the Prednisone clinical trial, and our report in the New England Journal of Medicine in 1989 was the entree to treatment for this disease. Glucocorticoids are now the standard of care. As PI in the development of gene therapy for spinal muscular atrophy, we achieved a major breakthrough. By establishing safe and successful delivery of high titer systemic AAV. This paved the way for treatment of DMD, another horrible disease with high unmet need.

DMD is a well-characterized, rare, fatal, X-linked, monogenic disease affecting one in 5,000 newborn males. Duchenne is caused by mutations of the DMD gene that results in reduced or absent functional dystrophin. Lack of dystrophin is the sole cause of DMD. It is a crucial protein that localizes to the muscle membrane, protecting the muscle fiber from damage during muscle contraction. Without functional dystrophin normal activity leads to muscle cell damage, inflammation, fibrosis, and irreparable muscle fiber loss. This is an irreversible process, and over time, muscle loss is cumulative, leading to muscle weakness and loss of limb function. Even a modest increase in dystrophin confers clinical benefit. The number of boys with DMD losing ambulation year by year is astounding. Almost 400 boys end up in a wheelchair each year, and the total number of non-ambulatory boys is over 2000 within five years. As for death, the median

survival is 28 years, but functional loss is severe by that age. Current therapy cannot save the lives of more than 400 per year, with more than 2200 deaths over five years.

Now let's focus on the early beginnings of the disease and stepwise progression to see where opportunities are greatest for intervention. Muscle damage from DMD begins in utero, resulting in highly elevated creatin kinase, or CK, at birth. From birth to age two, development is slowed, with delays in standing and walking. Large calf muscles are noticeable by age three to four. By age five to seven, stairs are difficult to navigate. By age 10 to 11 falling is frequently, and boys fatigue more easily. In the early teen years, ambulation is lost. In their late teens, upper limb function progressively declines, and ventilatory support is needed as respiratory muscles are compromised. Cardiac muscle fiber loss progresses until patients typically die of heart failure in their twenties.

Clinicians have learned that the North Star Ambulatory Assessment, NSAA, is a reliable measure of skeletal muscle function. The North Star is a global measure of both arm and leg function. Inclusive of 17 individual tests. Healthy, typically developing boys at a total score of 34 by four years of age, compared to boys with DMD who achieved a peak score of 26 at around six years. The beauty of the North Star is that the total composite score can be followed as the disease progresses. Functions are lost one at a time, and the North Star progressively declines as the disease gets worse. Changes in this score have an intrinsic meaningfulness, as the score is a literal count of ability to perform skills relevant to everyday life. For each function, scores are graded on a scale of three. Two is normal. One is loss of function, and zero means that the task cannot be performed.

On the next slide, we will see examples showing that each point carries significant weight. The examples of the North Star scoring are well illustrated on this slide. On the left, we

see a boy who gets up from the floor without difficulty and scores two. In the middle panel, we see partial impairment. He gets up slowly, pushes off his lower limbs and climbs up, climbs up his legs to maintain full posture. This is referred to as the goer sign. The North Star score for this patient is one. On the right, the score is zero. He uses his hands and arms to sit up and roll over. Then he manages to get up on one knee, but doesn't have the muscle strength or function to stand, so his legs collapse. Despite attempting many maneuvers, he is unable to stand. As you can see, even a one-point change in the North Star is clinically meaningful.

My message as a translational clinician with 50 years of experience in neuromuscular disease is that DMD is a devastating disease with compelling reasons to change current outcomes. DMD is progressive and universally fatal. There have been advances in the treatments. They are modest and mainly supportive. Corticosteroids delay time to loss of ambulation and other critical functions, but do not address the underlying cause of DMD and are associated with significant, debilitating, or life-threatening side effects. And RNA based molecular treatments restore lower levels of dystrophin in only a limited patient population with specific mutations. While life expectancy may be 28 years, for some the quality of life with loss of ambulation, gradual loss of arm function, and riding in wheelchairs pushed by parents or friends, and ultimately death due to cardiopulmonary failure is motivation for those of us in the medical community to do everything we can to change the outcome for these patients. We desperately need more treatment options.

Our understanding of the dystrophin gene and advancements in gene therapy provide the ability to address the underlying cause of DMD. This has the potential to stabilize disease progression with goals of preserving critical muscular functions, improving quality of

life, and extending survival. Thank you. And I will now turn the presentation over to Dr. Louise Rodino-Klapac.

Evidence for Surrogacy — Dr. Louise Rodino-Klapac

Dr. Rodino-Klapac: Thank you, Dr. Mendell. I'm Louise Rodino-Klapac, Executive Vice President, Head of R and D, and Chief Scientific Officer at Sarepta Therapeutics. Before joining Sarepta five years ago, I was head of a gene therapy research laboratory at Nationwide Children's Hospital, where I, along with Dr. Mendell, invented 9001, as well as a number of other gene therapy constructs using the same AAV RH 74 platform. Let provide some brief background on this discovery and 9001 specifically.

The journey to develop 9001 has been decades in the making. It involved the parallel understanding of the genetics of DMD and the development of AAV biology. The dystrophin gene was identified in 1986, followed by the critical discovery of shortened functional dystrophins in 1990. We began the nonclinical studies in 2005 for 9001, which led to the first human IV clinical studies starting in 2018.

So with that, let me provide some background on dystrophin. Dystrophin is a protein that lines the inside of the sarcolemma, the muscle cell's membrane, and it acts as a link between the extracellular matrix and the intracellular cytoskeleton. And the last panel on the right is a cross section of a muscle biopsy stained for dystrophin outlining the membrane of each fiber. Its purpose is to maintain the integrity of the sarcolemma, protecting against contraction induced injury to muscle fibers. Dystrophin is made up of 24 spectrin-like repeats, denoted by an R in this diagram, that can coil an uncoil like springs in response to mechanical strain, enabling dystrophin to act as a shock absorber, protecting the relatively fragile sarcolemma during muscular contractions.

Essential to the function of dystrophin are several key domains that act to localize dystrophin to the sarcolemma and anchor it to the structures within the cell. The actin binding domain binds to actin, which is part of the cytoskeleton. Spectrin like repeats R1 to R3 and R10 to R12 bind to the sarcolemma directly. The cystine rich domain binds to and drives assembly of the dystrophin associated protein complex, or DAPC, which links dystrophin to the extracellular matrix. And flexible hinge regions allow the protein to bend to make these important connections. Although dystrophin is known for being a large protein, interestingly, all of these spectrin-like repeats are not necessary for dystrophin to retain a high degree of function as long as these key anchor points are included. Essentially, you could have a long spring or a short spring, but it still functions as a shock absorber for the sarcolemma.

The realization that large portions of the dystrophin protein are less critical came from findings in natural history, specifically in Becker muscular dystrophy patients. Becker is a mild form of dystrophinopathy caused by in-frame deletions in the DMD gene, creating shortened, functional dystrophins. The first example was reported in a seminal paper by Professor Kay Davies in 1990. Her patient had a mild Becker muscular dystrophy at age 61. He could still walk short distances with assistance of a cane, have very little weakness in his arms, and could still drive a car. Genetic testing confirmed that this patient with Becker dystrophy was actually missing nearly half of the dystrophin protein, specifically a large stretch of spectrin-like repeats in the middle. This provided the first scientific evidence that this center section of the protein was not essential for dystrophin to retain a large degree of function.

Although missing a long stretch of the spectrin-like repeats in the middle, this patient's dystrophin retained the key domains discussed earlier, the actin binding domain and the cysteine rich region that drives assembly of the DAPC, and extracellular linkage R1 through R3

sarcolemma binding that supports the muscle cell membrane. Importantly, this patient did not retain the ENOS binding domain, which the FDA has highlighted as another potentially important region. This natural, profoundly shortened dystrophin enabled this patient to live a long, mostly ambulatory life rather than suffering the typical course of DMD disease.

It's important to note that this patient is not an isolated case, but part of an extensive pedigree with mild disease progression. While the case reported by Professor Davies is one of the most well-known examples of shortened dystrophins leading to a mild dystrophinopathy, numerous other examples of significantly shortened dystrophin with mild phenotypes have been identified. This slide shows five additional patients with different mutations. Notably, while all these individuals have different mutations, they all retain key functional domains of the actin binding domain, the cysteine rich domain, and some portion of the sarcolemma binding domain. These findings lay the groundwork for the development of shortened dystrophins, such as 9001 dystrophin, for use in AAV gene therapy.

The design of 9001 followed principles established by highly functional, shortened dystrophin found in patients with mild dystrophin as just described. In fact, we designed 9001, which is shown on the right, to retain these key elements. Years of nonclinical and clinical studies demonstrated that 9001 restores the same biological cascade as dystrophin.

Studies by other laboratories have independently confirmed the design principles underlying the design of 9001. This experiment directly measured the ability of mouse muscles to generate force. The MDX mouse model is a well-established nonclinical model for DMD that's widely used in academia and industry. These mice do not produce functional dystrophin. This study created transgenic MDX mice expressing various dystrophin designs to test their functionality. It found that a construct containing the same keyed regions as 9001 was among the

best performing. This is highlighted in yellow. Interestingly, designs that added additional length or retain the ENOS binding domain to dystrophin perform no better, and constructs that lacked the key functional domains perform more poorly.

Our laboratory also performed a head-to-head study with 9001 versus other shortened dystrophin constructs, this time delivered with AAV in the MDX mouse model of DMD, and subjected them to functional testing. For orientation, 9001 is highlighted here in yellow. Let me call your attention to two other constructs. One contains the C terminus of the protein at the expense of including spectrin repeat two and three, as well as a third hinge. As you'll note, there was no improvement in force versus MDX sham controls. We also tested a larger dual vector construct that contains the same domains as 9001 with additional spectrin repeats and the ENOS domain. Importantly, function did not reach the level of 9001.

Now that I've described the 9001 transgene in detail, I'd like to describe the 9001 product in totality. First is the promoter. We use MHCK7, which drives transcription and determines expression levels and specificity in skeletal and cardiac muscle cells. Next is the transgene, which is the 9001 gene, the shortened functional version of the dystrophin gene. And last is the vector. We selected an AAV vector called AAV RH 74 that has great trophism or affinity for muscle, both skeletal and cardiac. The AAV RH 74 vector is responsible for delivering the cargo and is what will firstly be exposed to the immune system.

Now I'd like to address the empirical evidence for surrogacy of 9001, starting with the nonclinical evidence. First, as mentioned, we use AAV RH 74 for its affinity for skeletal and cardiac muscle. We measure transduction or the ability to deliver to the cell nucleus by quantifying vector genome copy number for nucleus. Next, we use the MHCK7 muscle-specific promoter that expresses 9001 robustly in muscle. We measure total protein levels by western blot

as a percentage of normal. Next, the 9001 protein correctly localizes to the sarcolemma or muscle membrane. We quantify this both by the percentage of dystrophin positive fibers, termed PDPF, and intensity. 9001 dystrophin localization at the membrane restores the proper assembly and localization of the DAPC. DAPC restoration in turn normalizes the muscle microenvironment as measured by improvements in histology and decreased serum CK.

Finally, 9001 dystrophin's ability to restore this biological cascade leads directly to functional benefit as measured by the North Star Ambulatory Assessment, or NSAA. The next several slides will describe the nonclinical evidence supporting the biological cascade. We performed our nonclinical studies in the MDX mouse model of DMD. The model's well-characterized and lacks the dystrophin protein. Following a single intravenous injection of 1.33 times 10 to the 14 vector genomes per kilogram of 9001, we saw robust expression of 9001 dystrophin protein in all muscles, including the heart and the diaphragm. In the first column, we've stained for dystrophin. You'll appreciate that 9001-treated MDX mice have robust, correctly localized 9001 protein expression similar to normal muscle. We next stain for Beta-sarcoglycan as a representative protein from the DAPC. You'll recall that the DAPC is the protein complex associated with dystrophin at the membrane, as shown in the diagram on the left .Without dystrophin, this complex is not localized. We see a significant increase of beta-sarcoglycan correctly localized at the membrane with 9001 treatment as evidenced by the merged images on the right. This is in sharp contrast to MDX untreated muscle in the middle row with no expression.

Here I'm showing the evidence that 9001 is reasonably likely to predict clinical benefit by demonstrating non-clinically that expression leads to improvement of muscle function. The 9001 protein expression and restoration of DAPC leads to normalization of muscle

histopathology. Looking at the histology images on the left, you'll note the dystrophic features in untreated MDX muscle on the top, which is variable fiber size and central nuclei resulting from cycles of degeneration and regeneration. These features are improved with 9001 treatment, which is shown on the bottom, where fiber size is normalized.

Finally, this normalization of the muscle microenvironment results in improved function measured by skeletal and diaphragm muscle. We demonstrated significant improvements in force generation in the tibialis anterior and diaphragm muscles, as well as a significant reduction in eccentric contraction-induced injury compared to MDX sham treated controls.

The empirical evidence seen in the nonclinical model supports the results observed in the clinical setting. The results across the clinical studies similarly demonstrate consistent transduction, expression, and localization based on the muscle biopsies taken at 12 weeks after 9001 infusion across all studies. The mean quantity of 9001 dystrophin expressed is an order of magnitude greater than the results from currently available therapies. 9001 expression restored the DAPC and stabilized the muscle microenvironment leading to reductions in serum CK. This chart shows the mean reduction in serum CK from pre-infusion baseline to week 12 post infusion. Focusing on the center bars representing the double-blind placebo-controlled study 102, the 9001 treated group is depicted in purple, and the placebo group is depicted in gray. Both the 9001 and placebo groups received the same corticosteroid regimen including peri-infusion steroids, but the 9001 treated group had a significantly larger reduction in serum CK at week 12, indicating an improvement in sarcolemma stability over and above that was provided by steroids alone. The magnitude of change in CK is unprecedented based on the standard of care and is not expected in this age group based on the natural history of the disease.

The effect of DSE restoration is also visible on histology images from muscle biopsies. Example images depicting the four patients from study 101 are shown here, stained with picrosirius red, which highlights collagen in pink as a marker of fibrosis. The top row is their pre-treatment histology, which demonstrates evidence of collagen deposition that distorts or thickens the endomysium between myofibers, as indicated by the yellow arrows. The bottom row represents their 12-week post-treatment histology, which is notable for a mean reduction in collagen of roughly 26%, indicating an improvement in muscle fibrosis and muscle health noted by more uniform muscle fiber size.

So now that I've shown you the restoration of the biological cascade, both non-clinical and clinically, I'd like to focus on the association of 9001 dystrophin expression to function, starting with nonclinical. Literature evidence on endogenous dystrophin provides important insights on the biomarker to functional relationship to be expected for 9001 dystrophin. Shown on the left is an external published study using MDX mice expressing varying levels of endogenous dystrophin protein. A statistically significant association was determined between cardiac contractile force and dystrophin levels. However, moderate magnitude of linear correlation at 0.46 was observed, largely because low levels of dystrophin conferred functional improvement, which became saturated and plateaued at higher levels of dystrophin expression. For 9001 dystrophin shown on the right, we see the same magnitude of correlation at 0.42 that is highly statistically significant. Like the endogenous dystrophin, a saturable profile was observed, with muscle contractile force that clearly plateaus at higher levels of 9001 dystrophin. This demonstrates the biomarker to function relationship of 9001 dystrophin mirrors the response of endogenous dystrophin that occurs in nature.

Additionally, a saturable response is still compatible with a strong underlying biological relationship between the presence of 9001 dystrophin and improvements in functional outcomes. Consistent with the conclusions drawn by the FDA, a positive association was observed between 9001 dystrophin and NSAA one year change in patients. For protein expression endpoints by either Western blot or immunofluorescence methods, a statistically significant correlation was determined. In the case of 9001, a high linear correlation coefficient is not expected based on biological evidence of a saturable relationship demonstrated for both the endogenous dystrophin and 9001 nonclinical studies. Nevertheless, this data shows that levels of 9001 dystrophin expression at levels of typically observed after 9001 treatment are predictive of clinically important gains on NSAA at one year.

In summary, dystrophin is a protein that acts as a link between the extracellular matrix and the intracellular cytoskeleton in muscle cells. Evidence from nature inform the rational design of 9001 to include critical components needed for function. 9001 restores the biological cascade that's downregulated in the absence of dystrophin. And 9001 protein expression is correlated with improved function in nonclinical and clinical studies. This evidence supports the accelerated approval criteria that 9001 is reasonably likely to predict clinical benefit. Now I'll turn the presentation over to Dr. Stefanie Mason to discuss the clinical trial results.

Clinical Trial Results — Dr. Stefanie Mason

Dr. Mason: Hello, I'm Stefanie Mason, the clinical development lead for 9001 at Sarepta. Today I will review the clinical trial results from our development program. Before describing the trial results, however, I would like to take a moment to discuss the natural history of physical function in DMD. DMD has a heterogeneous progression, which can be seen in this graph of NSAA score over time. These data represent the natural history of NSAA by age, as described by

the UK's North Star Network. Nevertheless, there is a common pattern, with an initial maturation and physiological gain of function, though boys with DMD have a lower peak function and reach that peak later than healthy boys. This maturation phase is followed by an inevitable decline during which motor functions such as ambulation and independent feeding are irreversibly lost.

Whilst the heterogeneity between individuals is high, trajectories of progression are predictable using key prognostic functional characteristics. As an example, this figure shows five predicted trajectories for loss of ambulation based on a composite score of time to rise from floor and 10-meter walk run that was developed from the Collaborative Trajectory Analysis Project, or CTAP, database. These predictions were independently validated in the Synergy study. These predictive factors of baseline functional status are important for interpreting our trial results and external control analyses. And keeping in mind the pattern of disease is important for interpreting the treatment benefit seen with a disease stabilizing approach like gene therapy. A disease stabilization goal has been reported by parent project muscular dystrophy as a clinically meaningful outcome to the DMD community.

In the short term, 9001 is expected to produce a similar magnitude of treatment benefit across the ambulatory population. However, these effects may manifest differently based on whether the patient is in the skill gaining versus functionally declining phase of the disease. A patient in the maturational phase may have an increased gain in function and a higher peak NSAA score after 9001 treatment compared to an untreated patient, even though both patients may improve relative to their own baseline. A patient in the declining phase of the disease may experience no decline in function after 9001 treatment, as compared to an untreated person, who may experience the described natural history decline.

Beyond one year and over the longer term, treatment with 9001 is expected to result in DMD disease stabilization, but it cannot regenerate lost muscle. Therefore, with stabilization, the magnitude of treatment benefit that is seen in one year may grow over subsequent years of follow-up, as treated patients remain relatively stable and untreated patients experience the more severe declines that are part of the long-term DMD natural history. With this in mind, I would like to walk you through the results of studies 101, 102, and 103.

Study 101 was an open label, first in human study consisting of four participants aged four to seven years of age. The primary endpoint was safety, with key additional endpoints covering the biologic and functional outcomes, including the NSAA. As will be true for all three studies, patients were required to be on stable doses of corticosteroids and have low or undetectable levels of antibodies to the vector. The four participants in Study 101 all demonstrated increases on their NSAA scores and have maintained those gains over four years of follow up. For each of the four patients depicted in the grouped bar charts, the light purple bar is their pre-infusion baseline NSAA score. Each subsequent purple bar represents one year of post infusion follow up. I would draw your attention to the yellow shaded boxes at the bottom of the slide, which depict their age at year four. These boys are now between 8 and 10 years of age and demonstrate disease stability, with none yet demonstrating the expected decline that natural history would have predicted.

Study 102 was a double-blind, randomized placebo control trial comprised of 41 patients. The study was conducted in three parts. In part one, 20 participants were randomized to receive 9001, and 21 participants were randomized to receive placebo. After the initial 48 weeks of follow up, participants entered the blinded crossover part two, during which those who received 9001 in part one received placebo, and those who received placebo in part one now

received 9001. After an additional 48 weeks of follow-up participants entered part three, which is an open label extension phase. All of the participants are now in part three, and this study is unblinded.

This is a table of the baseline Demographics of the intent to treat population. Age was the only stratification factor due to the small trial size. However, age alone does not sufficiently describe the variability between patients. Functional scores are importantly prognostic of performance. Not stratifying for measures of physical function at baseline was a design limitation in this trial, and it resulted in an imbalance in the six- to seven-year-old stratum. Subsequent trials have measures to balance physical function scores.

This graph depicts the change from baseline in NSAA total score over 48 weeks in the intent to treat population, which was the primary functional endpoint of the study. The treated group, depicted in purple, exhibited a numerically greater change from baseline NSAA score compared to the placebo group in gray at every time point. However, the difference was not significant.

These plots depict the LSM change from baseline, starting from the mean NSAA score at baseline over the 48 weeks of follow up in each of the age groups. On the left are the results for the four- to five-year-old subgroup. With the 9001 treated patients in purple and the placebo in gray. The functional scores in this age subgroup were balanced at baseline, and the 2.5-point difference in NSAA score at 48 weeks was numerically higher and nominally significant. On the right are the results for the six- to seven-year-old subgroup, again with the treated patients in purple. Here, there was a significant imbalance in baseline prognostic functional characteristics, which complicates the interpretation of these results. And more data is

necessary to understand the potential treatment benefit in this group. Dr. Signorovitch and McDonald will present some of this data shortly.

Study 103 was an open-label trial. This study is comprised of multiple cohorts, totaling 40 participants, all of whom are included in the safety database. However, at the time of the submission, only cohort one, which is comprised of 20 participants aged four to seven years old, had reached one year of follow up, and therefore only cohort one functional results will be shown. On the right are the demographics of the enrolled patients. The graph on the left depicts the mean total NSAA score over the 52 weeks of follow up. As a cohort, the mean change in NSAA was a four-point increase at one year. To provide context to this result, we employed an external control comparison, and I would like to introduce Dr. James Signorovitch, who will speak more about the external control methodology.

External Control Analyses — Dr. James Signorovitch

Dr. Signorovitch: Thank you. I'm Dr. James Signorovitch, co-founder of the Collaborative Trajectory Analysis Project, or CTAP. CTAP is a collaboration of biopharmaceutical companies, non-profits, and noted clinical experts dedicated to learning from clinical data in Duchenne to improve drug evaluation. We've had the opportunity to study the clinical trajectories of over 2,500 boys with DMD. Today, I've been invited by Sarepta to talk about the principles of external controls in DMD trials and specifically their pre-specified external control analysis.

The purpose of this analysis is to contextualize clinical outcomes for patients receiving 9001 and to further test the evidence for surrogacy of 9001 dystrophin expression. But first, the external controls need to be reliable. Without randomization and blinding, comparisons to external controls carry risks of bias. I'm going to explain the evidence for reliability of

external controls in DMD generally and for the external controls used in this application specifically. Dr. McDonald will next explain the findings in their clinical interpretation.

There are three primary risks for external controls in DMD, which FDA also noted in their briefing document. First, we need to consider the NSAA as a performance-based outcome. The worry is that motivation could be higher in treated patients, leading to artificially better performance compared to external controls. Second, we need to understand whether background standards of care differ between treated patients and external controls and whether NSAA outcomes are impacted. Third, we need to recognize important prognostic factors and whether they differ across groups. These are critical concerns for any external controls in DMD.

Let me briefly discuss a recently published CTAP study that directly tested these concerns .Within the CTAP collaboration, we have NSAA data from over 500 boys from a diverse collection of sources. We examined these data thoroughly and did not find any evidence of differences in NSAA outcomes across data sources, geography, or years. Importantly, our data included blinded clinical trial placebo arms and natural history settings. We looked directly for evidence that boys perform differently across these settings. The figure on the right shows the difference in 48-week change in NSAA for trial placebo arms versus natural history studies. This shows about one point worse NSAA for blinded placebo. We also adjusted this comparison for differences in known prognostic factors. After adjusting, the difference was reduced to 0.2 NSAA units, and we saw no significant differences between blinded placebo and natural history. These results give us confidence that external controls can be informative in DMD.

With this background, I will now introduce the external controls used in this BLA. To identify a sample of external controls, the sponsor evaluated multiple data sources based on data quality, the ability to secure rights to share patient level data with regulators, as is required,

and the availability of key endpoints such as the NSAA. The selected data sources were two clinical trials and one high quality natural history study. Subjects in these studies were then required to meet pre-specified inclusion criteria to align with the inclusion criteria and baseline functional ranges of the 9001 trials. Subjects meeting these criteria were available as external controls. The primary external control analysis was pre-specified in terms of the study population, target dose, outcome, external comparator, and detailed statistical methods.

A battery of sensitivity analyses was also pre-specified. I am going to highlight one of these sensitivities, which is particularly informative because it used different data sources and methods than the primary. In this key sensitivity, predicted controls were generated from a model independently developed by CTAP from natural history data on over 260 boys and presented at the World Muscle Society in 2022. Dr. McDonald will share key efficacy findings from both of these methods.

But before we look at efficacy outcomes, let's evaluate the baseline similarity of the primary external controls. This table shows that important baseline prognostic factors are similar between the external controls and the 9001 treated patients in the primary integrated analysis, especially for the key prognostic factors, NSAA, time 10-meter walk run, and time to rise. This gives us confidence that the treatment and external control groups are comparable. Note that the baseline balance in this table is better than seen for the randomized groups in study 102. This highlights the value of well-matched external controls for contextualizing outcomes, especially when randomization fails to balance baseline prognostic factors in small trials.

There is one more important check on the external controls. Because 102 was a randomized blinded trial with placebo, we can directly test the consistency of the external controls against this placebo. Bias in our external controls due to different background standards

of care, unobserved prognostic factors, or motivational effects on the NSAA should show up in this test. We ran this test and did not see significant bias. On average, the placebo arm patients had only 0.6 points higher NSAA compared to the primary external controls. We also ran this analysis for the separate predicted controls. This test also identified no significant difference. The placebo arm patients in 102 had slightly worse outcomes by 0.4 NSAA units compared to the predicted controls.

The outcomes of these two tests give us confidence in the external controls in the BLA. External controls always carry risk of bias, but we can use evidence to assess that risk. In this case, we've seen multiple lines of evidence that support the reliability of our external controls. An independent assessment found that NSAA outcomes were consistent across multiple data sources. Likewise, we saw internal consistency between our external controls and placebo for two very different external control sources. Taken together, this evidence gives us confidence that the external controls in the BLA are informative and, in particular, can add to the evaluation of reasonable likelihood of clinical benefit for 9001. To that end, I will now pass the presentation to Dr. McDonald.

External Control Results — Dr. Craig M. McDonald

Dr. McDonald: Thank you. I'm Craig McDonald, Director of the Neuromuscular Medicine Research Center at the University of California Davis. I'm also the principal investigator of the Cooperative International Neuromuscular Research Group, Synergy, Duchenne Natural History Study funded by the Federal Government and patient organizations. Over the past 30 years, I've been involved in the treatment of over a thousand patients with Duchenne. Sadly, the majority of these patients are no longer with us. I've been a principal investigator on many clinical trials in

Duchenne, including the trials for 9001. During the next few minutes, I would like to present the external control results.

The pre-specified primary external control analysis was the integrated summary of efficacy. This integrated dataset is comprised of a total of 52 participants from three studies, all 20 participants in cohort one of study 103, all four participants in Study 101, and 28 of the participants in Study 102. 13 participants from the 102 trial were excluded, 12 because they did not receive the 1.33 times 10 to the 14^{th} dose, and one, because their NSAA data was incomplete due to surgical recovery. The results of the propensity weighted analysis demonstrated that the treated group, depicted in the purple bar, have a mean 2.4-point NSAA gain when compared to external control, shown in yellow. As a sensitivity analysis, the comparison was repeated with the predicted control analysis technique on a distinct and independent external control pool. The results were directionally consistent and similar in magnitude.

I will next show external control results from the individual studies. In study 103, the 20 treated patients in cohort one depicted in purple showed an LSM mean increase in total NSA of 3.2 points versus 91 propensity score weighted external control patients, depicted in yellow. For study 102, I will discuss the results in terms of the age strata described by Dr. Mason in the four- to five-year-olds. The expected treatment benefit would be a greater gain in function than untreated counterparts, which is what was observed in the well-balanced four- to five-year-old strata where baseline prognostic measures were similar. However, more data was needed to interpret the unbalanced six- to seven-year-old subgroup.

Here we see the treated six- to seven-year-olds in purple and the placebo six- to seven-year-olds in gray. Their differences in baseline function would imply a different expected trajectories over 48 weeks based on a wealth of natural history data. When we overlay the

external controls shown in yellow, the untreated propensity weighted external control group had an indistinguishable course when compared to the untreated placebo group. In contrast, the external control group that was propensity weighted to align with the SRP-9001 treated group, experienced a very different course over 48 weeks. The treated patients remained essentially stable, while the external control group had a decline in NSAA score. The resulting LSM 2.1-point difference between the groups was nominally significant and similar in magnitude to the 2.5-point treatment effect demonstrated in the four- to five-year-old age group.

Lastly, in study 101, The 9001 treated patients, depicted in purple, showed disease stability over four years, while their propensity score weighted external control comparators, depicted in yellow, decline over time. By year four, the difference between the treated and external controls has grown to a dramatic nine points on the NSAA. This change in trajectory is evident using both the propensity weighting on the left and the predicted control method on the right. These forest plot data from three clinical studies demonstrate that a one-time infusion of 9001 led to consistent and significant increases in 9001 dystrophin expression by Western blot, regardless of age or baseline function. Similar forest plot data also demonstrate the treatment with 9001 results in improved or preserved muscle function, as measured by the NSAA. Treatment effect estimates are clinically meaningful and consistent across key subgroups such as age and baseline function. These treatment benefits on the NSAA have not previously been seen in patients with DMD and support the empirical evidence of surrogacy presented by Dr. Rodino-Klapac. Thank you, and I'll now turn the presentation over to Dr. Darton.

Summary of Safety — Dr. Eddie Darton

Dr. Darton: Thank you, and good morning. I'm Eddie Darton, Executive Medical Director of Safety Evaluation Risk Management at Sarepta Therapeutics. I will review the safety profile of

9001. Based upon the 120-day safety update report, there are 85 patients in studies, 101, 102, and 103 who have a cumulative 183 patient years of exposure with a mean follow up time of 2.2 years. A total of 1,230 treatment emergent adverse events were reported, 13 of which were serious. 98.5% of all AEs were mild to moderate in severity, and 95% of patients have their first AEs within 90 days following 9001 infusion. None of the AEs led to discontinuation, and there are no deaths in the program.

Following 9001 infusion, the most commonly observed adverse reaction was vomiting. Vomiting typically occurs in the first one to three days post infusion. And resolved spontaneously or with antiemetic therapy. Other frequent adverse reactions included elevations and liver function tests, pyrexia, and thrombocytopenia. With regards to treatment emergent serious adverse events, a total of 13 were reported in 11 patients. Nine of these SAEs, as marked on the slide, were considered to be related by the investigators, except for the events of immune mediated myositis and myocarditis. All of these SAEs resolved without problem. The vector for 9001 is AAV are 874. Adeno-associated viruses, or AAVs, are the most commonly used and studied capsids for gene therapy. A wide range of AAV stereotypes with different tropisms, routes of administration, and doses have been studied across a variety of diseases. From this experience, several potential risks of a gene therapy have been identified. As also noted in the FDA's briefing book, the severity of these risks differ across gene therapy programs, AAV, serotypes, and diseases being addressed.

Reviewing these journal AAV risks, starting with hepatotoxicity, it is important to point out that patients with DMD have elevated serum ALT and AST levels based upon leakage from damaged muscle, making it difficult to use these markers to assess liver injury. Therefore, Sarepta used the definition on the slide for acute liver injury. Based upon this definition, 36.5%

of all patients dosed with 9001 met at least one criteria for acute liver injury. Another important biomarker used for evaluating patients for acute liver injury was total bilirubin greater than two times the upper limit of normal. Three patients met this criterion. Liver biomarker increases occurred 4 to 8 weeks post 9001 infusion, with all cases started within the first 90 days. There were no cases of acute liver failure or acute or increased INRs. All events recover either spontaneously or with corticosteroid treatment, with a median resolution time of 35 days. Liver enzymes will be monitored pre- and post-infusion as part of our proposed risk management program.

Next, let's talk about myositis. Immune mediated myositis was received in one ambulatory nine-year-old patient with an exon three to four to three deletion mutation. This patient presented with muscle weakness, dysphagia, dysphonia, difficulty sitting and standing and walking four weeks after 9001 fusion in the hospital. He was treated with intravenous steroids, plasmapheresis, and four days prior to discharge start on tacrolimus. The boy, who remains ambulatory, recovered with residual muscle weakness. Based upon the patient's clinical presentation, genetic mutation, ELIspot findings, and the timing of the event, the etiology is thought to be an immune reaction to the 9001 dystrophin protein. Epitope mapping identified a highly immunogenic region that is contained within the one transgene, and patients who have of this region may lack cell tolerance to the transgene protein. These findings, in conjunction with experienced treating additional patients with mutations in this region, as well as the clinical experience of industry partners of other DMD gene therapy programs, indicate that patients with deletions fully included exons 9 to 13 may have the highest immunogenic risk. As such, for risk mitigation, we have proposed a contraindication for patients with any deletion that fully includes these exons.

Now let's focus on myocarditis. One patient had a serious adverse event of myocarditis. This 11-year-old patient was initially admitted for management of vomiting, which started shortly after 9001 infusion. Discharge blood work showed an incidental finding, elevated troponin-I leading to further cardiac monitoring and treatment with steroids. The patient had transient chest pain that resolved without any intervention and not associated with other acute cardiac symptoms, ECG, or echo changes. The patient was observed and discharged after a few days. Based upon cardiac MRI findings, an adjustment of his medication for preexisting chronic cardiomyopathy, the event was assessed as recovered with sequala. A second case of myocarditis not in this database was reported in the ongoing 301 study. This six-year-old patient, whose treatment assignment still blinded, but also initially admitted for management of vomiting when an increased central troponin was detected on bloodwork. This boy was monitored in hospital for additional few days and fully recovered. For proposed risk mitigation, troponin levels will be monitored weekly for the first month following 9001 infusion.

Next, complement activation. Serious events related to complement activation have not been seen in the 9001 program. Transient decreases in complement, specifically C3 and C4 ,have been seen at week one post infusion and resolved at week two. These decreases were not associated with clinically significant events. No cases of TMA have been with 9001. Transient decreases of platelets were also seen within one week post that resolved without intervention by week two. There were no cases of platelet counts under 50,000 or thrombocytopenia requiring additional medical treatment. All of these events resolved spontaneously. Our proposed risk management plan includes monitoring and platelet counts weekly during the first two weeks post-infusion.

Lastly, oncogenicity. Oncogenicity on a basis of AAV integration is a theoretical risk. Recombinant AAV is generally not integrated. AAV gene therapy used for other indications have not revealed any safety signal related to oncogenicity. Published literature in the hemophilia field with AV delivery have shown low integration in animal studies. However, no tumor formation has been noted at up to six years. No such events have been seen in the 9001 program. Despite this lack of observed evidence, a long-term follow-up study for up to 10 years has been proposed to better characterize any potential risk.

In summary, we have identified important safety risk mitigations during our development program. 9001 is well tolerated. It has a favorable safety profile and a proposed context of use. The adverse events are monitor and manageable with standard medical care. In addition, there were no deaths in our study. The proposed risk mitigations for 9001 include monitoring liver enzymes, troponin, and platelets, a contraindication for patients with any deletion that fully includes exons 9 through 13, and a long-term follow-up study. I will now turn the presentation back to Dr. McDonald.

Clinical Perspective — Dr. Craig M. McDonald

Dr. McDonald: Thank you. I'd like to conclude today's presentation with my clinical perspective on the overall risk benefit profile. All patients with DMD, regardless of mutation or ambulatory status, are in urgent need of effective and safe therapies. The disease is relentlessly progressive, and even in a one year period, there can be a substantial loss of function. Time is of the essence, and for Duchenne patients, time is muscle. Based on survey results published by the Parent Project Muscular Dystrophy Advocacy Group, patients and family members have indicated that long-term functional stabilization is of profound importance to them. Interventions

are needed now to help boys and young men with DMD preserve muscle and respiratory function in order to extend their quality and duration of life.

From a clinician's perspective, any determination of the risk benefit profile of 9001 must first start with the demonstration of a favorable safety profile of this unique viral capsid, promoter, and replacement gene construct. It's essential to keep in mind that the experienced and organized centers with sufficient infrastructure will be the places where future Duchenne patients are treated, monitored, and managed with 9001. Fortunately, in the US, we have robust neuromuscular disease centers experienced in using approved AAV gene therapy in spinal muscular atrophy.

It is reassuring to know that while important risks have been identified, such as acute liver injury, myocarditis, and immune mediated myositis, the adverse events are readily identified and manageable. For example, we have GGT to employ as an adequate biomarker to monitor for an early liver injury from the viral vector. It is also reassuring to know that no cases of thrombotic microangiopathy or significant thrombocytopenia have occurred in treated patients. 9001 has an acceptable safety profile within the context of the intended goal of disease stabilization. In addition, the genetic inclusion criteria has mitigated the risk of immune mediated myositis.

The clinicians that have the most treatment experience with 9001 have shared many videos with the FDA demonstrating clinically meaningful benefits. Allow me to share some videos of a representative patient. This is a nearly six-year-old patient, and despite being on steroids prior to his treatment with 9001, he must use the railing to descend stairs, and his velocity is slowed as he tries his best to descend the stairs in a reciprocal pattern. In the middle is the same patient six months following treatment with 9001. He easily climbs up many stairs

reciprocally without the use of a railing. Similarly, his stair descending function is essentially normal. This stair climbing and descending ability is translated to the real-world environment when viewing this patient on a playground structure, six months following treatment with 9001. You cannot detect appreciable differences in this child from as other peers on the playground.

Assessments in the real-world environment capture other important meaningful treatment effects, not evaluated by our traditional clinical trial endpoints. Here's the same patient just shown. On the left, the running ability, sustained endurance over long distance, and joy of movement is evident in this patient and something I have never observed in my more than three decades following patients with DMD. On the right, he's riding his bike in the community as a newly developed skill.

I've seen such sustained and meaningful benefits for up to two years in the 15 patients I've treated with 9001, and Dr. Mendell has seen sustained benefits and unprecedented stability of function for up to four years. This day marks an important opportunity to continue to advance the treatment landscape in DMD. 9001 treatment shows persuasive results in this relentlessly progressive disease. There is sufficient evidence based on many lines of biologic and clinical evidence, demonstrating that 9001 expression is a surrogate endpoint reasonably likely to produce clinical benefit. It has biologic activity similar to endogenous dystrophin.

The clinical findings of the three studies are meaningful, and the totality of clinical evidence from both the placebo controlled clinical study and pre-specified external control comparisons are sufficient to support accelerated approval. SRP-9001 treatment relative to control leads to a two- to three-point benefit on the NSAA at one year, which translates into subsequent long-term disease stabilization. This functional impact is profoundly important to patients and their families. Additionally, we see a positive benefit risk profile for 9001. The risks

can be monitored and are manageable, and the magnitude of likely benefits far outweighs the possible risks.

Finally, the confirmatory study 301 is fully enrolled and nearing completion of the first year of treatment. Over many years of conducting clinical trials with the Duchenne patient community, I have been impressed by the dedication and consistent commitment of our patients and their families in maintaining their steady participation in all double-blind placebo controlled clinical trials. As an investigator, I consider it highly unlikely that any of the boys in this trial would drop out in the four or less months prior to guaranteed treatment at their trial sites experienced in gene therapy in order to seek uncertain commercial access. This study will be completed as planned with complete acquisition of data.

The FDA is asking you to vote today on whether the benefits and risks support accelerated approval of SRP-9001. From a clinician's perspective, the totality of data are sufficient to conclude that 9001 produces a dystrophin product that is reasonably likely to predict clinical benefit. I've had the privilege to treat 15 patients with 9001 and have seen compelling clinical results. Time is muscle for patients with DMD. Many children will predictably and irreversibly lose muscle fibers and important functional abilities in the near term if they do not have access to SRP-9001. We cannot afford to delay access to this transformational treatment. Thank you. I'll now turn the presentation back to Dr. Louise Rodino-Klapac.

Dr. Rodino-Klapac: Thank you, Dr. McDonald, Dr. Assan. I'd like to note that we're prepared to come back with any data before the discussion that we were not able to provide during this morning session and would appreciate the opportunity to do so. So thank you and I'm happy to address your questions.

Q & A

Dr. Ahsan: Great. Thank you for those presentations from the Sarepta team. Now is our time to ask some questions of this team regarding their presentation and their BLA. Keep in mind for the committee members that we do have time this afternoon for general discussion. But this is really questions towards the speakers at this last presentation. So if you can indicate by raising your hand, and I'm doing this in order that they're appearing. Buddy, if you would like to start by unmuting yourself and going on camera.

Mr. Cassidy: Hi. Yes. I was just hoping this is, yeah, this would be a question for Dr. Mendell or Dr. McDonald. But if you could just briefly explain for the rest of the committee again, what exactly the North Star Ambulatory assessment is. What's the point of it? What it is looking at? And if you could also maybe go over what Gowers Maneuver or Gower's sign is. Again, I'm familiar with these as a patient, but just if you could just quickly go over that for those outside of the Duchenne community.

Dr. Rodino-Klapac: Sure. I'd like to invite Dr. McDonald to answer your question.

Dr. McDonald: Craig McDonald from the University of Davis. In an answer to your question, again, this demonstrates as Dr. Mendell showed on the videos, the rise from floor ability with the patient essentially transitioning from a normal score in terms of rise from floor ability to the middle, where he actually uses compensatory mechanisms to actually enable him to rise from the floor. Just a one-point change in NSAA going from a one to a zero would actually indicate complete loss of this particular function. So one point change is really analogous to a gain or loss of one function or decline or improvement of one function. A 2-point change would represent the decline or improvement of two functions or the complete loss or gain of a normally

performed function. And there's been recent published work showing that patients and parents perceive a one-to-two-point change on NSAA as clinically meaningful to them.

Mr. Cassidy: And just to clarify in terms of like the Gowers maneuver, having to do that or not would be a difference of one point. So in your opinion as a clinician, would it be really possible for a patient to get so psyched up they don't do the Gowers maneuver?

Dr. McDonald: No. I think it's important to note that on these functional abilities that are ascertained in the North Star, these compensatory maneuvers that would result in a one-point change are continually performed by the patient as compensatory strategies for their weakness. You cannot will yourself by motivation to transition from a NSAA score of zero to an NSAA score of one, and the patient in the middle cannot will themself based on motivation to transition from a score of one to a score of two. So we really don't believe, and I think the natural history data and the validity data would bear this out, that the NSAA is really not subject to motivational biases or patient effort.

Mr. Cassidy: Thank you.

Dr. Ahsan: Great. Thank you. Next, I have Dr. Steven Pavlakis.

Dr. Pavlakis: Thanks. My question is related to the last question so we can — hang on, I'm trying to get my video going here. Anyway, when I, again, a clinical question, you know, Gowers from having a Gowers to not being able to get off the floor is pretty dramatic, and that's easy. My question is, we talk about clinically meaningful improvements or stabilization, and at higher scores in 20s an' 22s, I'm not sure what that exactly means, you know, clinically. So for example, that six-year-old boy did look much better on the video. Again, you, you know, taking a patient at one point in time when they have a neurological problem, if they're tired, they can look worse and all that. But that was pretty impressive. Do you, and if you clinically think these patients get

better, do you have the same example in older kids? Because you know, the data at least looks like it's better 'n there's more improvement or stabilization in the younger children down to four.

Dr. Rodino-Klapac: So again, clinically, this is more to, I guess, to Dr. Mendell or to Dr. McDonald. Okay. I'd like to invite Dr. McDonald.

Dr. McDonald: Yeah, with, with regard to the patient in the video, that patient had a baseline NSAA score of 25. And at six months after treatment, the score had increased to 27. Actually by two years of follow up, that patient's score had actually stabilized at a score in excess of 30. And so in terms of the clinical meaningfulness, really across the scale, what we see is that patients that perceive these one and two changes across the full range of the NSAA have really determined these to be clinically meaningful to daily life. And so some of the early skills such as improvements or stabilization in jumping, hopping, running would really correlate with improvement in playing, accessing sports, keeping up socially and physically with peers. Even a score such as later in the disease process, climbing up and off a box step can be important for negotiating stairs, outdoor mobility, negotiating curves for independence, walking throughout the school and the community. Standing up from a chair can be realized in terms of improved toilet transfers, ease of classroom transitions, transfers from bed in wheelchair, and the NSAA has been prognostically very important for also predicting future functions such as loss of ambulation.

Dr. Pavlakis: That's not really, my question is you showed a child that was relatively young and looked very improved on the video. Do you have personal examples of that in kids that are seven?

Dr. McDonald: We have numerous examples of older patients that have actually shown stability of function, not necessarily an improvement in the NSAA. An improved NSAA score is not something that's a requirement to really show treatment benefit. But we have had patients

that we've followed into the teen years who were ambulatory. I've had patients that I've treated with 103 that have achieved disease stability of their disease progression. And these are born out more in some of those functions assessed down lower in the NSAA scale. So the scale, actually the beauty of it, it really assesses a functional progression in Duchenne, really across the spectrum of disease, including the boys, the older boys you mentioned where we really are happy when we see disease stabilization.

Dr. Pavlakis: Thank you.

Dr. Ahsan: Great. Thank you. Next, Dr. Caleb Alexander.

Dr. Alexander:Yeah, I have a question about dosing. And the question is this: what amount of, what's the right amount of product expression and target tissues that optimizes the risk benefit balance of the therapy? And the reason that I ask is that there were three different doses inadvertently studied in study 102, and my understanding from the FDA is that they felt that quantitation of Western blots were highly variable, precluding determinations of a minimum level of expression associated with clinical benefit. And I also understand, if I'm correct, that there was not, that those that got the full intended dose in study 102, which is the main study that I would put my money on, because it's the only one that's double blinded placebo controlled, that those that got the full intended dose had the poorest outcome.

And if you look at the FDA's, for example, Figure 12 of the FDA's briefing, at the scatter plots for the people receiving treatment. The micro dystrophin change from baseline is all over the place. I mean, there're one or two or three that are way up at 80 or 100 or 125%. And most don't seem to exceed 10%. So again, the question is what is the company's position on the amount of product expression and target tissues that optimizes the risk benefit balance of the therapy? Thank you.

Dr. Rodino-Klapac: Yep. So there are several questions in there. First, just talking about dose selection in general, the dose was selected based on nonclinical studies in which lower dose was sub-efficacious and a higher dose did not provide any additional benefit. But let me have you, I'm going to have Dr. Lily East talk through the dose levels in study 102, and then we'll follow up with the associations that we've seen.

Dr. East: Good morning. Lily East, Quantitative and Clinical Pharmacology at Sarepta Therapeutics. There is a totality of the evidence that we have demonstrated in terms of clinical efficacy, safety, and PKPD evaluations supports the clinically proposed dose at 1.33 times 10 to the 14^{th} mg per kg. As noted by Dr. Dr. Rodino-Klapac, of the three doses that we studied in patients, there was dose-dependent increase in biological response, with the highest observed at the clinically proposed dose. And this level of protein expression also translated into meaningful clinical benefit in patients, as observed in NSAA total score, one year change from baseline. A higher dose than the clinically proposed dose was studied non-clinical through the extensive dose ranging evaluations performed. However, marginal improvement was observed in both the functional outcome as well as biological response.

As to your question, specific to the FDA's analysis that show no dose response with NSAA, there are a number of considerations that are important to take into account. The FDA analysis was limited to study 102 part one. It showed that at the clinically proposed dose, 95% confidence interval of the LS treatment difference include a zero. And further concluded that the sample size was too small to draw any conclusion about the treatment effect at the clinically proposed dose. We can address the sample size limitation by including data at the clinically proposed dose from other trials.

Dr. Alexander:I'm sorry to interrupt you, but I think I'm asking a simpler question or a little bit different question. I'm simply asking what percent product expression in target tissues is what you believe optimizes the risk benefit balance of the drug. So I'm not really asking what the dose should be or what the relationship is between, you know, 12-week protein and 48-week outcome. I'm just trying to understand what the company's position is on what the right amount of product expression is in the target tissues.

Dr. Rodino-Klapac: Sure. Thank you for clarifying your question. I'm going to invite Mr. Mullen to address.

Mr. Mullen: Good morning. Chris Mullen, biostatistician with NAMSA. So we've done a variety of analysis to explore this question, and there's no specific threshold that we've been able to identify. I'm going to try to pull up a slide here. This was from the presentation showing change in NSAA scores. This is for study 102 and 103. Looking at change in NSAA scores on the vertical axis, and then western blot protein expression on the horizontal axis. And what you've may have seen in this slide, seen in slides of the briefing book, and then there are a few other slides I'd like to show you. There's this relationship where there's a relatively or somewhat steep curve at the initial levels for small amounts of expression, and then a plateau. And that plateau creates some challenges with correlation coefficients and so on. But there's no specific threshold that we've been able to identify.

So I can show you few more slides on this topic. First, this is NSAA change on the vertical axis for these three different panels. And then on the horizontal axis on the left, we have Western blot protein percent positive fibers and fiber intensity. Again, we see a same similar relationship. No specific threshold, but these are Spearman correlation coefficients on the bottom that range from .33 to .38, all nominally statistically significant. We see similar phenomenon

with another measure time to 100-meter one year change. Vertical axis is now that outcome. Note, however, that now a decrease is an improvement clinically. We again see nominally significant correlation values, no specific cutoff value, but a consistent finding. And then also we see the similar phenomenon, time to rise from floor. Looking at the correlation again with the three measures. Again, lower values here improved, nominal significance. Finally, time to ascend stairs. Just a second for that slide here. Again, lower values are clinically improved. The middle p-value is not nominally significant, 0.10 there. But these findings of this consistency gives us great comfort. Again, no ability to identify a specific threshold.

Dr. Alexander:Thank you.

Dr. Ahsan: Great. We're going to extend the Q and A by just a little bit, because there are quite a few questions, but I encourage everyone to be very direct in their question and very direct in their answer so that we can get it through as many questions as possible. Dr. Raj Ratan, please.

Dr. Ratan: Yes. I'm wondering whether you've done any experiments that address the possibility that having a shortened dystrophin, as in Becker's, from the moment of development is very different than actually delivering it by AAV as kids get older. And so I guess the question would be have you either taken the Becker and expressed it later, or have you taken 9001 and expressed it early in development to see whether there's a difference in the robustness of your effect on outcome?

Dr. Rodino-Klapac: Yeah, so to address your question, they're transgenic mice, and we show them in the core presentation of small dystrophins made by the group, which do express those small dystrophins from birth and their UD do see significant improvements. I can just put this slide up quickly.

Dr. Ratan: Yeah, I saw that. But I guess what I would be interested in is I think you'd really need effluxed shortened to address my question, because you'd want to only have it expressed after the onset of the disease as you are doing with your AAVs.

Dr. Rodino-Klapac: Yeah. Yes. There are mice that do have that same phenomenon. What I'd also like to mention is that we've dosed both the MDX mice and rats at different ages and saw a functional benefit in, regardless of age as well.

Dr. Ratan: Thank you.

Dr. Ahsan: Okay, great. Moving on, Dr. Lisa Lee.

Dr. Lee: Thank you. My question really is about the assessment tool of the NSAA. We've had some discussion about it, but I'm wondering if you can address a couple of things. One is, what is the inner radar reliability of, of this instrument? You had mentioned that there's probably not a motivational bias, but what about an observer bias? Second, in Study 101, who did the NSAA assessment? Study 102, when did that assessment occur during the blinded phase or the open label phase?

Dr. Rodino-Klapac: Thank you. Okay. For the first part of your question about NSAA reproducibility, like to ask Dr. Stephanie Mason to address.

Dr. Mason: Stephanie Mason, Sarepta Therapeutics. The NSAA has been widely validated and has been shown to have high inter- and intro-rater reliability greater than 0.95 for both of those measures. And that has been demonstrated across multiple trial sites, in multiple countries as well. I believe the second portion of your question was regarding the administration of, or the NSAA in the trials. It's administered by trained clinical evaluators that have been trained by master physiotherapists with a scripted administration. So that is, consistent every time. Family members and other persons are not permitted to be present at the time of the evaluation. And it is

performed at multiple time points in the trial, during all phases of the trial. So both the blinded portion as well as the open label portions.

Dr. Lee: Thank you.

Dr. Ahsan: Great. Dr. Anthony Amato, please.

Dr. Amato: Yeah. I congratulate you. I thought that was a very impressive presentation. I wasn't sure how far along you were in the confirmatory study, so that alleviated some of my concerns about finishing that study. I was more interested in that one subject with the immune mediated necrotizing myopathy and, you know, why we're convinced that that was immune mediated. I'm assuming that you're thinking that there was an immune response against the dystrophin that was now being produced, but do we have to limit, if the drug is effective you know, do we have to not give the drug to patients that have these exons deleted? Could this have been a myositis related to the viral vector? A transient? And how's that participant doing? Did they stabilize in regards to their, or improve in regards to their function? Or did the myositis actually cause them to deteriorate?

Dr. Rodino-Klapac: Okay. So several parts there. Just to address your question around was this specific to the transgene: we saw a very specific T-cell response directed against the region that the patient is deleted where the 9001 dystrophin was expressed. So it was very specific for this patient's deletion and confirmed through the immunology testing as well as other findings in other sponsors' studies as well. And so I just want to have Dr. Eddie Darton do the quick follow up on the patient's current status.

Dr. Darton: Eddie Darton. Sarepta Therapeutics. Yes. This patient initially had a baseline NSA at 23. At last follow up, it was 17. He's still ambulatory. He had no cardiac changes or findings that were concerning as far as being related to the immune mediated myositis.

Dr. Amato: Thank you very much. Great. Thank you. Dr. Donald Kohn.

Dr. Kohn: Yes. Thank you. I actually have two questions. The first one, in the integrated analysis, there were 12 patients excluded because they got a different dose. I'm not clear, was that intentional or they were at a different dose cohort, or that just there was a problem, they didn't get their full dose delivered?

Dr. Rodino-Klapac: Yeah, it was not intentional. In part one of the study, the patients received the intended dose using a tittering method called supercoil titering. Then the method was then further validated using a linearized standard, and upon retrospective titering is when the different dose levels were identified.

Dr. Kohn: Okay. And then, then my other question is, it went by quickly, but it looked like the vector copy number in 102, or I guess it's 103, the study using the process B virus, the vector copy number on average was lower. And did that correspond to a lower percent positive fiber in that group and lower change in their NSAA scores?

Dr. Rodino-Klapac: Yeah, let me pull that up. It was study 103, the vector genome copy number' If you're comparing 103 to 102, it was 3.4 in 103 in study 102. So it was higher in 103.

Dr. Kohn: Well, I guess I'm asking that about in 102, the one that had the lower vector copy number and the lower percent positive fibers, did that correspond to change in, less of a change in their NSAA scores? Like less of a beneficial effect?

Dr. Rodino-Klapac: Yeah, this is in part one of study one and two. Maybe I can have Dr. Mason comment on the functional results.

Dr. Mason: Stephanie Mason, Sarepta Therapeutics I would like to show you a slide that demonstrates on the top row the dystrophin expression that we saw for each cohort in each study. And on the lower row, you see the NSAA change when compared to an appropriate comparator

cohort. And as you can see, across the different studies we see both consistent expression followed by consistent levels of NSAA gain compared to their comparators. And that includes study 102 versus study 103.

Dr. Kohn: Thank you.

Dr. Ahsan: Great. Moving on to Dr. Richard Kryscio.

Dr. Kryscio: Yeah, I had a study a question for, I guess it's the biostatistician. I wanted to know in study 102 part one, where the data was stratified by age four to five versus six to seven, was that the pre-specified in the protocol?

Dr. Rodino-Klapac: Dr. Mullen?

Dr. Mullen: Chris Mullen. So the age groups were pre-specified. There was no powering, however, for those age groups and no specific alpha control for any sort of subgroup analyses. I think this is a really vital question regarding 102 and that imbalance. And if I could quickly just share this data. This really illustrates, it's both an imbalance and a separation, right? In terms of the baseline NSAA and another baseline function, we really have purple patients, treated SRP 9001 patients, that really don't have a good match for corresponding placebo patients. So the separation based on these baseline factors is what inhibits our ability to perform adjustments to address the imbalance.

Dr. Kryscio: Well, how does that work then in, in the, in the study that's now being conducted? Is there any power on the 300? I think it's, I'm sorry. I don't have the numbers of all of them, but I think it's the 300, that's the study that's going in in September. Sorry.

Dr. Mullen: Yes. No worries. Thank you. I'll ask Dr. Stephanie Mason to address your question on 301 and how we've made adaptions for that.

Dr. Mason: Stephanie Mason, Sarepta Therapeutics. We did take some learnings from what happened in Study 102 and have stratified study 301, our confirmatory study, not only by age, but also by baseline NSAA score. Further, our inclusion and exclusion criteria have both a floor and a ceiling for the NSAA score, and we have a maximum time to rise for all patients in the study of five seconds. This reduces the heterogeneity in this sample and gives us confidence that we will have comparable overlapping populations.

Dr. Kryscio: Okay, thank you.

Dr. Ahsan: Very quickly, could you say what those thresholds were on the NSAA for the study 301?

Dr. Rodino-Klapac: Okay. Dr. Mason?

Dr. Mason: Stephanie Mason, Sarepta Therapeutics, the NSAA a had to be greater than 16 and less than 29.

Dr. Ahsan: Thank you. Moving on to Dr. Nirali Shah, please.

Dr. Shah: Hi, thank you. So my question is that the majority of the results presented are from the trials that use process A, in particular the double-blind randomized study. The confirmatory trial uses process B, and I think the only data that we have at present that are from process B are the open label study. Can you speak to what you think the differences in the products may be, as I understand it would be process B that would move forward?

Dr. Rodino-Klapac: Sure. Process A and B, we performed both non-clinical and clinical studies to show the similarity between process A and process B. To date in the study 103 we've dosed 41 patients. And then in study 301 we've dosed more than 120 patients across these two. With study 301, we've dosed over 110 patients in totality, which have passed the 90-day window, and we haven't seen any differences in terms of safety or efficacy between A and B.

Dr. Shah: But we don't have the results from the 301 yet, correct?

Dr. Rodino-Klapac: No results. That's still blinded. Yes.

Dr. Shah: Thank you.

Dr. Ahsan: Great. Thank you. And Dr. Susan Ellenberg?

Dr. Ellenberg: Yes. Thank you. I have a question about the ongoing confirmatory study. I assume that's being monitored by an independent data monitoring committee. And if that's correct, I'm wondering whether there is some kind of a monitoring boundary for efficacy that would permit that study to be terminated early with results announced if the results were very strong.

Dr. Rodino-Klapac: There is a monitoring committee. I will have Dr. Mason comment on the second part of your question.

Dr. Mason: Stephanie Mason, Sarepta Therapeutics. There is a DSMB, Data Safety Monitoring Board, that is monitoring the trial. However, we have no interim analysis planned prior to the completion of part one. So the first time that we will look at the efficacy is at the completion of part one, which will be in a few months.

Dr. Ellenberg: Yeah. Does the data monitoring committee see those data though? Do they see the efficacy data when they review the ongoing data for the study? Do they see both efficacy and safety?

Dr. Mason: I'm going to have to take a look at the charter, and I'll see if I can bring you that information after the break.

Dr. Ellenberg: Thank you.

Dr. Ahsan: That would be great. We can get to that answer later in the afternoon. I think we have gone through our questions. I'll take this opportunity to ask one or two questions of my own. On slide 63, you stratify it by age, and you talk about not having the match of the original

NSAA score for the six- to seven-year-olds. Can you walk me through where on the natural trajectory you expect those to be? Because I would've expected either the placebo to, natural history, to go down or the SRP effect to have gone up instead of, based on the differential and where they are on the trajectory.

Dr. Rodino-Klapac: Sure. I'd like to invite James Signorovitch to address.

Dr. Signorovitch: So, as you can see on the right-hand side, there was a tremendous imbalance in baseline NSAA. As Dr. McDonald explained, the placebo patients were starting with a much higher NSAA score, and that puts them in a place where they're expected to remain stable. And we saw that kind of validated by the matched external controls at that baseline NSAA level. In contrast, the patients who were randomized to SRP-9001 had that baseline imbalance that Mr. Mullen showed. That was partly due to a complete lack of overlap. Those patients had much lower NSAA and also much longer rise from floor times at baseline. And so if we appropriately match them to an external comparator, we can see that these are patients who, in natural history, are clearly expected to decline in function.

Dr. Ahsan: Great. Could you just point very quickly to me where the placebo is, where it's actually stable and not having actually a greater derivative on the natural history?

Dr. Signorovitch: Sure. In the right-hand panel the pair of lines starting at the top around NSAA —

Dr. Ahsan: No, sorry. On the natural history progression that you have on the left, I don't see the point in which the placebo remains stable.

Dr. Signorovitch: Yeah. So when patients kind of reach the top of that curve, that's a period where they would remain stable. So that like, there's no time scale denoted there, but that would roughly represent, you know, 15, 16, 17 years for the full scale at baseline in the figure on the

left. So when patients are reaching that crest, that's when they would remain stable over the one-year period studied in the trial.

Dr. Ahsan: Thank you. I think with that we have to move on for the lunch break to allow us to prepare for the Open Public Hearing. And so I, I'd like to thank all the speakers and for the question and answer session. We will be returning at 12:30, at which — so we're going on our lunch break. We'll be returning at 12:30 at which we'll have that open public hearing. And so I'll hand that over to — oh, I think we don't need to hand it over. I think we can just come back at 12:30. So thank you very much and I'll see everyone then.

Open Public Hearing

Dr. Ahsan: Thank you everyone for returning from the lunch break. We are now going to start the open public hearing portion of today. I have a statement to read, and then after that Marie will handle, has an additional statement, and we'll handle the administrative aspects of the OPH.

Welcome to the open public hearing session. Please note that 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, FDA believes that it is important to understand the context of an individual's presentation. For this reason, 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 expenses in connection with your participation in this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any 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.

Okay. And now I'll hand it over to Marie, the DFO, to manage the open public hearing.

Ms. DeGregorio: Okay. Thank you, Dr. Ahsan. Welcome everyone. Before I begin calling the registered speakers for today's OPH, I would like to add the following guidance. FDA encourages participation from all public stakeholders in its decision-making processes. Every advisory committee meeting includes an open public hearing, OPH session, during which interested persons may present relevant information or views. Participants during the OPH session are not FDA employees or members of this advisory committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during this open public hearing session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate agency agreement with the statements made.

So in fairness to all OPH speakers here today, since this is a one-hour session, we ask that you please remain within your three minute timeframe. We greatly appreciate your cooperation. When I call your name, please unmute your microphone and start your presentation. So next slide please. Could we have the next slide? There we go. First we have Daniel and Lindsey Flessner, parents of Mason and Dawson Flessner.

Mr. Flessner, you may begin when you're ready.

Mr. Flessner: Hello, I'm Daniel Flessner. My two sons, Mason who is five and Dawson who is two, both have Duchenne Muscular Dystrophy. My wife found out she was a carrier after the boys were diagnosed. Our oldest, Mason, is currently in the Sarepta SRP-9001 confirmatory trial. We are here today to continue the conversation about the impact of DMD Plain Eye. For both boys, gene therapy is a hope for them to be able to walk unassisted for longer. It means the

hope of not seeing our children suffer as their muscles fail, and it means hope that our children will not die young.

My oldest son Mason was diagnosed when he was three years old in 2021. The diagnosis crushed us, and the more we knew about the disease, the more hopeless our family became. As the days went on, we began to find ourselves and pull ourselves up out of the hopelessness and try to find our way to fight the disease. Our journey began at Larry's Children's Hospital in Chicago, where we learned about some trials that were coming, one of them being Sarepta's SRP-9001 gene therapy trial that we had a shot at getting Mason enrolled in.

After several tests that were done on Mason to see if he would be a good candidate or not, we found out that he would be accepted into the trial. The decision was made to enroll Mason after several sleepless nights staring at the ceiling and researching as much as we could. We decided that we knew the outcome of Duchenne was fatal, so we were going to choose to do something instead of nothing.

As a family, we are now committed to doing our part as research participants. We, as well as all the other families in the study, know how important it is to remain in clinical trials, even after these therapies are approved, so that data can be collected and other boys can be treated. But for us, it's even more important because Mason is currently in the trial, and his baby brother Dawson is waiting for access. As we continue to take Mason to clinical trial visits, we often find ourselves being saddened. We are the lucky ones, for we have been blessed with this opportunity of hope and optimism for what this therapy could do for our boys. Our hearts break for the ones that are in a holding pattern, their sons waiting on this drug.

To that, there are DMD expert doctors, physical therapists, advocacy leaders, and families with true experience in SRP-9001 speaking today. I urge the committee to prioritize

these voices over the ones that are inexperienced in Duchenne gene therapy and have no children or family members directly impacted. There are four principal investigators in the SRP-9001 studies that were unable to get an OPH spot. I hope the committee has watched their testimonies on the written document. We are committed to this study. We are committed to this fight, and we are passionate about this fight. And due to these new therapies, there is hope.

FDA, please exercise regulatory flexibility for Duchenne. Now is the time. Thank you.

Ms. DeGregorio: Thank you, Mr. Flessner. We deeply appreciate your testimony, and thank you. Up next we have Mr. Brent Furbee. You may go ahead, Mr. Furbee, when you're ready.

Mr. Furbee: I have no financial, so my opening, I have no financial connection to anybody within this hearing. So my name is Brent Furbee. Please play video. Thank you. My name is Brent Furbee. I'm the father of Emerson Furbee. Emerson is a current participant in Sarepta's Endeavor trial, the 103 trial. In February of 2021, at the time of Emerson's enrollment in Study 103, the only approved therapeutic for him was steroids. As you can see in the video, he struggled with stairs and other daily activities a typical four-year-old would be doing.

My wife and I had scrutinized data, watched videos, and spoken to different clinicians surrounding emerging treatments for DMD. None of them compared to what we had seen from the boys who had been dosed with SRP-9001. At that time, we determined that Emerson was reasonably likely to benefit from this treatment. Next slide, please.

Within days of receiving the gene therapy, we began to see physical improvements, and there is nothing ambiguous about these improvements. In November of 2023, months before being dosed, Emerson scored a 19 on his North Star assessment. 66.3 seconds on the timed 100-meter run, 5.4 seconds on the 10-meter run, and 3.7 seconds rise from the floor. Three

months post-treatment, Emerson scored a 23 on the North Star. 53.1 seconds on the 100-meter run, 5.1 seconds on the 10 meters, and 3.5 seconds to rise, all improved.

To answer the question of sustainability and durability, in his most recent clinical visit, 22 months post-treatment, Emerson continues to get stronger. He scored 27 on the North Star. 44.3 seconds on the 100-meter run, 4.75 on the 10 meter, and 3.2 seconds to rise from the floor. These are all clinical visits done outside of the trial, but it hasn't just been the physical improvements that have been at benefit to Emerson. Emerson began expressing a new aura of confidence around his physical abilities that allowed him to participate in activities he hadn't been able to in the past.

This video shows Emerson pedaling his tricycle independently for the first time only seven days post infusion. The newfound confidence and greater physical strength allowed him to spend that first summer playing T-ball, swimming independently, and running around with other neighborhood children. The progress he had made became so noticeable, that a neighbor who was aware of Emerson's condition made the remark, Is Emerson on a new medicine? He looks so strong. Next slide, please.

The commitment we have made to the clinical trial process was to get us to this point. These visits have allowed us to see the progress he is making, but in a clinical setting. Watching the doctors and physical therapists be in amazement as he rises from the floor with no Gower’s maneuver or stands on one foot for three plus seconds is always uplifting.

With Emerson, there were no serious adverse events. The only notable event was six or eight days prior or post infusion, he vomited upon waking up, just one time. Within an hour, he felt well enough to attend his preschool program that day. If you ask just about any parent of a DMD son, they would trade some vomiting for the increased strength and endurance we have

seen in Emerson. They would sign up for this treatment tomorrow. While only six years old, still we have explained to Emerson the importance of what he did and continues to do by making all of the clinical visits. On a very routine basis, Emerson will ask us when other boys will be able to receive the same medicine he did, and we hope we are able to tell him that that moment will come very soon. Thank you.

Ms. DeGregorio: Thank you, Mr. Furbee. We very much appreciate your story and for sharing with us. Thank you again.

Mrs. Melanie Hennick, parent of Connor, SRP-9001 trial participant. Mrs. Hennick, you may proceed when you're ready.

Mrs. Hennick: Thank you. I have no conflict. Please play the video.

Hello, my name is Melanie Hennick, and I'm here on behalf of our 12 year-old son Connor, who joined the SRP-9001 effort back in 2019. Connor is in sixth grade and likes social studies and English. He's obsessed with sports, and last season he moved up to the advanced baseball league. He is practicing percussion to join the school band this fall, and he has a crush on a young lady named Macy.

This all sounds like a pretty normal 12 year old, perhaps like a 12 year-old child that you may have had or known. I'm sure you can picture them. Now, imagine someone told you your child was born with a condition for which there is no cure, no cure and a ticking clock. Connor lives with Duchenne Muscular Dystrophy, but please note that I very deliberately say lives with, because he does just that.

At 12 years old, he lives an active life. Beyond the fun you see here, he climbs the stairs in our home. He is not wheelchair bound, and he is not solely reliant on accessible accommodations. And while there may not be a cure, I and others are here today with something

else. We're here with hope, hope in the future because of the dedicated teams who have worked tirelessly on SRP-9001 to help our sons. We're here with faith in the science and years of research to ensure that this therapy is safe and effective and faith in what we've seen it do for our sons and what it can do for others. And above all, we're here with love, the love that only a parent can have for their child.

We were so fortunate to join the trial when Connor was seven, getting the life-changing news when we were mere days away from aging out of qualification. At nearly eight, he should have started slowing down, withdrawing from physical activities due to disability. Many of his Duchenne peers of the same age followed that expected path, but Connor did not. His current mobility at 12 is quite literally unheard of. You have heard about the science and the data behind this treatment and its participants, but look at the video. Earlier someone asked about older boys. Look at our Connor. Watch him jump and run and play. But know that it's more than the physical, it's the mental, emotional, and social stability that Connor enjoys because of how well he is doing.

Again, he is living with Duchenne, not suffering from it. This therapy gave him that. Exon-skipping was not an option for Connor. This gene therapy was our hope. Otherwise, the natural course of this disease would've been our reality. Don't all children deserve that opportunity to live and enjoy their childhood without worrying about declining or if these steps are their last ones or about a ticking clock? We know this treatment is not a cure, but it is an extremely significant difference. Please approve SRP-9001 and keep our hope, faith, and love alive. Thank you for your time and consideration.

Ms. DeGregorio: Thank you, Mrs. Hennick, for sharing your, you know, your wonderful story. I thank you for that. Okay. Next slide. We have Dr. Linda Lowes.

Linda, you may proceed when you're ready. Dr. Lowes, please begin when you are ready. Okay. Dr. Lowes, unless, okay. Dr. Lowes, you might need to press asterisk six, star six, on your phone to unmute. Okay. Dr. Lowes, we will return back to you at the conclusion, and we will proceed to the next OPH speaker.

Ms. Kelly Maynard, you may begin when you're ready.

Ms. Maynard: Thank you, and I have no conflict. I'm Kelly Maynard, and I'm here to talk to you about the treatment effect of SRP-9001 and the non-treatment effect for boys like my son, Jack, those boys who have not been treated with gene therapy because Jack's reality is the lived reality of so many with Duchenne at this moment. Start the video please.

This patient from the trial, dosed at six years old, rides a bike with no difficulty. This is Jack at age seven performing a six-minute walk test. Jack's legs crumble, and he cannot get back up on his own. This happened many times each day as he lost ambulation. Jack was never able to ride a bike. This eight year-old patient from the trial, dosed at age five, is confidently traversing a ropes course. And this is Jack at that same age trying to play basketball with a friend who is a year younger than him. This 11 year-old patient from the trial is hiking with his family, and this nine year-old patient has the strength to give his little sister a piggyback ride, while Jack at age eight and a half attempts to simply stand up from his chair. Heartbreakingly, he can't.

This 10 year-old patient in the trial is paddle boarding. At age nine, Jack struggles to high five his baby cousin. This 11 year-old patient from the trial is running, running through a mall. Jack also at age 11 is attempting to get himself a snack. He uses, excuse me, the armrest of his wheelchair to support his arm, and then walks his hand over to the door handle. This 11 year-old patient is, from the trials, playing handball. This is Jack in a PT visit at age 10. He can no longer

lift his arms to pull on a shirt, lift a fork to his mouth, or to hug me. Our untreated Duchenne story is about so many more like Jack. Next slide please.

Uh, next slide. Thank you. Image number one is Anthony. Six months after losing ambulation, he had incredibly painful and risky spinal fusion surgery. Image number two is Joseph at 11, heel cord lengthening on both legs, was in cast for eight weeks, and never regained function lost during his recovery. Image number three is Christopher. At age 12, he fell by trying to sit down and broke a leg. He never walked again. And number four is Noah, full spinal fusion at 15. At 24, acute perforated peptic ulcer, pneumonia, tracheostomy, colostomy, Foley, and feeding tube. This is the certainty of Duchenne untreated.

Next slide please. And finally, more certainty of Duchenne untreated, Danny gone at 16; Austin, gone at 16; and Mitchell, gone at 10. A delay in approval, even for a few months, means many kids will irreversibly lose function, and we stand to lose another generation. Our Duchenne community understands risk, and our families have a long track record of fulfilling our end of the research bargain. We live with risk every single day. The need is urgent. Thank you.

Ms. DeGregorio: Thank you, Ms. Maynard, for your very compelling presentation. Ms. Debra Miller, Founder and CEO of Cure Duchenne and mother of Hawken Miller, age 26. You may proceed, Ms. Miller, when you're ready.

Ms. Miller: Thank you. I have no conflict, and I am the CEO and Founder of Cure Duchenne and the mother of an incredible son, Hawken, who has Duchenne Muscular Dystrophy.

I'm here today to represent the voice of patient advocacy organizations serving those impacted by Duchenne, all of whom are in support of the accelerated approval of SRP-9001. We recognize the central question is whether the micro-dystrophin delivered via an AAV and quantified on biopsy with study participants is reasonably likely to predict clinical benefit.

Duchenne patients with very low levels of revertant fibers have a milder disease phenotype, and therefore any increase in protein is beneficial. There is considerable peer-reviewed evidence that micro-dystrophin delivers similar long-term benefit in multiple Duchenne animal models and improves strength in time function tests in patients participating in these clinical trials. The accelerated approval program allows for faster approval based on surrogate endpoints for serious conditions with an unmapped medical need like Duchenne. Clear evidence of efficacy has been seen in participating patients, and we believe that the risk benefit profile is well understood by the community.

Equally as important, principle investigators in the open label studies have provided testimony that the drug provides a meaningful benefit. Furthermore, the company has fully recruited its confirmatory trial, and enrolled patients are committed to completing the study. And we value more data to make continued informed decisions about our children's health. All of this supports using the accelerated approval pathway to get this drug to patients earlier than would normally happen. A failure to do this would bring in to question the purpose of the accelerated approval mechanism.

Science is progressive. We do not have the luxury of waiting for the perfect drug. It will instead happen through scientific evolution. One approval will lead to further improvements in better treatments in the future. Approving 9001 is a huge step forward.

For the past 20 years, Cure Duchenne has invested in most of the Duchenne therapies that are in clinical trials today. And over the last few years, Cure Duchenne has identified and funded promising next generation gene therapy technologies, including non-viral delivery and other strategies for overcoming neutralizing antibodies and barriers to re-dosing. 9001 is the bridge

that will allow for preserved muscle function and keep patients walking and living long enough to benefit from future scientific progress.

The threat to losing function in survival is real, as the lack of dystrophin leads to muscle degeneration. Once a muscle is wasted, there is no repairing it. Any delay in approval ensures, with a hundred percent certainty, the continued progression of this devastating disease. Frankly, it will be too late for many. They will have needlessly lost ambulation that will never return, and their cardiac function, the ultimate cause of death, will deteriorate.

Families facing Duchenne cannot afford any delays. Their clocks are ticking. Our community has a steadfast commitment to completing the confirmatory study for the benefit of all individuals with Duchenne. Help us make this the first generation of individuals that survives Duchenne.

Ms. DeGregorio: Thank you, Ms. Miller, for sharing your story. We greatly appreciate it.

Okay. So up next is B. Scott Perrin, Jr., PhD. Dr. Perrin, you may proceed when you're ready.

Dr. Perrin: Okay. Hello, we are Clara (phonetic) and Scott Perrin. We do not have a financial relationship with the sponsor. Our son is in the SRP-9001 phase three clinical trial. The day before Mother's Day, 2021, our lives were up ended when a blood test revealed that our, then, three year-old son Luke had Duchenne Muscular Dystrophy. As two scientists, we dove into the research and quickly realized that with the diagnosis of Duchenne, time is equal to irreversible muscle loss. We needed something effective and quick, but the outlook was grim.

Some hope was gained when a genetic test a month later revealed that Luke had one of the more common DMD deletions. He was amendable to Exon 51 skipping with which there was an approved treatment Exondys. While we hear many positive experiences with Exondys, it

exhibits an incremental improvement, providing less than 1% dystrophin, the protein Luke is missing. The next generation Exon 51 skipping therapies have great preclinical results. But at the time we were making a decision to join the Sarepta gene therapy clinical trial, the phase one Exon-skipping trial was on clinical hold by the FDA.

We realized that micro-dystrophin gene replacement therapies would give Luke a greater amount of significant smaller pro-dystrophin than Exon-skipping. We also weighed the risk, compound a single-dosed micro-dystrophin with possible liver damage, preferable to a weekly or monthly dose PMO with the Exon-skipping technology, which is known to cause hypomagnesemia, both of which can be fatal. Sarepta and Pfizer's gene therapies were both recruited in phase three with excellent phase two results. So we joined the gene therapy wait list and eventually received a spot in the Embark 9001 clinical trial.

There's a 50% chance that Luke initially received the placebo and will not receive the gene therapy until July of this year. This guarantees the treatment before Luke is six, and we expect children dosed younger to have the best results, as they have the most muscle and least damage, again, highlighting the urgency to get these boys treated early. Among those with fatal rare diseases, we are fortunate that so much is available for Luke.

Luke is a relatively well-mannered boy for someone on daily steroids. Many boys with DMD are unable to consistently follow directions and excluded from clinical trials. This obliges us to follow through with the trials available to us and help the community the best we can, but we must advocate for immediate access sooner, as the benefits outweigh the risks. We are eager for Luke to receive the second dose in the SRP-9001 clinical trial.

Independent of the outcome of this review, we are committed to following through this clinical trial, seeing the impact for ourselves, and advocating for fast approval and greater access

to any therapy that improves the lives of boys with Duchenne. We greatly appreciate your consideration for our experience, but please remember time wasted is muscle loss.

Ms. DeGregorio: Thank you, Dr. Perrin. We really appreciate your sharing of your story. Thank you.

Okay. Next slide. We have Ms. Marit Sivertson. Ms. Sivertson, you may proceed when you're ready.

Ms. Sivertson: My name is Marit Sivertson. I am here on behalf of my son Brecken Kenny (phonetic), who is nine years old and in third grade. He is a participant in study 102 of the SRP-9001 clinical trial. I have no disclosures. While I'm speaking, you will see comparison videos of Brecken before and after receiving gene therapy. Six years ago, Brecken was diagnosed with Duchenne. It was not long after this diagnosis that my family quickly learned what the absence of dystrophin meant for our son.

It meant that my son would not leave my side while his brothers and friends played because he knew that he couldn't keep up. It meant that when we get together as a family, we'd have to hide our tears and look away from each other when we'd see Brecken struggle to walk up the stairs or even lift himself off the ground. It meant that we had to think about Brecken's future in terms of mobility, braces, wheelchairs, and whether he'd even have friends. Without dystrophin, hope was a scary, dangerous thing to even think about. Having a child with this horrific disease meant that we couldn't let ourselves dream about the future because it was too painful, but now we aren't afraid to hope for his future.

Today, Brecken isn't just climbing stairs and standing up with ease, he swims, he dives, he runs, he bikes, he jumps. He is living the life that every sweet nine year-old boy ought to be living. Our plans for his future don't revolve around worrying how we will help him get dressed,

walk up the stairs, or feed himself. Now, when Brecken talks about what he wants to do when he's older, my husband and I no longer force a smile. We smile because his dreams are a reality now. We no longer just have hope. What we have here is real progress.

The changes we've experienced firsthand aren't reasonably likely to predict clinical benefit. These are obvious clinical benefits. The nearly 200 boys who participated in this trial now have hope. But as I sit here today, I think of my friend Sarah, who has two sons with Duchenne about the same age as Brecken, who just the other day told me that she has no hope as her precious boys continue to slip away from her.

Sarah's sons deserve the same life-changing opportunity as my son, and there are thousands of other boys who could share the same story of Brecken. And that story, the one that changed the course of his life, started with the FDA approving this clinical trial. You must recommend accelerated approval of this therapy. The time is now. The science supports it, and the lives of thousands of other boys across this country depend on it. Thank you.

Ms. DeGregorio: Ms. Sivertson, we appreciate your story. Thank you very much.

Up next we have Sheila Ungerer, Will's mom. Ms. Ungerer, you may proceed when you're ready.

Ms. Ungerer: Hi. I have no conflict. My name is Sheila Ungerer, and my son Will was the first patient in the SRP-9001 102 clinical trial at Nationwide. I am imploring you to consider the patient data that is presented today and to approve this for broad use in boys with Duchenne. I come from a unique perspective. Rather just after his fifth birthday in 2018, Will received the gene therapy that has dramatically changed his life and his future.

I come from a unique perspective. Our firstborn son, Luke, passed away from pediatric cancer just one year before Will was diagnosed with Duchenne. We went from never having

thought much about rare diseases to being brutalized in the worst way possible by two totally separate, devastating diagnoses in two of our children. But thanks to gene therapy, we have real hope for Will's future.

In life, you hear about days that changed everything. The day of Will's gene transfer was absolutely one of those days. Before, he fell down a lot, and worrying about injuries was relentless. He was unsteady, and our hearts would pound in distress and fear, apprehensive about him being knocked over or not being able to participate and feeling left out. Will needed help to get dressed, brush his teeth well, and stairs were really hard.

As you can see in this video, thanks to gene therapy and the decades of diligent science and rigor behind this trial, Will's childhood has not been hindered by Duchenne. This has meant days free of the dread and constant worry that was part of life before. After gene therapy, everything changed immediately. Soon after dosing, Will said, remember when my legs used to hurt all the time? Well, they don't hurt anymore. The worry about falls was eliminated. He was so much more steady and had the ability to climb stairs reciprocally for the first time ever, and it wasn't hard for him. For the first time in his life, he was upside down on the couch, running, climbing, rolling down hills, playing on the floor, leaning, reaching across his body and behind him.

Each new experience meaning increases in confidence and who knows how much value for his sense of identity and overall development. Will joined our neighborhood swim team and swims up to 500 meters at daily practices just like his peers without Duchenne. He's experienced non-adapted baseball, soccer, and tennis, feeling like a member of the team. He enjoys water slides and all the steps to access them, and he rides his bike without training wheels. Full days at zoos and parks, the beach, sledding, miles of trick-or-treating, walking down the street to play

with friends. I mean, he had his ninth birthday party at a laser tag park. None of this seemed possible before.

Will has always been bright and curious, but his intellectual abilities were noticeably improved. He has even better focus and memory now. This increase in dystrophin made a huge difference. We didn't hesitate to enroll Will in this trial. There are no risks that would've deterred us. We would've done anything to be able to see this life change for Will.

It's been nearly five years. He's nine and a half now, and he's a happy, friendly, confident third grader, and we are so proud of him. And on Monday next week, he'll get himself ready for school. He'll climb the steep steps of the bus with his backpack, walk into school, play in the field at recess, and carry his own lunch tray. His life is completely different now. So much more is possible. Please approve this therapy. This isn't a hope for things to come. This is a possibility right now. Thousands of other boys need this same opportunity soon.

Ms. DeGregorio: Thank you, Ms. Ungerer. We greatly appreciate that testimonial of yours. And thank you again. We'd like to reverse back to Dr. Linda Lowes who had some technical challenges earlier. Ms. Lowes or Dr. Lowes, are you able to hear us?

Dr. Lowes: Hello? Yes, can you hear me?

Ms. DeGregorio: Oh, wonderful. Great. You may proceed. Dr. Lowes, are you there?

Dr. Lowes: Yes. Can you hear me?

Ms. DeGregorio: A bit. Would you like to go? We'll see if it works. Oh, I think the signal.

Dr. Lowes: Hello?

Ms. DeGregorio: Yes. The signal's fading in and out.

Dr. Lowes: Can you hear me now?

Ms. DeGregorio: You're fading in and out, Dr. Lowes, but we could try. Okay. All right. Well, let's see. I think that we may need to move on. I don't think the connection's working. Okay. Could we proceed to advance the slides for Dr. Lowes? I believe there was a presentation there. Okay. All right.

Okay. Well, apologies for the glitch there. We're going to proceed with Dr. Michael Abrams.

Dr. Abrams: Yes, good afternoon. Can you hear me okay? Good afternoon. Can you hear me okay?

Ms. DeGregorio: Yes, we can, Dr. Abrams, you may proceed.

Dr. Abrams: Okay. Thank you very much. Michael Abrams here, Public Citizens Health Research Group. No financial conflicts of interest on this matter. The analysis conducted by the FDA that you're going to hear about later, FDA scientists determined that SRP-9001 has yet to demonstrate sufficient data warranting its approval to treat DMD.

The most credible evidence provided by the sponsor for this application comes from the single randomized trial, which we heard about. 20 subjects received the novel micro-dystrophin gene using a viral vector, and 21 subjects received placebo. 48 weeks after infusion of 9001, motor functioning was assessed. Basic analyses did not show significant motor function changes in patients receiving the 9001 compared to controls in that important experiment. Accordingly, the sponsor now seeks accelerated approval based on a surrogate marker rather than the usual standard of demonstrated clinical impact.

A surrogate endpoint must, of course, as most of you know, the statutes state clearly that there must be a scientific consensus that it is reasonably likely to the yield clinical benefit. Unfortunately, available clinical and animal data, again, that the FDA's going to be talking about

later, is not conclusive in this regard. That is likely because micro-dystrophin is an engineered molecule, as we heard from the sponsor this morning, that contains less than half of the structure of natural dystrophin, native dystrophin, excluding many plausibly important functional components. The lone randomized trial failed, in fact, to show that micro-dystrophin protein levels at week 12 correlated with muscle function at week 48, a null result that weakens distinctively the reasonably likely argument for clinical benefit related to this surrogate marker, at least at this time.

Instead, such a correlation only became evident when 40 open label subjects were added to the analysis. And, of course, open-label design introduces bias clearly. It should finally be noted that though the DMD therapy is somewhat novel, it has substantial mechanistic overlap, via dystrophin shortening, with four previous accelerated approvals, still unconfirmed by FDA mandated follow-up studies. Accordingly, it is concerning that a fifth therapy might be introduced based on a biomedical, biochemical mechanism so tightly aligned with four questionable therapies already on the market.

Such serial approvals contradicts the important concept that speculative fast track pathways should be reserved for therapies that provide meaningful therapeutic benefit over existing treatments and where there's a scientific consensus that the surrogate marker is a clear harbinger of clinical benefit. That is not the case here, unfortunately, not at this time. Thus, we strongly urge the advisory committee and the FDA to reject application SRP-9001 for accelerated approval. Both effectiveness and regulatory history concerns, not to mention safety, which I didn't have time to talk about today, make that rejection necessary. Thank you very much.

Ms. DeGregorio: Thank you, Dr. Abrams, for your story and for sharing your remarks. Thank you. Okay. Please, next slide. We have Mr. Mohamed Ali. Mr. Ali, you may begin.

Mr. Ali: Okay. Hello. I am Mohamed Ali from Egypt. My son Ali is a patient with Duchenne. He's seven years old. We discovered this disease when Ali was two and a half years old. He's my only son for the mother Okaya (phonetic) after 18 years of infertility, and she cannot give birth again as the doctor said. We received the greets from the doctors in a great shock. But the biggest shock was when the doctors told us that there is no DMD actual and adequate treatment. What can we do to face this deadly progressive disease to attend to the lives of our children? What is actual treatment that my son has taken since we discovered the disease so far?

A many question that have no answer, but when answer, there is no treatment for this deadly disease. Any disease must have a treat to be confronted except for Duchenne, a deadly and an advanced disease. It's known many losing the ability to walk independently by 10 to, 9 to 10 years, and it has no treatment so far. Even some of the existing drugs are temporary and do not treat underlying causes of the disease and cannot stop its development. Hence, we knew that there is a gene therapy for Sarepta, and when the clinical trial started, the return, the hope returned again. We saw many positive result and great effectiveness by increasing the dystrophin protein. The delivery of micro-dystrophin is thought to be fundamental and necessary to protect muscle fibers. The progression of the disease will be slower, which leads to preserving the muscles. This will help my son Ali to remain healthy and maintain his muscles after producing his dystrophin protein. And thus he will continue to practice his life, play, jump, and walk without, with any help from anyone, which provides us with a sense of hope. And this is what we dream of.

We want many ambulatory children to take this treatment. We extremely need you to allow different ages of children to take this treatment. This is the only chance for all, for all of us now to approve gene therapy. 'Cause Duchenne is a deadly and an advanced disease. And its developed is known Sarepta 9001 has achieved positive result and great effectiveness. It'll give a positive benefit for our children. All children urgently needs this gene therapy as soon as possible. It will end their suffering and slow its develop. The approval in the US would be the first step to ensure the broader access to Sarepta 9001 globally, especially here in my country, Egypt, because there are many families waiting for this gene therapy as soon as possible. Thank you all.

Ms. DeGregorio: Thank you, Mr. Ali, for your dedication to attending today. And we appreciate your remarks. Thank you.

Mr. Ali: Thank you so much.

Ms. DeGregorio: Thank you. Okay. Next we have Dr. John Brandsema. Dr. Brandsema, you may proceed when you're ready.

Dr. Brandsema: Hello. My name is Dr. John Brandsema, and I would like to thank the FDA for this opportunity to represent the teams of clinicians and researchers that care for DMD. I am a child neurologist and the neuromuscular section head at the Children's Hospital of Philadelphia, and I have been practicing for over a decade as a clinician and a clinical trialist. I have been a consultant for Sarepta. I will keep my thoughts about the approval of delandistrogene moxeparvovec brief.

Based upon the data I have seen thus far from the ongoing development program, I am convinced this therapy should be approved. Discovery of the dystrophin gene in the late 1980s was viewed by the DMD community as the key to a future cure. It has taken nearly 40 years to

come close to the realization of this dream, and I could not be more excited to see this becoming a reality. With all truly innovative advances in healthcare comes the responsibility to steward these exciting new therapies carefully, humbly, and with a long-term perspective. We do not yet fully know the durability of efficacy, short and long-term safety, and effects of delandistrogene moxeparvovec on other tissues in the body.

We must provide an interdisciplinary long-term care approach as we launch gene therapy for DMD. Care teams need to be fully informed about potential side effects, including those related to viral vectors, immune suppression and immune recognition of a transgene and a protein, micro-dystrophin, that these boys have not previously seen. Guided by experience with bone marrow transplant, solid organ transplant, and other lifesaving therapies, we advocate for similar survivorship models of prospective surveillance for the DMD community.

We can also learn from our collective experience with the launch of onasemnogene abeparvovec or Zolgensma for spinal muscular atrophy. We celebrate the remarkable transformation of SMA Care but recognize several valuable lessons. First, we need to be able to manage expectations of desperate families seeking immediate access to gene therapy. We know that DMD patients can safely wait several months to receive their dose, but we also know that several months will feel like an eternity to a family watching their child decline.

To address this reality, we will need clear messaging, support, and ethical action plans across the country. Second, we know that the complex authorization access, dosing, and monitoring will require centers with the appropriate resources and expertise. We would not allow a surgeon to perform an organ transplant without a team in place to manage the pre and post-surgical care. Why then is gene transfer any different? Third, we need to consider mechanisms for financial support for the entire process of gene therapy. Bundled care offered by the third-

party payers would allow gene therapy treatment teams to use dedicated codes for lifelong routine post-gene therapy surveillance, as well as its known complications. The neuromuscular community must create a network structure similar to the Children's Oncology Group, enrolling every child treated into consensus platform protocols to elucidate optimal care.

We are pioneered in a novel area of medicine, both excited by the potential and humbled by the responsibility. We have the tools to bring innovative therapy to reality, and I hereby advocate for that opportunity on behalf of our patients. Thank you again for hearing my voice, and my email is brandsemaj@chop.edu if anybody wants to reach me to discuss further.

Ms. DeGregorio: Oh, thank you, Dr. Brandsema, for sharing your viewpoint and providing remarks today. Thank you. Next we have Dr. Anne Connolly. Dr. Connolly, you may go when you're ready.

Dr. Connolly: Thank you for the opportunity to speak. I am Anne Connolly, a pediatric neuromuscular neurologist, and I'm also board certified in neuromuscular pathology. I worked as a sub-investigator to Dr. Mendell at NCH on the micro-dystrophin gene trial. When I began in neuromuscular practice in 1990, corticosteroids alone was standard of care. Over the last 10 years, FDA approved exon-skipping therapies have allowed boys to walk a little longer and young men to breathe a little longer without support. But none ever approved function over their own baseline like we have observed with 9001. As a neuromuscular pathologist, I have diagnosed Duchenne pathologically long before we could do so with dystrophin immunostaining. HNE readily demonstrates fibrosis, degeneration, and regeneration. I know the committee is well aware of the robust micro-dystrophin expression and restoration of the sarcoglycan complex with micro-dystrophin gene transfer.

I am asking you to also review and consider restoration of muscle fiber size and reduction in fibrosis, clearly demonstrated in published muscle biopsies from treated boys. These changes, micro-dystrophin expression, restoration of the sarcoglycan complex, and reduction in fibrosis, are the physiologic underpinnings of my observations. As a clinical trialist, I have used the NSAA for many years. Please note that an imbalance of five points on this scale reflects groups at very different disease stages. Baseline function must be considered.

Against that background, I will now tell you what I've seen in the care of more than 40 boys after micro-dystrophin gene transfer. Motor function gains vary from boy to boy and include skills I have never seen in any boy with Duchenne. These include loss of the need for Gower's maneuver to stand, the ability to jump and shoot baskets, the ability to ride a bike without training wheels. These motor skills require both proximal and distal strength.

In clinic, I speak directly to the children. These days, if they have had gene transfer, I dare to ask what new things they can do rather than what they have not yet lost. Parents sit quietly and proudly and smile as their sons share their own stories. Allow me to share one brief story. One father, whose son was dosed at age five, explained that before gene transfer, if his son got on base during the T-ball game, children would round past him on the bases after the very next hit. One year after gene transfer, he is now able to run, and no one passes him on the bases. His son was very proud of being a left-handed T-ball player, a great advantage.

In short, over the last four years working with Dr. Mendell and his team, I have watched bits of childhood being restored one boy at a time. These clinical observations are very important since the five point baseline imbalance in the 102 study did confound the analysis. The mechanism of action of gene therapy supports a broad label. Thank you for your time and attention.

Ms. DeGregorio: Thank you, Dr. Connolly, for your remarks. We appreciate them. Mr. Paul Melmeyer, you are next.

Mr. Melmeyer: Thank you for the opportunity to speak to you today. I am Paul Melmeyer, Vice President of Public Policy and Advocacy at the Muscular Dystrophy Association, and we serve all individuals with neuromuscular diseases, including Duchenne Muscular Dystrophy, in a variety of ways, including advocating for the accelerated development of more and better therapies for the neuromuscular disease patient population. I have no financial relationships to mention.

The Muscular Dystrophy Association does not participate in product specific advocacy, and thus will not make a specific recommendation on this treatment. Instead, I'll outline the flexible regulatory approach we expect the FDA and this advisory committee to utilize when considering this and all rare neuromuscular disease therapies.

First, we urge the FDA to flexibly and consistently use the accelerated approval pathway for approving rare neuromuscular disease treatments when proving clinical effective, effectiveness in heterogeneous, often slowly progressing, neuromuscular diseases in a timely manner is not possible. Most neuromuscular diseases, including DMD, are irreversible in their progression; and, consequently, the muscle damage lost while waiting for new therapeutic approvals cannot be regained upon later approval of the therapy.

As Dr. Peter Marks, Director of CBER, recently stated at NDA's clinical and scientific conference, quote, we can't be so careful about our approvals, under accelerated approval, that we prevent potentially lifesaving therapies from getting to market in a timely manner, end quote. We understand some have called for more infrequent use of the accelerated approval pathway, but to do so may essentially halt all possibility of safe and effective treatments reaching some

neuromuscular diseases, an absolutely unacceptable result. We urge the agency to continue to flexibly apply the accelerated approval pathway in rare neuromuscular diseases while utilizing the authorizations pertaining to post market confirmatory trials enacted by Congress last year.

Second, we reiterate the various ways in which substantial evidence and effectiveness can be demonstrated. FDA has elsewhere stated that, quote, our regulations allow for regulatory flexibility to expedite the development and valuation and marketing of new therapies intended to treat persons with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists, end quote. FDA has demonstrated several recent examples of flexibly using the accelerated approval pathway in subsequent confirmatory trials to support approval of neuromuscular disease treatments. And we encourage the agency to continue to do so.

Finally, the FDA has a well-established record of approving treatments for serious and life-threatening rare diseases without the traditional level of proof of effectiveness required in more common or less serious diseases. Analyses have shown that at least two thirds of rare disease drugs are approved by the agency flexibly considering whether the effectiveness evidence is adequate. These flexibilities have been reiterated by the three most recent PDUFA re-authorizations and consistently supported by patients, their loved ones, the organizations that serve them, their clinicians and their elected officials. Thank you again for the opportunity to testify today.

Ms. DeGregorio: Thank you, Mr. Melmeyer for your remarks. I want to point out that we have four speakers remaining, and we're running to the end of our time. So I'd ask the remaining speakers be efficient with their remarks. And we'll just continue from here. So Mr. Nathan Plasman, you may go. Thank you.

Mr. Plasman: Thank you FDA officials and fellow Americans for this opportunity to speak. Greetings from suburban Chicago. As stated, my name is Nate. I'm 43 years old. I was born in late July of 1979, which would make me a contemporary of brothers Christopher and Patrick Furlong of Middletown, Ohio, if Duchenne hadn't prematurely ended their earthly days back in October of '95 at the ages of 17 and 15 respectively.

My wife, Sarah, and I have three children. Our youngest, Andrew, is 8.83 years old. He'll celebrate his ninth birthday on July 1. He was diagnosed with Duchenne on Saturday, July 2, 2016, the day after his second birthday. Just four days ago, Sarah, Andrew and I ventured to Nationwide Children's Hospital for Andrew's SRP-9001, study 102, week 182 appointment. Our quick 26-hour trip was uneventful and went according to plan. 4.33 years have passed since Andrew was dosed with micro-dystrophin on January 10, 2019.

Original study 102 trial protocol required patients to stay in Columbus for 30 days following week one dosing. So Sarah and I decided that she would stay in Ohio with Andrew, and I would return back to Suburban Chicago to be with our two older kids. During this interim separation, phone calls, Sarah often opened with her excitingly exclaiming, You're never going to believe what Andrew just did today. Or we'd connect over FaceTime, and she'd very discreetly whisper, Nate, Nate, check this out, showing me live footage of Andrew doing the unexpected racing upstairs, climbing indoor playground equipment, running, jumping, popping up off the ground after sitting or laying on the couch. We cried nearly a quadrillion tears of joy during this period of separation.

Today, Andrew is a rising second grader at Timothy Christian School. He blends in with the other students and has minimal accommodations because he functions like a normal second grader. Totally defined the natural history trajectory of this awful, awful disease. His classmates

view him as a healthy, happy, capable peer, and they're totally unaware of his medical condition. Andrew loves animals and hopes to be a national park ranger. We envision Andrew proudly walking across the auditorium stage in 2033 to receive his high school diploma.

We're forever grateful to Dr. Jerry Mendell. We trust him implicitly. He, along with his wife Joyce, have together dedicated over 110 years to arresting the awful progression of this cruel disease. Additionally, everyone at Nationwide Hospitals, Sarepta Therapeutics, and Parent Project Muscular Dystrophy have showered us with love, encouragement, and support. Each of these three organizations is the best of the best, the gold standard in each of their verticals or industries. They feel their questions and respond to our emails and text messages and voicemails without fail. They execute on their promises, and they make things happen.

Gene therapy changed the trajectory of Andrew's life. For the past 4.33 years, gene therapy has successfully arrested the progression of this awful condition. It meets an unmet need. Clinical trial perfection in this disease space is tricky. Micro-dystrophin has produced a transformational improvement and tangible benefit for Andrew. Our son is proof that gene therapy is effective and should be approved. Thank you.

Ms. DeGregorio: Thank you, Mr. Plasman for your compelling remarks. We appreciate them.

Dr. John Porter, you're next. Thank you.

Dr. Porter: Can you hear me?

Ms. DeGregorio: Yes, we can. Thank you.

Dr. Porter: So I have no financial relationships with the sponsor, its product, or its competitors to disclose. So I'm retired from 21 years in academic research, 10 years at the NIH and several years with patient advocacy, all in neuromuscular space. At the NIH, I was the

Designated Federal Official for the Interagency Muscular Dystrophy Coordinating Committee, and I also managed a large portfolio that included research grants that have supported much of the academic work between SRP-9001. I thank FDA and the advisory committee for the opportunity to make remarks on the micro-dystrophins that are used in gene therapy programs for Duchenne.

Based upon genotype phenotype relationships in the closely related Becker Muscular Dystrophy, FDA accepted the expression of, of truncated dystrophins produced by Exon-skipping were reasonably likely to predict clinical benefit. Moving beyond this regulatory precedent, there's compelling evidence that micro-dystrophins are structurally and functionally superior to some Becker protein analogs, and more likely than those from Exon-skipping drugs to yield improvements in patients with Duchenne. Although the packaging capacity of AAV vectors can’t accommodate the full 11.5 KB dystrophin coating sequence, decades of research have shown that size is not critical for dystrophin functionality. Micro-dystrophins delivered in gene therapy are not nearly short dystrophins, but rather reflect a highly rational design. The specific functional sequences in micro-dystrophins include, encode the most critical protein domains such that the resulting product functions better than some skip dystrophins. Moreover, inclusion of properly phased spectrum repeats in these constructs confers superior durability of protein expression, a vital factor in efficacy, and the duration of therapeutic effectiveness.

Preclinical studies have established that dystrophin micro-genes produce consistent and controlled protein expression that's targeted to the proper membrane loci and that interact with binding partners in the correct ways. Biological plausibility that micro-dystrophin has functional

benefit has been demonstrated in numerous small and large animal models using a variety of viral delivery vectors.

Perhaps what's most importantly proof of concept for AAV delivery of a functional micro-dystrophin has been established in several clinical trials where micro-dystrophin was appropriately membrane localized and consistent, consistently doing its job in recruiting other members of the dystrophin associated glycoprotein complex that's so necessary to dystrophin function. Taken together, the strategically designed micro-dystrophin exhibits appropriate biological activity and is superior to skipped dystrophin surrogates already approved through the accelerated approval pathway. I would encourage the committee to conclude that micro-dystrophin is an acceptable surrogate for accelerated approval. Thank you.

Ms. DeGregorio: Thank you, Dr. Porter, for your commentary. We greatly appreciate it. Dr. Aravindhan Veerapandiyan, you're next to speak.

Dr. Veerapandiyan: Good afternoon everyone. Thank you for the opportunity. I am Aravindhan Veerapandiyan. I'm a pediatric neuromuscular neurologist at Arkansas Children's Hospital. I care for about a hundred boys with Duchenne Muscular Dystrophy and have experience treating boys with SRP-9001 in the phase three clinical trial.

Although the multidisciplinary proactive approach has enhanced care for these boys and men with Duchenne Muscular Dystrophy, there is still unmet need for this progressive devastating disease, particularly with genetic therapies targeting dystrophin. SRP-9001 addresses this significant unmet need. As we heard, boys treated with SRP-9001 have shown expression of micro-dystrophin and also shown functional improvements.

There is robust natural history that are available for Duchenne Muscular Dystrophy. Though the disease is heterogeneous, the clinical course is highly predictable; and we, as

clinician experts in this disease, know how our individual patients are declining and how with treatment they're behaving differently. In a progressive disease like Duchenne Muscular Dystrophy, our treatment goal is stabilization of the disease. However, with SRP-9001, I have observed dramatic and meaningful improvements changing the trajectory and potential future of these boys.

In addition to these functional improvements that we see in clinic, there are improvements of the activities of daily living that are more meaningful to the families and to the boys that have not been seen prior to therapy, such as standing up in a tub and taking a bath with no Gower's sign, running faster walking, faster running and walking longer distances, playing outdoors longer with their siblings and friends, spending time with their families, riding bikes and hiking trails. These are all evident with SRP-9001.

As a clinician, I also value the importance of a phase three confirmatory trial. I want to point out that the phase three confirmatory trial for SRP-9001 is fully enrolled, well underway, and all of the patients will be dosed by end of September. I do not know of any family that isn't committed to seeing this through and not any that would risk giving up guaranteed dosing within a very short timeframe. I thank you again for the opportunity to share my perspective as a clinician, and I hope you take this information into consideration while making the decision on approval for SRP-9001.

Ms. DeGregorio: Dr. Veerapandiyan, thank you very much for your comments. We greatly appreciate those. Dr. Diana Zuckerman, you may proceed.

Dr. Zuckerman: Thank you. I'm Dr. Diana Zuckerman, President of the National Center for Health Research. Our non-profit think tank scrutinizes research on the safety and

effectiveness of medical products, and we do not accept funding from companies that make those products, so I have no conflicts of interest.

Duchenne Muscular Dystrophy is a terrible, terrible disease. Patients and their families deserve an affordable treatment that is proven to be safe and effective. If the evidence doesn't meet FDA standards because a study is not well-designed, or the clinical results are in the right direction but not statistically significant, then patients should have access to experimental treatments at cost through the FDA's excellent expanded access program. As a parent and scientist who's conducted research at Harvard and Yale, I wish the data were more persuasive. Unfortunately, Sarepta has a track record of three DMD accelerated approvals based on questionable data that have never been confirmed in required post-market studies.

One confirmatory study was not even started for five years, five years after the drug was already being sold under accelerated approval. Sarepta's one randomized clinical trial being discussed today includes only 20 boys who received 9001 and 21 boys on placebo. The analyses did not show significant differences in motor function in patients receiving the drug compared to controls at week 48. We've seen compelling videos of boys who've done well on 9001 today, but it's clear that these individual examples are not consistent with the scientific data. The data indicate that there are boys doing as well on placebo and boys on 9001 who are doing poorly. And although this sponsor is seeking accelerated approval based on a biomarker, the randomized trial found that those protein levels at week 12 did not correlate with muscle function at week 48.

We agree with the FDA that since the engineered molecule contains less than half of the structure of natural dystrophin, its value as a surrogate endpoint is not known. The correlation only reached statistical significance in an open label portion of the study, which, as we all know, is biased and merely hypothesis generating rather than scientifically valid. In addition, the safety

issues of gene therapy are well known. Some gene therapy patients have died as a result of treatment. Equally important are the ethical issues a panel member brought up this morning. If this drug is granted accelerated approval, it is unlikely that the confirmatory study that is almost done will, in fact, ever be appropriately completed because placebo patients will switch to treatment.

Ms. DeGregorio: Oh, Dr. Zuckerman, we're at time. I'm sorry.

Dr. Zuckerman: Yeah. In conclusion, there's an unmet need for effective treatment, but there are already four treatments for DMD on the market, none of which have been proven to work. In fact, European and Canadian regulatory agencies have not approved these DMD drugs, and if the FDA no longer represents the gold standard for approval, that poses risks for all Americans with serious diseases. Thank you very much.

Ms. DeGregorio: Thank you, Dr. Zuckerman. We appreciate your comments and the comments of everyone that's come today. We're going to try Dr. Lowes one more time, very briefly, to see if her tech works. And if not, we're going to move on to break.

Dr. Lowes: Um, hello?

Ms. DeGregorio: Hi.

Dr. Lowes: Can you hear me now?

Ms. DeGregorio: Yes.

Dr. Lowes: H. I'm terribly sorry. The reason I'm having difficulties is I am actually training people how to do the North Star in Amman Jordan, and if you'll play my slides, we can skip through them quickly. The reason I had felt so strongly for getting on is I know there's some questions about whether the DMDs, the people do the NSAA the same way every time. Obviously you can go to the next slide. And the answer is yes, because if you see the, one more

for me. If you see the sites on the map where the clinical trials were done, and then we're going to put on the sites where the, where the external control data came from. And now we're going to put on the sites where I've done all the training.

So over my 15 years, I have trained in 10 countries and close to 30 states, so I can guarantee you that everyone does it like me. We'll go to the next slide. And I think what's, what you might not understand is how difficult that it is to conduct these trials in a rare disease. That is why I am in Jordan is because you do not have enough individuals with the specific mutation to enroll in these trials. That's why I think it's very important to take the information that we've been given through this trial and do accelerated approval.

You can go one more for me, please, and I realize I'm talking rather fast, but I wanted to get to the last slide and show you a 12 year, 11 and a half year-old boy. One more for me please. 11 and half year-old boy who is still running and jumping and playing all because he was on this, this medication. This disease is relentless and there is no, no one gets better from this disease without a treatment. And we have seen boys improve.

The natural history would suggest that this boy should be in a wheelchair within the next couple months, and he's hopping up off the floor and he's running and I forgot to say I am affiliated with Sarepta. They pay me to train, they pay Children's Hospital for me to do training all over the world because it's a, it's a rare disease and it's a niche field that I'm in of being an expert in rare outcome measures. But that is how I can confidently say that the data from the external controls are identical to the data collect, that I collected in Columbus, Ohio. And I urge you to approve this, this compound accelerated approval.

Ms. DeGregorio: Thank you, Dr. Lowes, very much. I'm glad that you were able to join. I want to thank everyone for sharing your comments, your personal stories, and for coming on today. Thank you again. I turn it over to Dr. Ahsan.

Dr. Ahsan: Thank you, Marie, for administering the open public hearing. We're a little bit behind, so we're going to abbreviate our break. We're going to take five minutes as our break, and we will start at 10:45 sharp, I'm sorry, 1:45 sharp.

FDA Presentation

Dr. Ahsan: Welcome back everyone. We're promptly starting at 1 :45. Let's see, we're moving now on to the FDA presentations. There's several presenters, but I'll introduce the first and then they will pass it along. The first presenter will be Dr. Mike Singer, Clinical Reviewer, The Office of Clinical Evaluation, Division of Clinical Evaluation and General Medicine, part of OTP, CBER.

Overview — Dr. Mike Singer

Dr. Singer: Thank you. Good afternoon. I'm Mike Singer. I'm a clinical reviewer in the Office of Therapeutic Products. My colleagues and I would like to thank the patients, families, caregivers, clinicians, and community members who are participating today and have provided input to FDA. Your voices are vital, and they inform every part of our work. We'd also like to thank the team from Sarepta. We recognize and appreciate that we are all working towards the same urgent goal, safe and effective treatments for Duchenne Muscular Dystrophy.

We will now be presenting FDA's review of the evidence submitted by Sarepta in support of their application for accelerated approval of SRP-9001 for treatment of ambulatory patients with DMD. Next slide, please. Duchenne Muscular Dystrophy is a serious, progressive, and fatal condition. As Dr. Sherafat noted, the improvements in standard of care still are not able to keep patients with DMD from losing their ability to walk and to use their arms and hands, or to

prevent death by young adulthood. There's no question that DMD fulfills both of the criteria for accelerated approval, a serious condition for which there is an unmet medical need. Next slide, please.

It is essential to develop new and better treatments for patients with DMD. Since 2016, FDA has approved four exon-skipping drugs for DMD under the accelerated approval pathway, but they're limited to specific DMD mutations and so are intended for only a minority of patients, and the clinical benefit still has not been confirmed for any of the four. Next slide, please.

Let's turn now to SRP-9001. Because DMD is a genetic disease, gene therapy is a promising approach for treatment. Adeno associated viruses, AAVs, are commonly used as vectors to deliver gene therapies to cells, but these viral vectors can only contain DNA sequences, smaller than about 4,700 base pairs, 4.7 kb. Genes that do not fit within that size limit cannot be delivered using AAV vectors. The gene encoding dystrophin is the largest human gene, spanning over 2 million DNA base pairs. Just the coding sequence, that is the introns, is still huge, more than 14 kb, but since AAVs for gene therapy can only contain DNA sequences smaller than about 4.7 kb, various research groups have designed proteins called micro-dystrophin that are made up of just selected parts of the normal dystrophin protein so that the DNA sequence would fit into an AAV vector.

The protein encoded by SRP-9001 is Sarepta's micro-dystrophin. Sarepta's micro-dystrophin is missing many parts of normal dystrophin. One of my colleagues will talk more about the implications of that in a moment, but the rationale is that while SRP-9001 wouldn't be a cure for DMD, it may be able to slow or stabilize progression of the disease, and that would still be an important advance. But as we'll see later, that kind of change can be difficult to detect in the relatively short time of a clinical study. Next slide, please.

As Dr. Sherafat discussed, FDA may exercise regulatory flexibility to expedite delivery of safe and effective treatments, particularly for serious diseases like DMD. We recognize that DMD patients and caregivers are willing to accept increased risk. And, of course, as we heard from Dr. Witten, accelerated approval inherently carries uncertainty as to whether the treatment is actually beneficial. I mentioned the four exon-skipping drugs have received accelerated approval. So what makes the situation different with SRP-9001?

There are many shortened forms of dystrophin. Some occur naturally in patients with Becker Muscular Dystrophy. The exon-skipping drugs are intended to enable DMD patients to generate shortened forms of dystrophin. Similar to those in Becker patients, the micro-dystrophins, like Sarepta's, are engineered. They don't occur naturally. Now these proteins are all very different from one another, and the ability of each to treat DMD has to be assessed individually on its own merits.

Because Sarepta's micro-dystrophin doesn't occur naturally, we don't have any information about it from studying Becker patients. The only data we have about whether it may be reasonably likely to predict clinical benefit for accelerated approval comes from the SRP-9001 clinical development program. And, as we'll discuss, FDA has a number of concerns about those results. Another important difference between the exon-skipping drugs and SRP-9001 has to do with the special risks of gene therapies.

Because gene therapies are delivered by viruses, the immune system responds to them like it would to a viral infection, so patients treated with a gene therapy can only receive a single dose. If that dose isn't effective, it can't be given additional doses because subsequent doses may cause dangerous immune responses to the viral vector. And because that risk of immune responses is broad, cross-reactive, patients who receive a gene therapy that is not effective for

them likely will not be able to receive a different gene therapy in the future. Also, the effects of gene therapies are likely to be long lasting, which may help treat the disease over the long term, but any safety problems may be long lasting as well. Again, different from the exon-skipping drugs. Next slide, please.

In its POA submission, the applicant proposes to use expression of Sarepta's micro-dystrophin as a surrogate endpoint reasonably likely to predict clinical benefit. FDA has a number of concerns regarding this application. Some have to do with the manufacturing of SRP-9001. Others involve the non-clinical data, the results from animal studies. Additional uncertainties have to do with whether expression of Sarepta's micro-dystrophin suitable as a surrogate endpoint considered reasonably likely to predict clinical benefit and how to know which patients it might help and which it wouldn't.

Then there are considerations regarding safety of SRP-9001 and of similar types of gene therapy products in this class. Finally, we would like to discuss the potential effect that accelerated approval might have on whether the applicant will be able to complete its phase three study, the study that's intended to confirm whether SRP-9001 has clinical benefit. Next slide please.

But, first, some of the terms that we'll be using in this presentation differ from those used by the applicant. I want to take a moment to explain why. The applicant refers to the protein encoded by their gene therapy product as SRP-9001 dystrophin. But as my colleague Dr. Adu-Gyamfi will discuss, it differs in important ways from normal dystrophin and from the shortened forms of dystrophin made by Becker patients or with the exon-skipping drugs. So to prevent any confusion, we refer to it as Sarepta's micro-dystrophin.

Similarly, when discussing muscle biopsy results, the applicant refers to percent dystrophin positive fibers. We'll refer to them as Sarepta's micro-dystrophin positive fibers. When measuring the level of dystrophin expression in muscle tissue, the applicant is referred to percent normal expression in Western blot. We will instead say expression of Sarepta's micro-dystrophin measured on Western blot compared to control. The control is normal dystrophin protein expressed in normal baselines.

Finally, the applicant has referred to its analysis in different age groups, the younger and older DMD patients in its study 102, part one, as pre-specified; but as we'll explain, that analysis was not succinctly rigorous. It wasn't pre-specified for hypothesis testing, and it didn't use a pre-specified multiplicity adjustment strategy, which prevent reaching mistaken conclusions. Next slide, please.

I'll now discuss FDA's concerns regarding manufacturing of SRP-9001. Next slide, please. It's important to highlight that the SRP-9001 manufacturing process underwent substantial changes during development between the initial nonclinical and clinical studies and the subsequent ones. These changes affected the purity of the SRP-9001 product, which was not analytically comparable, for the product used in the earlier versus the later nonclinical and clinical studies.

A bit of background on that. The purification process for AAV based gene therapy products yields two main populations of AAVs. One population contains the DNA for the AAV vector genome. That population is called full capsids. The second population does not contain the DNA genome. Those are generally referred to as empty capsids. On the right is a representative image, it's not from the apple, made with a trans-electron microscope. Because of the method used to generate the image, full capsids appear as these gray rings and empty capsids

have a dark dot in the center. The SRP-9001 used for the initial nonclinical and clinical studies was prepared using process A. Process A resulted in a higher percentage of full capsids.

The applicant then changed the manufacturing to process B. Process B yields SRP-9001 with a lower percentage of full capsids. The dose of SRP-9001, like for other AAV based gene therapy products, is calculated based on vector genomes, that is the DNA component rather than the viral capsid that delivers it. The potential therapeutic product corresponds to the full capsids, those containing the DNA genome. So the empty capsids, impurities, they provide no therapeutic benefit. And as we'll discuss later, lower purity can have important implications both for the efficacy and the safety of SRP-9001.

My colleague Dr. Chen will now present FDA's concerns regarding the applicant's nonclinical studies. Next slide, please.

Nonclinical Studies — Dr. Teresa Chen

Dr. Chen: Thank you. Good afternoon. I am Theresa Chen, a pharmacology toxicology reviewer in the Office of Therapeutic Products. In the next three slides, we will describe the submitted nonclinical data that are relevant to today's discussion. Next slide, please.

The applicant has conducted proof of concept, has provided proof of concept data from two rodent models of DMD. The MDX mouse and the MDX red. For the MDX mouse model, although it is widely used, this model has important limitations that should be understood when considering the potential for clinical benefit. This mouse model has a less severe phenotype compared to patient with DMD, generally showing no visible impairment of locomotor function. However, a reduction of muscle specific force can be measured compared to normal mice, and that was used as a primary functional readout for the proof of concept studies.

The applicant conducts studies with process A and process B product in four to eight weeks of MDA X mice with a single intravenous administration of SRP-9001. This result in a

very different micro-dystrophin protein expression profile compared to wild-type dystrophin expressed from the indigenous DMD gene with a very high level of micro-dystrophin expression in the heart, exceeding normal dystrophin level in healthy mice and a low level in skeletal muscle and diaphragm. And in some studies, low levels of micro-dystrophin protein would also express in the liver, despite the use of muscle specific promoter. And this was also, this also resulted in partial improvement in specific force in anterior and diaphragm in a partial correction of dystrophic muscle pathology.

The applicant also conducted an exploratory correlation analysis of data from these mice and found no correlation between muscle specific force and micro-dystrophin protein expression by Western blot. These studies highlight the differences in the expression profile and functionality of Sarepta's micro-dystrophin protein compared to normal dystrophin protein expressed from the indigenous DMD gene. Next slide please.

The applicant conduct two study with process B product in the MDX red in two different age groups, one in young reds at three to four weeks of age, one in older red at three to five months of age. This model except a more severe phenotype compared to MDX mouse with a reduction in muscle strength and reduced locomotor function measured by spontaneous activity beginning at three months of age. In young MDX red, intravenous administration of SRP-9001 resulted in robust micro-dystrophin protein expression and increased spontaneous activity and partial improvement of dystrophic muscle pathology at the 12 and 24 weeks post administration. However, in older MDX red, robust micro-dystrophin protein expression was also observed, but no improvement of muscle function or dystrophic muscle pathology was observed. These studies highlight that expression of Sarepta's micro-dystrophin protein alone did not predict functional

response in the MDX rat, since moto function improvement was observed in young, but not in older rats. Next slide, please.

Although this nonclinical data support the potential activity of SRP-9001, the function of Sarepta's micro-dystrophin protein cannot be directly extrapolated from animal studies to human, due to several factors. First, there are multiple species specific differences between the MDX mouse rodent model and human, including disease pathophysiology, compensatory mechanism present in rodent models, regenerative capacity of the muscle fiber, which is higher in rodent compared to human, and physiology of skeletal and cardio muscle, which are different in terms of muscle volumes and for sustain.

Additionally, there are study design limitations. As this study were non GOP proof of concept studies, which are lack of robustness, potential for bias, and missing data. Therefore, this study form the basis for the clinical development of SRP-9001, but they were not designed to determine the adequacy of the candidate surrogate endpoints. Now I will turn it over to my colleague, Dr. Adu-Gyamfi to discuss surrogate endpoint concern in BLA submission. Next slide, please.

Surrogate Endpoints — Dr. Emmanuel Adu-Gyamfi

Dr. Adu-Gyamfi: Thank you very much, Dr. Chen. Good afternoon everyone. My name is Emmanuel Adu-Gyamfi, and I am the lead chemistry manufacturing controls reviewer and the chair of the BLA review committee.

I would like to start our discussion regarding FDA's concerns about the surrogate endpoint. First, by looking at the uncertainties related to using Sarepta's micro-dystrophin, is the surrogate endpoint considered reasonably likely to predict clinical benefit? Next slide, please.

So the question is: How do we determine whether a surrogate endpoint is reasonably likely to predict a clinical benefit? This judgment is made on a case-by-case basis. There are

several key considerations that we have to take into account in making this determination. First, the surrogate endpoint should predict an effect on a clinical endpoint, that is an endpoint in a clinical study that directly measures whether patients feel or function better or they survive longer in the case of DMD. Second, we look for support from three key sources in making this determination. And this includes biological plausibility, empirical evidence, and clinical studies. In the next few slides, I will discuss biological plausibility. Let's go to the next slide, please. Next slide, please.

I will provide a brief description of the structure and function of the normal dystrophin, as well as the design of Sarepta's micro-dystrophin. The war type dystrophin shown here on the left side of your slide is central to the formation of an oligomeric complex of proteins that span the membranes of skeletal and cardiac muscle cells. Now, this complex, as described earlier, transmits and absorbs the shock that is associated with muscle contraction. It helps maintain the integrity of the muscle fibers and prevents muscle damage. And so DMD patients with the mutation in the dystrophin gene, therefore, cannot maintain the integrity of the muscle cells, and this leads to chronic muscle breakdown and ultimately loss of function.

The applicant designed micro-dystrophin on the schematic is shown on your, on your right side of the slide. That retains some of the essential function, essential elements of the protein necessary to form the complex needed for muscle function. In addition to the size differences, the current scientific understanding in the field is that dystrophin does, the normal dystrophin plays an important scaffolding role by recruiting other signaling protein, such as nitric oxide synthesis or NNOS shown here in the schematic that works to prevent vessel constriction. This and other several domains are missing, other interacting domains are missing in the

Sarepta's micro-dystrophin. Next slide, please. Can we go to the next slide, please? If you could go back one more slide. I'm sorry. All right.

So Sarepta's micro-dystrophin was designed based on a patient with milder symptoms, often referred to as Becker Muscular Dystrophy or BMD. Now, even though the micro-dystrophin was rationally designed to mimic the Becker Muscular Dystrophy protein or the BMD, it is important to point out that the Becker Dystrophin and Sarepta's micro-dystrophin have structural differences as highlighted here in the red box and the circles on this slide. Let's go to the next slide, please. Okay.

So this slide provides an additional illustration of the structural differences between Sarepta's micro-dystrophin and the shortened dystrophins found in Becker Muscular Dystrophy patients reported in the literature. Of all these structures, Sarepta's micro-dystrophin is the most truncated as highlighted in the red box here in the middle. Again, as a short orientation, the portion of the protein indicated by the straight lines highlights the regions of the protein that are delete, that are deleted or truncated relative to that of the normal dystrophin. Next slide, please.

This slide focuses on the differences between Sarepta's micro-dystrophin and the mutated shortened dystrophins from Becker Muscular Dystrophy patients. I would like to direct your attention to the figure highlighted in the red box. This schematic compares Sarepta's micro-dystrophin and the Becker dystrophin that is found in a 61 year-old patient used to model the Sarepta's micro-dystrophin. Again, as a quick orientation, the straight lines here represent the regions that are truncated relative to that of a normal dystrophin. So the large truncated portion, including the C terminal domain, makes the Sarepta's micro-dystrophin uniquely different from the truncated versions that are produced by the various Becker patients. And based on the scientific literature, we believe that the differences in the structure are important and thus

contribute to the overall uncertainty of the bio plausibility of the Sarepta's micro-dystrophin as a surrogate marker reasonably likely to predict clinical benefit. Next slide, please.

So I would like to summarize these points by saying that there are important differences in the structure of Sarepta's micro-dystrophin and that of the normal or war type dystrophin. Again, Sarepta's micro-dystrophin, as I showed you, is also different from the shortened dystrophins produced by the Becker Muscular Dystrophy patients. And so there is an uncertainty as to whether Sarepta's micro-dystrophin can function in patients in a manner that is either similar to the normal dystrophin or the shortened dystrophins that are produced by the Becker patients or the exon-skipping products that are known to skip very few portions of the normal dystrophin protein. Thank you very much, and I would like to hand it over to my clinical colleague Dr. Singer. Next slide, please.

Dr. Singer: Thank you. This is Mike Singer again. I'd like to now discuss the role of empirical evidence in our assessment of whether SRP-9001 can serve as a surrogate endpoint considered reasonably likely to predict clinical benefit. Next slide, please.

Empirical evidence may include epidemiologic, pathophysiologic, therapeutic, and pharmacologic data. As Dr. Adu-Gyamfi just discussed, Sarepta's micro-dystrophin is an engineered protein, and so it is not naturally found in any patients. Understandably then, we don't have any epidemiologic data. This situation is very different from that with the exon-skipping drugs. In those cases, the drugs promote formation of shortened forms of dystrophin similar to those seen in some patients with Becker Muscular Dystrophy.

As I mentioned earlier, treatment with SRP-9001 is intended to slow or stabilize progression of DMD, but, again, since Sarepta's micro-dystrophin is not present in nature, we don't have any information outside of clinical trials of what effect Sarepta's micro-dystrophin

may have in altering the pathophysiology of DMD. Therapeutic data can be obtained, for example, from off-label use of a drug to treat a disease other than the one for which it received approval. Understandably too, that's also not available in this case.

Finally, pharmacologic data, for example, with an enzyme, it may be possible to measure levels of substrate Zen product. Again, that's not the case here. The applicant has provided data on creatine kinase, CK levels. But creatine kinase is nonspecific, and levels can be affected by many different factors. So we also lack clear pharmacologic support for Sarepta's micro-dystrophin. Next slide, please.

We will now turn to our analysis of the data from the three clinical studies which Sarepta submitted in support of their application for accelerated approval of SRP-9001. Next slide, please. First, I'd like to provide some background on the North Star Ambulatory Assessment, which the applicant used as a clinical efficacy endpoint. The BLA submission is for treatment of ambulatory patients with DMD, so patients who are able to walk. The NSAA is an important tool to evaluate that for DMD patients In clinical trials, as you've heard the NSAA measures lower extremity function. The score ranges from zero to 34, and a higher score indicates better performance.

The NSAA is validated and is widely used in DMD clinical studies, but in contrast to an objective endpoint such as survival, the NSAA has some important limitations that we have to keep in mind. First, it is effort dependent. Performance can be affected by motivation and effort and by encouragement from family and caregivers and from the clinicians scoring the exam. Because of that, results from open label studies are challenging to interpret. Patients typically score better than in double blind studies. We'll hear, we'll hear more about that later in the presentation. Also, the NSAA is process dependent, that is results can differ based on how

consistently the test is given and scored by the clinical staff. That means that we can't rigorously compare scores from a clinical study to scores from, for example, a natural history study or a registry or even to scores from clinical trials of other drugs for that condition. Next slide, please.

And there's another important issue to keep in mind regarding the NSAA. We saw this figure earlier. Here, I want to first direct your attention to the spaghetti plot in gray. While worsening occurs in all DMD patients, progression for individual patients is very heterogeneous and difficult to predict. Now, let's look at the black line, which shows the average NSAA score as patients get older. Younger patients who receive standard of care treatment with corticosteroids, typically first show improvement on the NSAA until, on average, around six point, age 6.3 years. Then, on average, their scores decrease. That's important because the patients in the applicant's clinical studies start out in that age range where NSAA scores improve just with standard of care treatment. So it is crucial to separate that improvement from any improvement that may be due to treatment with SRP-9001. Next slide, please.

One other bit of background. As you heard, the SRP-9001 used for the applicant's first two clinical studies was prepared using process A. Process A resulted in a higher percentage of full capsids. The manufacturing was then changed to process B. Process B yields SRP-9001 with a lower percentage of full capsids, that is lower purity. So although the transgene is the same, lower purity raises concern for efficacy and safety. From the efficacy perspective, the increased number of empty capsids may interfere with transduction, that is it could hamper successful delivery of the SRP-9001 DNA into cells. From a safety perspective, the higher total number of capsids necessary to deliver a particular dose of vector genomes means that patients receive a bigger antigenic load, which may increase the risk of anti-capsid immune responses that can cause serious adverse events. Next slide please.

The three clinical studies described in the BLA are summarized here. All three of the studies enrolled ambulatory patients aged four to seven years old. So remember in that age group, DMD patients can show improvement on the NSAA just with standard of care alone. The two studies in blue used SRP-9001 manufactured by process A. Study 101 was the first inhuman test of SRP-9001 and was open label, which makes the NSAA results difficult to interpret. Study 102 was a crossover study. The data included in the BLA was from part one and part two. Part one was randomized, double blind, and placebo-controlled. At the start of part two, all the patients, caregivers, and evaluators knew that by that point, everyone had received SRP-9001. So we consider part two essentially to be open label.

Study 103 in purple was intended as a bridging study to compare the results from study 102 with regard to safety and expression of Sarepta's micro-dystrophin. Study 103 used the process B, lower P, SRP-9001. And study 103 was also open label. The reason why these patients from study 103 are shown in gray is because their data were not used for the efficacy analysis. They were included in the safety analysis, which I'll discuss later in the presentation. Next slide, please.

I want to step back for a moment to discuss the implications of study design on our ability to interpret the efficacy data for SRP-9001. In certain circumstances, data generated by open-label studies are readily interpretable. That was a situation, for example, with Zolgensma, the gene therapy that was approved in 2019 for spinal muscular atrophy, type one. That disease is homogeneous. The treatment had a large effect, and the clinical endpoint could be objectively assessed. But here, disease program is heterogeneous. Improvement on the NSAA occurs with standard of care alone. Any effect of SRP-9001 is likely to be moderate. And as we discussed, the NSAA is effort dependent and process dependent. So without randomized double blind,

placebo-controlled studies, it's challenging to clearly determine the effect of SRP-9001. Next slide, please.

2018 FDA guidance for industry explain our viewpoint on the importance of study design to enable clear assessment of effectiveness of new treatments for DMD. Let's now examine the efficacy results of the applicant's clinical studies. Next slide, please.

We're going to discuss four different analyses, the data from the applicant's clinical trials. The first analysis was performed on data from Study 102, part one, the only randomized, double blind, placebo-controlled study in the BLA. We'll be looking at the change in the NSAA total score in patients who received SRP-9001 compared to the NSAA change in patients who received placebo. Next, we'll discuss the applicant's comparison of change in the NSAA for patients from all three studies who received the intended dose of SRP-9001 versus the NSAA scores from external controls. For analyses three and four, my colleague Dr. Wang will discuss whether expression of Sarepta's micro-dystrophin is associated with change in the NSAA. She'll look first at results from study 102, part one, and then a pooled data from studies 102 and 103. Next slide please.

Let's now look at the NSAA results from Study 102, part one. Next slide, please. Study 102 assessed the effect of SRP-9001 on the NSAA total score from baseline to 48 weeks at one year. This graph shows change in the NSAA over the weeks of study. The red line shows the NSAA scores for patients who received SRP-9001. The blue line shows the NSAA scores for patients who received placebo. While the least squares mean for patients who received SRP-9001 was higher compared to the placebo group, that difference was not statistically significant. So in sum, this study failed to demonstrate statistical significance on its primary endpoint. The failure

of this study to demonstrate statistical significance on its primary endpoint is important to keep in mind as we look further into the results. Next slide, please.

The applicant discovered afterwards that three different doses of SRP-9001 were given to the patients in part one. Six patients received half of the intended dose. So that's the column second from the left. Six patients received two-thirds of the intended dose. The table shows five because one didn't undergo NSAA testing one year. And eight patients received the full intended dose 1.33 times 10 to the 14 vector genomes per kilogram. The 95% confidence intervals, the mean for each dose, includes zero, that is no effect. And patients who received the intended dose had the poorest outcome. That's the column furthest on the right in the red box. But because there are so few subjects at each dose, we can't draw definite conclusions from this analysis. Next slide, please.

The applicant then looked at the results by age, SRP-9001 and placebo patients who are four to five years old at the start of the study, and, separately, SRP-9001 and placebo patients who are six to seven years at the start of the study. And let's look at each of those in more detail. Next slide, please. For the four to five year-old boys, the SRP-9001 group appears to have a better outcome. But this is not a rigorous analysis. The subgroup analysis was not pre-specified for hypothesis testing and no pre-specified multiplicity adjustment strategy was used. So while P-values can be calculated, they're not meaningful statistically. Most subgroup tests like this performed after an overall non-significant outcome in the population as a whole, can only be considered hypothesis generated. So we don't know whether SRP-9001 would help four to five year-old boys with DMD. Next slide, please.

Now let's look at the six to seven year-old boys. Here there was essentially no difference between the SRP-9001 group shown in red and the placebo group shown in blue. This analysis

also is only hypothesis generated. The applicant proposes that the reason for this outcome was an imbalance in baseline NSAA scores for the SRP-9001 group compared to the placebo group. The placebo group showed essentially no deterioration, and the SRP-9001 group showed essentially no improvement after one year. Is that because SRP-9001 was ineffective for them? Were they too old to benefit or perhaps had too much muscle loss? Was it just the small sample size or the specific DNA mutations or perhaps some other cause or maybe a combination of factors? We don't really know. Next slide, please.

Now, let's turn to the second analysis, the applicant's comparison of change in the NSAA for patients from all three studies who received the intended dose of SRP-9001 versus the NSAA scores from external controls. Next slide, please. Here the applicant used external controls from three different sources, a natural history study, the four DMD studies which compared three corticosteroid treatment protocols in DMD patients, and the placebo group of a study conducted by Eli Lilly and Company looking at the drug Tadalafil in patients with DMD. The applicant used propensity scores to try to match external control patients to patients from the SRP-9001 studies. But this comparison is challenging to interpret. Propensity scores can't suitably account for the heterogeneity of DMD progression, the effort driven and process-driven characteristics of the NSAA, or for any unknown factors, which in a clinical study could be balanced by randomization. My colleague Dr. Wang will now discuss analysis three and four. Next slide, please.

Analyses Three and Four — Dr. Xiaofei Wang

Dr. Wang: Thank you, Dr. Singer. Good afternoon. My name is Xiaofei Wang. I'm a clinical pharmacology reviewer in the Office of Clinical Evaluation, Office of Therapeutic Products, CBER. I'm going to present the collaborative work by Dr. (inaudible), the account reviewer from Office of Clinical Pharmacology, CBER, and me.

Dr. Singer just went over the clinical efficacy outcome assessed by NSAA total score for SRP-9001. In this application, the applicant proposed to use expression of SRP-9001 Sarepta's micro-dystrophin as a surrogate endpoint to support its accelerated approval approach. Now, let's take a look at the expression of SRP-9001 Sarepta's micro-dystrophin and the relationship between micro-dystrophin and NSAA total score change in study 102, part one. Next slide, please.

This slide shows the key biomarkers in the proposed mechanism of action of SRP-9001. After a single dose intravenous infusion, SRP-9001 distributes from plasma to peripheral tissues, including target muscle tissues, transduces into muscle fibers, and expresses trans-gene Sarepta's micro-dystrophin. Expressed Sarepta's micro-dystrophin located on sarcolemma membrane is expected to restore dystrophin associated protein complex, which helps to improve muscle function by stabilizing sarcolemma membrane. Next slide, please.

The applicant used two analytical methods to measure the expression of micro-dystrophin, Western blot and immunofluorescence staining. Sarepta's micro-dystrophin measured by Western blot was listed as primary endpoint for study 102 and 103. Western blot is a quantitative acid, measures the absolute quantity of micro-dystrophin expression and is adjusted with muscle content and normalized with the dystrophin levels in normal subjects. Immunofluorescence staining localizes expressed micro-dystrophin and provides information of immunofluorescence fiber intensity and percent of Sarepta's micro-dystrophin positive fibers, which we also called PMDPF.

PMDPF indicates a portion of muscle fibers expressing Sarepta's micro-dystrophin but not the amount of micro-dystrophin in each muscle fiber. The level of expressed micro-dystrophin in muscle fibers of a subject can vary substantially and may have different functional

impact on each of these muscle fibers. Therefore, we use the protein extraction measured by Western blot to evaluate the relationship between micro-dystrophin and clinical functional endpoint. Next slide, please.

This slide shows the expression of Sarepta's micro-dystrophin in Study 102. At week 12, after dosing, the expression of Sarepta's micro-dystrophin in muscle fibers increased in a dose dependent manner across three dose levels, ranging from 6.29 to 30.3 times 10 to 13 vector genomes per kg. For the highest dose level, which is also the intended dose for SRP-9001, we observed high interpatient variability for Sarepta's micro-dystrophin expression in both part one and part two. The mean values of Sarepta's micro-dystrophin was about 23% in part one and 42% in part two. Next slide please.

We conducted a correlation analysis to evaluate the relationship between Sarepta's micro-dystrophin expression at week 12 and NSAA total score change at year one, which was measured at week 48 using study 102, part one, data. The figure on the right shows partial Spearman analysis adjusted for baseline age and NSAA total score. As shown in this figure, there was a wide range of NSAA total score change at year one for both SRP-9001 treatment and the placebo groups. The range of NSAA total score change of these two groups were similar. Based on the limited data available for the evaluation, there's no clear association between Sarepta's micro-dystrophin expression and NSAA total score change. Next slide please.

Since applicant examined the differences in NSAA total score change between different age groups, we also evaluated the relationship between Sarepta's micro-dystrophin expression and NSAA total score change separately. For the 4 to 5 year-old boys and for the 6 to 7 years-old boys, the figure shows that group level relationship between Sarepta's micro-dystrophin at week 12 and NSAA total score change at year one with Spearman analysis. In general, at group level,

there is no clear association between micro-dystrophin expression and NSAA total score change based on the limited data. In the four to five years of age patient receiving SRP-9001 treatment, we observed improved NSAA total score with increased micro-dystrophin expression. However, because of the very limited data for this patient group, the result must be interpreted with caution. Next slide, please.

We will now explore the relationship between Sarepta's micro-dystrophin expression and NSAA total score change using the pooled data from study 102 and study 103. Study 101 was not included in our pooled data analysis because of the issues with threatened blood acid and very limited data. Next slide, please.

Before talking about the analysis results, I would like to discuss two major concerns regarding the approach of exploring correlation using pooled data. Our first concern is that the open label design may affect an NSAA total score change. The SRP-9001 clinical program has used different study designs. Study 102, part one, was a randomized, double blind, placebo-controlled study. While study 102, part two, and study 103 were open label studies, as discussed earlier. And NSAA is an effort dependent clinical endpoint. Blinding is critical for its assessment. Here we compared the NSAA total score change at year one between the different study designs. As shown in the right graph compared to the NSAA total score change in study 102, part one, which was a double blind, placebo-controlled study, the NSAA total score changes in the open label studies were higher. Therefore, our concern is that the open label design without the concurrent control may confirm the association between Sarepta's micro-dystrophin expression and NSAA total score change. We examine that next. Next slide, please.

As mentioned before, study 102 and study 103 did not have a concurrent control. In this situation, it is unclear whether the NSAA total score change was due to SRP-9001 or to open

labels design or to the baseline characteristics or to some combinations. Therefore, it is very challenging to interpret the correlation analysis results from the pooled data. The figure on the right shows the correlation between Sarepta's micro-dystrophin at week 12 and NSAA total score change at year one. The partial analysis was adjusted by baseline age and NSAA total score. The analysis indicates that Sarepta's micro-dystrophin accounts for 11% of variation in NSAA total score change. Here, our square is the square of correlation coefficient role, so even when the open label study data is included, the correlation is not sufficiently persuasive to consider expression of Sarepta's micro-dystrophin reasonably likely to predict clinical benefit. Next slide, please.

In summary, we have evaluated the relationship between Sarepta's micro-dystrophin and NSAA total score change using data from Study 102, part one, a randomized, double blind, placebo control study and pooled data from studies 102 and 103. The correlation analysis using Study 102, part one, only shows no clear association between Sarepta's micro-dystrophin expression and NSAA total score change. We observed improved NSAA total score with increased micro-dystrophin expression in four to five years old patient; however, because of the very limited data in this patient group, the results must be interpreted with caution.

Regarding the correlation analysis using pooled data, open label design without concurrent control, study 102, part two, and study 103, makes it very challenging to interpret the correlation analysis results. The correlation results indicate that Sarepta's micro-dystrophin accounts for 11% of variation in NSAA total score change after adjustment for baseline age and NSAA total score. The correlation is not sufficiently persuasive to consider expression of Sarepta's micro-dystrophin reasonably likely to predict clinical benefit. Correlation is necessary

but not sufficient to support candidate's surrogate endpoint. Now, I'd like to hand it over to my colleague Dr. Singer to continue our evaluation of SRP-9001. Thank you. Next slide, please.

Dr. Singer: Thank you. This is Mike Singer again. To recap FDA's concerns regarding Sarepta's micro-dystrophin as a candidate surrogate endpoint, while Sarepta's micro-dystrophin was rationally designed so that the DNA would fit into the small space of an AAV vector, important domains were left out, including ones present in the mutated dystrophin of the Becker Muscular Dystrophy patient on which it's based. While that's understandable, it also means that we don't have any empirical evidence to guide us. So the only way we can determine the effect of SRP-9001 is through clinical studies. And in the most interpretable study, randomized, double blind, and placebo-controlled, there is no statistically significant difference between SRP-9001 compared to placebo. The applicant's subgroup analysis wasn't performed in a statistically rigorous way, so we also can't predict which patients may benefit from SRP-9001 and which patients would not. The applicant's comparison of SRP-9001 patients to external controls is challenging to interpret even using propensity scores. They can't suitably account for the heterogeneity of DMD progression, the fact that the NSAA is effort driven, process driven, or for any unknown factors. Finally, as Dr. Wang just described, there's no clear association between expression of Sarepta's micro-dystrophin in clinical improvement measured by change in the NSAA total score. Next slide, please.

I'll now discuss FDA's safety concerns related to SRP-9001. Next slide, please. Safety concerns fall into three categories. First, safety signals observed in the clinical studies of SRP-9001: liver toxicity, myocarditis, and immune mediated myositis. Next, there are concerns about the possibility of cross-reactivity with other AAV based gene therapy products and the potential implications of that cross-reactivity for patients who don't benefit from SRP-9001. Finally, safety

issues such as hepatoxicity and thrombotic microangiopathy for AAV based gene therapy products as a class. Next slide, please.

We'll first look at the safety issues that arisen in the clinical trials with SRP-9001. The exposure analysis consists of the 85 patients who participated in studies 101, 102, and 103. Their mean age was 7.1 years. All received a single IV infusion of SRP-9001. 45 patients received SRP-9001 manufactured by process A, and 40 patients received lower purity SRP-9001 manufactured using process B. The study patients have been followed for mean integration 1.8 years. Next slide, please. There were no deaths. The most common adverse reactions were vomiting and nausea, followed by acute liver injury, fever, and thrombocytopenia. The adverse events of special interest were hepatotoxicity, cardiotoxicity, including myocarditis, and elevated troponin-I levels, a marker for heart muscle injury, and immune mediated myositis. And we'll also look at immunogenicity. Next slide, please.

When delivered intravenously, nearly all AAV vectors first passed through the liver. Hepatotoxicity is the most commonly observed adverse event in clinical trials involving IV administration of AAV based gene therapies. Less frequently patients may experience acute liver injury. Acute liver injury is detected by increase in blood levels of one or more of these liver enzymes, GGT, GLDH, ALP, or ALT rising above a specified threshold beyond the upper limit of the normal range. Acute serious liver injury is when the criteria for acute liver injury are met, and patient dies or experiences a life-threatening event, hospitalization, either initial or prolonged, disability or permanent damage, a congenital anomaly or birth defect, or another important medical event. Both acute liver injury and acute serious liver injury occurred in the clinical trials for SRP-9001. All those events resolved either spontaneously or after additional treatment with corticosteroids without clinical sequelae. Overall, hepatotoxicity was observed at

a similar frequency in patients who received process A SRP-9001 and process B SRP-9001. Next slide, please.

There were two reports of myocarditis in the SRP-9001 clinical studies. Both cases occurred in studies using SRP-9001 manufactured by process B. In the first case, the patient was over age seven. He developed chest pain on day three of the study. He was found to have elevated troponin-I, though we don't have the exact number, indicating heart muscle injury. His myocarditis resolved, but he showed residual changes on cardiac MRI, and he required additional medications for his underlying DMD cardiomyopathy. Second case involved a patient under age seven. He was taking part in a double blind study and developed symptoms within 24 hours of receiving SRP-9001. His peak troponin reached over 2,700. Normal is under 75. His blood pressure dropped, and he was admitted to the pediatric intensive care unit where he was treated with corticosteroids, antibiotics and IV fluids and his symptoms resolved without sequelae. Next slide, please.

Troponin-I was not assessed in the studies using process A SRP-9001. Elevated troponin-I has been observed in four patients in study 103, which is process B SRP-9001. Although none of these events had clinical complications or acute cardiac imaging changes, we don't know what the long-term effects of this heart muscle injury may be on the underlying cardiomyopathy in DMD patients. Next, please. Another patient who received process B SRP-9001, an eight year-old boy in study 103, with a deletion mutation involving exons 3 through 43 in the DMD gene, developed life-threatening immune mediated myositis about one month later. He presented with muscle weakness, impaired swallowing and speaking, difficulty sitting and walking. His muscle biopsy showed inflammatory myopathy in the setting of chronic changes due to DMD. He was

treated with additional corticosteroids, plasmapheresis, and tacrolimus. He recovered with residual weakness. Next slide, please.

Now let's look at immunogenicity. In clinical studies of SRP-9001, an enzyme-linked immunosorbent assay, ELISA, was used to check patients for preexisting antibodies that would bind into the SRP-9001 viral vector AAVrh74. Only patients with a titer less than or equal to one to a hundred were eligible for the SP-9001 clinical trials. Overall, four patients were excluded from the trials because of elevated preexisting antibody titers above one to 400. As expected, all patients who did receive SRP-9001 showed high titers afterwards. Next slide, please. Antibodies against the SRP-9001 capsid are important to consider because antibodies against one AAV serotype can cross-react with capsids of other AAV serotypes. Because of this cross-reactivity, patients who receive SRP-9001 and for whom it's ineffective likely will not be able to receive any future effective AAV based gene therapy treatment. This consideration, again, is very different than with the exon-skipping drugs. Next slide, please.

For AAV based gene therapies, overall, serious adverse events have included liver toxicity ranging from damage causing elevated liver enzymes in the blood to acute liver injury, liver failure, and death. Another serious adverse event for AAV based gene therapies as a class is thrombotic microangiopathy, TMA, which is manifested with thrombocytopenia, hemolytic anemia, and acute kidney injury. Some of these were not seen until after the product was approved, so it's important to keep them in mind when considering overall benefits and risks for any AAV based gene therapy. Next slide, please.

Finally, let's look, for a moment, at the applicant's phase three study, study 301, and concerns regarding the potential effect accelerated approval might have on the applicant's ability to complete it and the implications that that could have. Next slide, please. Part one of Study 301

is randomized, double blind, and placebo-controlled. The primary endpoint is change in the NSAA total score from baseline to one year, 52 weeks. Part two is cross-over. Patients who initially received SRP-9001 now will receive placebo and vice versa. The change in the NSAA total score will be measured again after another 52 weeks. Study 301 is fully enrolled. 125 patients aged four to seven years worldwide, about 80 of them in the United States, have been randomized one to one to receive either Process B SRP-9001 or placebo. Next slide, please. The last patient last clinical visit for the 52-week primary endpoint is expected to be completed by the end of this September, September of 2023. Topline data is expected to be available by late in the fourth quarter of 2023. The applicant has proposed that part one serve as the confirmatory study if SRP-9001 were to receive accelerated approval.

For the patients in the United States, by June 1st, 2023, about 25 may not yet have received SRP-9001. That's over one third of the patients in the placebo arm of the study. If SRP-9001 were to receive accelerated approval, some patients and caregivers understandably may want to withdraw from the study to find out whether they had received it or not. And some patients who received SRP-9001 understandably might not want to wait until the crossover begins. Breaking the blind and withdrawals could mean that there may be no way to confirm whether SRP-9001 is effective and to know who might benefit and who would not. Next slide, please.

To wrap up then, SRP-9001 made by process A and process B have major differences. Process B SRP-9001, which is intended for potential future marketing, is of lower purity. As we discussed, that may impact both its efficacy and its safety. Studies in the animal models did not show a clear relationship between expression of Sarepta's micro-dystrophin and effects on function. Because of shortcomings in how those studies were done, they can't give us much

insight into Sarepta's micro-dystrophin as a surrogate endpoint. And important differences between the animal models and human patients also make it difficult to draw any conclusions about whether Sarepta's micro-dystrophin may be considered reasonably likely to predict clinical benefit.

Next, while Sarepta's micro-dystrophin was designed so that the DNA would fit into an AAV vector, important domains were left out. That's understandable, but it results in a very different situation than that with the exon-skipping drugs. Here we don't have any empirical evidence to guide us. The only way we can assess the effect of SRP-9001 is through clinical studies.

The progression of DMD for individual patients is heterogeneous. NSAA scores are effort dependent and process dependent, and at the age range in the applicant's clinical studies, can improve with standard of care treatment alone. Treatment with SRP-9001 to slow or stabilize DMD then means that the effective SRP-9001 is challenging to determine without randomized, double blind, placebo-controlled studies. But in the only randomized, double-blind, and placebo-controlled study in the BLA, there was no statistically significant difference between SRP-9001 and placebo. The applicant's subgroup analysis wasn't performed in a statistically rigorous way. So we also can't predict which patients may benefit from SRP-9001 and which patients would not. And as Dr. Wang discussed, there's no clear association between expression of Sarepta's micro-dystrophin and clinical improvement on the NSAA. Next slide, please.

Regarding safety, patients receiving SRP-9001, manufactured by process A and by process B, developed hepatotoxicity. Patients who received process B SRP-9001 experienced cardiotoxicity, myocarditis, and heart muscle injury detected by elevated troponin-I. And one patient had mediated myositis. We also talked about the implications of cross-reactivity for

patients for whom SRP-9001 is not effective. And in considering potential benefits and risks for any AAV based gene therapy, we also have to keep in mind the serious adverse events with the other AAV based gene therapy products, including SAEs, which were seen only after the product was marketed and administered to a larger number of patients.

Finally, we discussed the understandable situation of patients in study 301 possibly wanting to break the blind and withdraw from the study if SRP-9001 receives accelerated approval, which could mean that there would be no way to confirm whether SRP-9001 is effective and to know who might benefit and who would not. Overall, the many uncertainties make it difficult to consider Sarepta's micro-dystrophin a surrogate endpoint reasonably likely to predict clinical benefit and are important to keep in mind when weighing the potential benefit and risk of SRP-9001. If part one of study 301 is completed, the data will be available later this year and should help clarify many of these issues. And that's key. Because like I said, patients likely only have one chance to receive AAV gene therapy, and it's critical that that treatment is effective and safe. Next slide, please. Thank you very much.

Q & A

Dr. Ahsan: Thank you to the FDA speakers in explaining and walking us through a lot of the data. We now have about 15 minutes to go through questions for the FDA speakers. So if committee members want to raise their hands, that would be great. I'll start first with Buddy Cassidy. I apologize, I missed you on the last one, so please go ahead and unmute and turn on your camera.

Mr. Cassidy: Okay. Yeah. So I am a bit puzzled about the characterization of the North Star Ambulatory Assessment in the investigative report. In the investigative report on page, I think it's page 44, it notes that performance, and on page five as well, but performance on the NSAA can be affected both by the consistency of administration, process dependent and by the effort of

the subject and/or coaching or encouragement by a family member. And so the citation in the investigative report is the FDA's DMD drug development industry guidance issued in 2018. So that is the source for that. But in looking over the report, on page eight of the guidelines, it says, There are many functional endpoints and such endpoints can be affected by the effort of the patient and/or coaching or encouragement by a family member or caregiver or medical staff so that blinding treatment is critical. And I'd like to note that it just says many functional endpoints, and the endpoints, broadly speaking, this isn't necessarily a problem specific to the NSAA. And I guess why I'm puzzled is because this doesn't really bear out in the literature and research.

In fact, the opposite has been well established with the NSAA that it is quite accurate, consistent, and really great efforts are made to mitigate bias. So I'm just, I'm confused because that assertion doesn't seem to be backed up in the literature.

Dr. Ahsan: So maybe, perhaps the question is if the FDA speaker could, direct us towards what their position is on the NSAA and why their position is that it is, effort, biased.

Mr. Cassidy: Well, it seems to depart significantly from the trends we're seeing in literature and research.

Dr. Ahsan: Sure.

Dr. Witten: So thank you for asking. That is a very good question and an important one. So I'm going to ask Dr. Singer to comment on it.

Dr. Ahsan: Great. Thank you.

Dr. Singer: Yeah, thank you for the question. So, yes, it wasn't, that wasn't meant to refer just to NSAA, but in general to many clinical outcome measures that have some, you know, that, so to differ, to distinguish rather between certain measures, for example, like looking at survival where, you know, that's an objective assessment versus scales like the NSAA and many others

that do depend on and can change with characteristics in the clinical studies. So, for example, Dr. Wang showed that, in one of her figures, the different scores for patients in the Sarepta studies comparing the double blind, placebo-controlled study versus the open labels. You can see that there were differences in those outcomes overall. You know, the NSAA is, as I mentioned, it's good studies.

Where the issue comes up is in interpreting differences that may be, you know, moderate or small, which could be important clinically. But you need to have the most rigorous comparison possible to, you know, to make sure that those are real and that you're not erring either one way or the other to where there is benefit or missing a situation where, where there may not be.

Dr. Ahsan: Great. Thank you, Dr. Singer. Let's move on to the next question. Dr. Caleb Alexander, please.

Dr. Alexander:Thank you. And I'm struck at the difference in interpretation of the, of the nonclinical data. You know, we've all heard that you can have your own, you're entitled to your own opinion but not your own facts. And I must say that, that the FDA and sponsor seemed to have very different interpretations of that data. But my question is just about one small piece of this, which is that the proof of concept studies did not, were, the FDA notes didn't reflect good laboratory practice. And I'm an epidemiologist. I'm not an expert in preclinical studies. So I just wondered if you could speak to how common, how significant a shortcoming is this? How surprised should one be? You know, if you look at a hundred BLAs, how many of them are, are likely to reflect similar absence of what's called good laboratory practice? And also, this probably isn't an all or none. So I guess I'd be interested to hear from the FDA, you know, a little

bit more nuance maybe you could provide for us regarding the degree to which this is a really important departure that we should consider as we try to interpret these data. Thank you.

Dr. Witten: Thank you. That's a very good question, and I'm going to ask Theresa Chen to respond.

Dr. Chen: Hi. In general that we will request a toxicology study under a GLP, meaning that we will have the protocol, and we, well designed study protocol, and very good documentation of the animal data. However, that is not required for proof of concept study. So in this case that I think we are looking at the proof concept study, we have seen some discrepancy as what the sponsor described in one of the parameter giving example. And then we went back to look at the data. It's really not consistent with the description that the sponsor described. They were a number of the, I think, the animal data may be not included, especially in a control group. And that's what we meant. Um, these could be the, the proof concept study could have some study design limitation, including a bias, including the missing data. And I'm hoping this can address your question.

Dr. Ahsan: Great. Thank you, Dr. Chen. Dr. Lisa Lee.

Dr. Lee: Thank you. I have two questions most likely for Dr. Singer. One, given that there are major differences in process A and process B with respect to purity, and the other data that, your data that you presented, given that these are so different, are study, are studies, are the study 102 results applicable at all to what we're talking about here with the product being designed under a process B? And how robust or valid are these pooled analyses that are basically using some different, some different, you know, a different product in some ways?

My second question is, you know, we did hear from many families and patients about the, we saw videos of some real impressive improvements. I'm wondering about what data, were, were

submitted for how many or, or what the characteristics were for the participants that did not have benefit from this? What does that look like? How many of them were there? What is their clinical, what is their, you know, kind of clinical profile, pre and post-treatment?

Dr. Witten: Yes. I'm going to turn these questions over to Dr. Singer also.

Dr. Singer: This is Mike Singer again. Thank you for the question. So, first, yeah, the process A and process B products and then the implications for that with regard to the pooled analysis, so that is potentially an issue; and, in order to have more rigorous bridging between process A and process B, FDA had recommended that study 103 would be a randomized, double-blind, placebo-controlled study. So it's, so it is difficult to be able to assess, not just looking at study 103 on its own, but also in comparison to the 101 and 102, the studies that use the process A product. So that's, that is an important concern with regard to trying to understand the effect of SRP-9001.

And then with regard to the videos, yeah, certainly they were, you know, quite impressive. As to the, as to whether there's, to what extent their pre and post videos, that's something I'd have to turn to the applicant to discuss. But I think that, nonetheless, it's, you know, one of the major issues here is not to say that it is not about whether SRP-9001 can, can have a positive effect, but determining and predicting, knowing which patients would benefit and which wouldn't is, you know, is very challenging based on the data that we have.

Dr. Ahsan: Great. Thank you. Just in order to maximize the transmission of information, let's try to be as efficient as possible with the questions and answers. Dr. Raymond Roos, please.

Dr. Roos: Yes. Thanks. I had a question about Sarepta providing data of external controls. And that wasn't dealt with at all in the FDA discussion, and I wondered why. And the other thing that wasn't quite clear to me was whether these external controls had steroid treatment.

Dr. Ahsan: Dr. Singer?

Dr. Singer: Yes. This is Mike Singer again. Thank you for the question. So if I understood you correctly, you said FDA's discussion of the external controls. So they were from, and, and then also whether they had received, the patients had received steroid. So, yes, they had. They, the controls were from the synergy national history study from the four DMD study that compared three different corticosteroid treatment protocols. And then the, the third one is from the Eli Lilly and Company study of tadalafil. And so the, the issue, you know, it's not specifically with, with one or the other of the external controls, but applies more generally that in situations where we're looking at a disease that's, where progression is heterogeneous, you know, for individual patients where a treatment effect, you know, may be moderate, which would be an important clinical advance, but is difficult to detect in a, you know, in clinical studies.

And, you know, in those kinds of circumstances, it's, using an external control is very challenging to be able to, to draw any conclusions. And so that's a different situation. Very different than, as I mentioned for, for Zolgensma where the disease progression was much more homogeneous where the, the magnitude of the clinical effect was large. And the outcome measure was, you know, outcome measures were objectively, could be objectively assessed, survival, for example, rather than, you know, a, an efficacy endpoint that may be validated but harder to discern small changes or the, the significance of small changes that may be detected from, from one group to another.

Dr. Ahsan: Thank you, Dr. Singer. Dr. Eric Crombez.

Dr. Crombez: Yes. Thank you. My question is on the last point that was made on summary slide number three and, and referring to that, patients will likely only have one chance to receive an AAV vector-based gene therapy for DMD. And I guess I'm wondering, with all of the work

being done with IDAs, the antibody cleaning enzyme, the various immunosuppressive regimens, and, most importantly, the tremendous work being done on novel capsid development. In fact, I have heard Peter Marks talk about this, and I know he is on the call today. And, you know, in partnership with trying to find an abbreviated pathway for approval, if you're using approved trans-genes and novel capsids. So I guess my question is, as a field and in partnership with the FDA, if this is a risk, aren't we already well on our way to mitigating this risk?

Dr. Witten: I'm not sure. Dr. Singer, do you have a comment on this or someone else on the team? I would say we're going by what, you know, what is the current, our current state of knowledge, but I guess things could always change in the future. I don't know if anybody on the team has anything to add on that.

Dr. Singer: So this is Mike Singer again. Yes. I would agree with Dr. Witten that, you know, certainly it's something that, you know, hopefully there'll be better approaches for in the future. But speaking with, as to what, for what we've got at the moment, you know, that's, that's the situation and that's the, as a result of this concern.

Dr. Ahsan: Great. Thank you, Dr. Singer. Dr. Kathleen O'Sullivan.

Dr. O'Sullivan: Hi. My question is for Dr. Singer. Given the concerns, the manufacturing concerns about process A versus process B, is there a scenario where FDA, or would it be overreaching for FDA to, to compel one process over another? Or is that not even a concern?

Dr. Witten: Yes, this is Celia Whitten. I think that's a question for Emmanuel Adu-Gyamfi.

Dr. Adu-Gyamfi: Yes. This is, my name is Emmanuel Adu-Gyamfi, and I hope you can see and, see me and hear me clearly. So we, the FDA does not have a specific, you know, recommendation as to, you know, how sponsors or applicants choose to manufacture their product. So we would typically look at the totality of the data that's submitted, and consider the,

you know, the risk benefit. Again, part of the reason why I think it's, it will be difficult to mandate that is every, every indication is different. You know, every route of administration is different. And so as a part, currently we do not mandate the, any applicant to, you know, use one particular method or one particular serotype to, to be able to develop their clinical trial. And we do not mandate the extent of the empty capsids or the full capsids. It, it's, we have to look at the data in its totality and assess the safety and efficacy.

Dr. Ahsan: Thank you. Dr. Rajiv Ratan.

Dr. Ratan: Yes, thanks for the great presentations. I thought Sarepta was trying to make the point that, that the micro-dystrophin is only a surrogate endpoint at, with relatively small levels of expression. So I was wondering if you've gone back and done the analysis where you're trying to compare Western blot levels with the NSAA, looking at, at different levels and actually comparing outcomes instead of doing it over the whole range and whether that, that analysis, as Sarepta did, would change your opinion.

Dr. Witten: Thank you for that question. That's a great question. I'm going to ask Xiaofei Wang if she can respond.

Dr. Wang: Hi. Yeah. This is Xiaofei, clinical pharmacology reviewer for this one. Thank you very much for the good question. Actually, yeah, we, the reason we conducted the group analysis data, all data listed, because in our presentation we have noticed that high interpatient variability observed in the micro, Sarepta's micro-dystrophin expression. That's, yeah, you can, if we go back, go to the slides number.

Dr. Ratan: Yeah. I remember the slide.

Dr. Wang: Yes. Slide, slide number 43.

Dr. Ratan: Yeah.

Dr. Wang: And number, number 43 and number 44, you can notice, yeah, for example, for the, yes, 43 you notice the wide range of the interpatient variability, so even with the, yeah, and considering the very small sample size, yeah, that's why we conducted the correlation.

Dr. Ratan: Great. Thanks.

Dr. Wang: Thank you.

Dr. Ahsan: Great. We're, we're now over time, so if we can be as efficient as possible, the next person is Buddy Cassidy.

Mr. Cassidy: Yes. I had a question about the biomarker endpoint. So I'm just, I, I'm a bit puzzled as to why there's such reluctance to accept the expression of the SRP-9001 micro-dystrophin as a surrogate endpoint. This seems, even low amounts of dystrophin seem to be able to make a difference. This is well supported in the, the literature. It's also the mechanism of action. I mean, it's been well established that shorter dystrophin occurring in nature, like in, in Becker, only a little bit makes a big difference. It's not how long the dystrophin protein is, and we often know things like even the stop codons can make a big difference. So I'm just, Sarepta's justification of the endpoint in terms of biological plausibility, it's in keeping with the literature, and the literature review says as much in this sponsored data. And so I'm confused about the reluctance and what possible alternatives could they have used that might have been a more acceptable biomarker.

Dr. Witten: Well, I'll ask Dr. Singer, but first I'll just say that is a question we're bringing to the advisory committee. The, I think that the, the team has laid out what the scientific concerns are in terms of interpretation. We're ask, going to be asking the committee later this afternoon to give their comments on it. So I think that's really an excellent question, and it's one we're hoping there's going to be a lot of discussion about. But, Mike, do you have something to add?

Dr. Singer: Just briefly. Yeah. And, and thank you for, for the question. So the, raises some very important issues. So one is with regard to a small amount of dystrophin having a clinical effect. The problem there is that, you know, shortened dystrophins are, you know, very different from one another. So, so it could be that a small amount of, of the wild type dystrophin can have a, you know, a major clinical effect or small amount of, some of the mutated Becker dystrophins, may have a notable effect. But since we don't have, since, since this is, you know, a novel, you know, engineered protein, it's rationally designed, but, you know, since it isn't in nature, we don't have that kind of information outside of the clinical trials to be able to, you know, assess what the, the effect of, you know, various levels of, of this protein, of Sarepta's micro-dystrophin, what their effect may be. And so that's one issue.

And then to get at the other issue that you raised with regard to predicting, you know, as a surrogate endpoint, surrogate endpoint, you know, it has to be able to predict an effect on a clinical endpoint, so on, you know, an outcome like the NSAA. And so here where we don't see, you know, a clear association, you know, that's another, you know, major difficulty in accepting the data as we have it for Sarepta's micro-dystrophin as a surrogate endpoint, in this category, reasonably likely to predict the clinical benefit.

Dr. Ahsan: Great. Thank you, Dr. Singer. Dr. Jay Chiorini.

Dr. Chiorini: Yes. Just to follow up, this may be a better question for the applicant, but how long did the high titer antibodies to the vector persist?

Dr. Ahsan: I, I suggest that we defer that, and we will bring that question back after the break so that it gives the sponsor a moment to collect themselves. If we can move on then to Dr. Anthony Amato.

Dr. Amato: Thank you. I was interested in the CK decline in, in the treated group, and, and I know CKs, you know, in general in population may not correlate. But that significant drop is something that we don't normally see. I was wondering, you know, was there a correlation in what you saw in terms of dystrophin expression based on the CK decline or any of the clinical efficacy? Again, this would be for the sponsor, was it just a few patients that had a big dramatic decline and that pushed the mean, mean down? Or, or was it, or, again, was there a correlation with the benefit, and did you, did you check it CK levels at screen and then a baseline to show that this was not just normal variability? But, you know, it, you know, if it's not, it, it does seem to be a, a marker to me that there is an effect of the micro-dystrophin on the sarcolemma. And maybe you don't have that data, but maybe the sponsor can come back with that. And the other thing that, that I wanted to know is, is in terms of, well, well, we may only have one chance to make an effect using AAV viral vectors in these boys that, I mean, do, are there any other candidate drug dystrophin deliveries with AAV? I mean, there's no candidate right now when we don't see something in the future, like in three to five years. And you have something that might be potentially effective now versus waiting three to four years? You know, I, I just don't know that you can make that say, well, you, we, we only have one chance.

Dr. Witten: Sorry. I think the first question, as you say, it's a question for the sponsor that maybe they can provide that data. And as to the second one, there's, there's, you know, products under development, but we really can't comment on any specific product or, you know, what, what is likely to be getting, you know, what is it, what stage of development.

Dr. Ahsan: Great. Thank you, Dr. Witten. Dr. Nirali Shah.

Dr. Shah: Hi. So my question is about the trial design. Just because I don't remember, can somebody comment regarding whether the, there is allowing for use of steroids, increase in

steroids or other standard of care, and what proportion of the patients were able to stop or be able to be weaned from steroids in either the experimental or the treatment groups on the, on the double blind randomized study?

Dr. Witten: Dr. Singer, can you comment on that? Uh, okay. I think that's a question for the sponsor.

Dr. Ahsan: Thanks. Great. I think, oh, we have, well, I think we'll allow the sponsor to speak when we come back after the break. So I, I see that raised hand, but we'll leave that response for after we get back. I do, I'll take the liberty of asking one additional question. So there was, you know, a lot of very, let's say the, the nonclinical studies were non GLP, the analysis of the current studies were a little bit of a hodgepodge. Can the FDA comment on the confirmatory study and the, and how it is powered? Because I, I believe it's meant to be stratified by NSAA as well as age. And as part of this accelerated approval, I feel that we need confidence that the confirmatory study would give us the information that we would need one way or the other. So could someone from the FDA please comment on that?

Dr. Witten: Uh, oops. Yes. I'm going to ask Cong Wang to comment on that question. Thank you.

Dr. Wang: Hi everyone. Hi everyone. This is Cong Wang. I'm the biostatistical reviewer for this BLA. Based on my knowledge, I don't think the sponsor pre-specifies the power during the study design stage for study 301 for the subgroup analysis. But I think this applicant may answer this question later. Thank you.

Dr. Ahsan: Okay. I'll leave that then for the sponsor when we come back. So we have a few questions for the sponsor. There are no more raised hands. I think, Dr. Witten, if you agree, we can move towards the break. I think it's good to maintain the 10 minute break, just because we

will be going for over two hours on the next section. So if we can all return at 3:39, that would be perfect and we could start right then. Thank you all.

Committee Discussion, Voting, and Vote Explanation

Dr. Ahsan: Welcome back everyone. Thank you for being on time. This is, we're now shifting to the discussion portion of the afternoon, and this is where the committee does the heavy lifting. Now we do have, we are a little bit behind, so I want us to be expeditious, but I know that Jay and Anthony had two questions that they wanted to ask the sponsor. If you still want to ask them at this time, please raise your hand. Oh, and I think Dr. Witten has raised her hand to say something. Let's let her speak. Dr. Witten, did you want to say something?

Dr. Witten: Can you hear me? Yes. Can you hear me?

Dr. Ahsan: Yes, now we can. Mm-hmm.

Dr. Witten: Oh, good. I never get used to this technology. I just wanted to clarify something that was asked before the break to make sure people, you know, people recognize the fact that we support that study 301 will provide us the information we need. I don't know whether that was understood by our answer to the advisory committee. So we, you know, we are looking forward to getting the results of the Embark study, which we think are important. And as to the design elements, though, I would defer that to the sponsor, but I just wanted to make that clear that we are looking forward to getting those results. Thanks.

Dr. Ahsan: Good. Thank you. I'll, I'll actually defer that part of my question until topic number four. So, Jay, did you want to go ahead and ask your question? If we can be quick, as I said, we're a little bit behind; and we do want to have a full-throated discussion.

Dr. Chiorini: Yes. It was basically how long do the antibodies persist for the, a greater than 400 titer?

Dr. Ahsan: Right. Is there someone on the sponsor side that can provide that answer?

Dr. Rodino-Klapac: Prepared to answer, and we have prepared to answer a number of other questions that were raised. In terms of the antibody titers, we have, antibody titers reach a peak around six to eight weeks, and then this persists for up to a year. So they do persist.

Dr. Ahsan: Great. Thank you. Well, I think Anthony deferred, but maybe Nirali wants to ask her question. Please go ahead.

Dr. Shah: I just have the question that I had asked before the break regarding the trial design, use of concurrent therapies, and if they have any information on outcome data, whether patients were a, you know, if they're allowed for escalation of steroids and if any patients, if they did, and weaning steroids or standard of therapy on the randomized placebo-controlled trial.

Dr. Rodino-Klapac: Yeah, we'd be happy to have Dr. Stefanie Mason address this.

Dr. Mason: Stefanie Mason, Sarepta Therapeutics. All of the patients in our trials, including the double blind, randomized, placebo-controlled 102 trial, were on DMD related corticosteroid therapy for a minimum of 12 weeks before entering the trial. The dose of those steroids was at the judgment of their treating physicians, but it was required to be maintained at a constant, constant dose throughout the first year of the trial, or, in the case of the double blind, randomized, placebo control trial, for both the first and second period of follow up. The only adjustments permitted were for weight. In terms of concurrent therapies that you mentioned, there were required washout periods for any experimental drugs that may have been given before or any exon-skipping therapies that may have been administered prior.

Dr. Ahsan: Great. Thank you.

Dr. Shah: Sorry. Do you have information on whether patients were able to stop their disease, their DMD therapies?

Dr. Mason: Stefanie Mason. So because the steroids were required to remain constant throughout the follow up period, none of the patients were weaned from their steroids because of the protocol requirements. However, in our ongoing open label extension studies, there is now more flexibility. So we hope to be able to have data like that in the future.

Dr. Amato: And did, did you have a chance to look at my question in regards to CKs?

Dr. Rodino-Klapac: Yes, we did. We're prepared to answer that. Dr. Lilly East will address the association between CK.

Dr. East: Lilly East, Sarepta Therapeutics. We see a statistically significant correlation between serum CK change at week 12 from baseline to SRP-9001 dystrophin measured by Western blot. There's also a striking difference in the values that we see in placebo group versus SRP-9001 treated group. There is a 10,000 unit change. Thank you.

Dr. Amato: Was there a correlation with the efficacy measurement, the North Star, by chance, with the drop in improvement or stabilization?

Dr. East: Between serum CK and NSAA total score?

Dr. Amato: The drop, the drop in the CK and whether there was improvement or stabilization?

Dr. East: Well, there's a timed difference. The serum CK that we're referring to here is week 12, change from baseline, whereas NSAA total score was measured at one year.

Dr. Amato: Was it measured at 12 months though?

Dr. East: Serum CK --

Dr. Amato: I mean, you, I think that it would've been measured at the time if you would do assessments at all the visits.

Dr. East: So in terms of the serum CK values, we also measured at one year. And what we can say is the level of reduction that we see at week 12 is sustained at one year. So the relationship, overall, would suggest that the, that there's a consistency between the serum CK reduction and NSAA improvement at one year. Thank you.

Dr. Ahsan: Okay.

Dr. Rodino-Klapac: We did capture two other questions that we'd like to answer, if that's okay with you.

Dr. Ahsan: Could you cite what those questions are just to make sure that the committee is still interested?

Dr. Rodino-Klapac: The one question was around the DSMB, and then the second was an important clarification on the nonclinical.

Dr. Ahsan: Okay. Go ahead.

Dr. Rodino-Klapac: Okay. Thank you. First, the DSMB.

Dr. Mason: Stefanie Mason, Sarepta Therapeutics. Dr. Susan Ellenberg had requested information about whether or not the data monitoring committee was able to review efficacy data. I would clarify that the 9001 data monitoring committee is a program-wide data monitoring committee. So they review data from all of the trials. In totality, it is primarily chartered to review safety data, but they have the option to request unblinded data, including efficacy data. This request would be to an independent statistician, and we would only be made aware if they subsequently made a, a request or recommendation based on that review. The last meeting was March 9th, 2023, and to date the only recommendations have been that the studies continue as designed.

Dr. Ahsan: Thank you. Then the second question.

Dr. Rodino-Klapac: Dr. Rachel Potter.

Dr. Potter: Hello, this is Dr. Rachel Potter, Sarepta Therapeutics. I would like to clarify that we completed three GLP toxicology studies and 13 proof of concept non-GLP efficacy studies. These efficacy or proof of concept studies are not required to be GLP as denoted in the guidance. Based on the FDA guidance for preclinical assessment for cellular and gene therapy products, we followed that guidance for proof of concept studies. Additionally, methodology throughout the development of nonclinical 9001 studies for function and histological evaluation in MDX mice followed treat NMD SOPs that are recognized as the gold standard for DMD preclinical research. And to address the missing data concern, these were due to various reasons, not related to study design or lack of documentation. Instead, an example would be lack of volume sufficient to identify or measure serum chemistries. So, regardless, the totality of nonclinical evidence is conclusive.

Dr. Ahsan: Thank you. Eric, did you want to ask a quick question?

Dr. Crombez: I did. Thank you. And I didn't see a natural place for it to come up in the discussion questions. There was just a lot of talk in the FDA presentation about process A and B, and I guess my question to the sponsor was is there, are there any other differences, other than the empty/full ratio changes? And do any see any differences in expression or change in benefit risk profile between those two processes?

Dr. Rodino-Klapac: Yep. The change in FD capsid is the major difference. We did not see any differences when we evaluated it in both nonclinical and clinical studies. Let me just show you the example of expression between process A and process B. Let me pull this up. We see no differences in expression between process A and process B. You can see by Western blot, 40%

by process A and 54% process B. Same levels of transduction across those. So we did not see a, a difference in efficacy in terms of expression, and we also saw no differences in terms of safety.

Discussion

Dr. Ahsan: Great. Thank you. And so now I'd like us to shift to the discussion portion of the afternoon. If the FDA can put up the discussion question, discussion topic one that I can read off. Sorry. Maybe someone from the AV side can remind me if we are actually going to display the slide for the discussion topic, or should I just read it off? Here we go. Great. Thank you. So discussion topic number one. Well, actually, before I read this off too, just to let everyone know, I will read off the topic. We have identified discussions that will start off the conversation for each topic, and that person will kickstart the conversation. After that, we will open it up. People will be able to have their voice heard on this topic. And then we will, I will summarize it, and we'll move on to the next topic.

Okay. So for discussion topic one: Please discuss the strengths and limitations of the available evidence supporting the use of measurement of Sarepta's micro dystrophin, expressed through administration of SRP-9001, as a surrogate endpoint "reasonably likely to predict clinical benefit" in ambulatory patients with Duchenne Muscular Dystrophy with a confirmed mutation in the DMD gene.

Okay. And so, Dr. Raymond Roos, you were going to start us off with some discussion points.

Dr. Roos: Yes. Thanks. I just will talk for less than five minutes. There are some issues related to the answer here to topic one. The NSAA is certainly sensitive to effort, and the micro-dystrophin that's provided lack certain domains, and its expression certainly may vary in different tissues. Despite these limitations, we should note that the treatment of rodents, mice and

rats, that have a model of Duchenne dystrophy show improvements with respect to this gene therapy, but I'm a little cautious about this. It's a different species and also a different disease. I think most compelling here is probably study 102, part one, in subjects that are four to five years old in which the NSAA score is 0.017.

One could be critical of this. There aren't a lot of subjects. There's no hypothesis tested. And individuals that are six to seven years old didn't show any improvement. However, we, we really, I'm impressed by the external controls that Sarepta showed, which suggests that, that, the gene therapy, even in age six to seven year olds, is helpful. And perhaps the difference in the lack of improvement in the six to seven years old is because they started at a different level, or maybe we need a second year to examine the effect of gene therapy.

I think gene therapy looks relatively safe. The risks seem to be manageable. And the bottom line is that Duchenne dystrophy is heterogeneous. The efficiency of treatment is going to depend on the age of the subject, how much muscle is there, the particular mutation that's involved, and the efficiency of delivery. And this may be responsible for some of the variability that we see. On the other hand, it appears as if ambulatory patients at a certain age will improve with gene therapy. It would, of course, be valuable to know the genetics of the Duchenne dystrophy in the particular individual, because that might be important as far as improvement. Thanks.

Dr. Ahsan: Great. Thank you very much for starting us off. If people want to raise their hands to, to make comments regarding this discussion topic, that would be great. Steven, if you want to go ahead.

Dr. Pavlakis: Sure. Let me just, in terms of biomarker, or surrogate endpoint, we used to call them biomarkers, in the olden days. I don't think they've proven this is a good biomarker. It may

be the best, but I don't think it's been shown. And I don't think we can use it in lieu of clinical data at this point. Maybe they'll have more data about it, you know, in the future. But right now we can't say that, oh, micro-dystrophin is better; therefore, the patient's better. And there are diseases you can do that with, but I don't think we're there for this.

And should I just comment about clinical endpoints? I can do that in, just to get it over with, in 30 seconds, if you like.

Dr. Ahsan: Sure. Go ahead.

Dr. Pavlakis: I think clinically, I, I mean the data doesn't show that it works. It suggests it might work in little, in small, younger kids, which would not be crazy, but it's not proven. I also think, as I'm also a clinician, and I think as a clinician, they didn't do a great job showing that, that there was a clinical effect. Having said that, my kind of, I think there's a good chance that some patients do get better and some don't, and I think we didn't really get, I think there's a lot of scatter, and they really didn't show it even when they were showing, you know, what, what a Gower's sign is and what it's not. Well, those are, that wasn't really correlated to what we're doing. They just showed, oh, this is how bad it can be, and it's really, it is an awful disease.

So I don't think they really did a, I don't think we have statistical evidence that this thing where, that the drug works. Although my guess is that some patients do get better and some don't, or not much. And they, they also didn't do a good clinical job. They just showed up some videos, and, yeah, they all look great, but that's not really much clinical data. And when I asked how, I asked actually how did the older patients do, and they said, oh, they, they're stabilized. But that was just very handwaving. So I wasn't very impressed with it, with, with what have, but I do think it might work, having said that.

Dr. Ahsan: Thank you, Steven. Raj, did you want to, Raj, would you like to go on camera and unmute yourself?

Dr. Ratan: Sure. Yeah. Sorry. It's a, all right. You can hear me. It says for some reason unable to start video. But the, I thought this, I thought the strengths were that they had shown that you could get expression of the micro-dystrophin, that it could bind near the plasma myeloma, that it appeared to inhibit the release of CPK. So it, it, it appears that they have demonstrated that there's some structural effect of the micro-dystrophin. What, what I think I found its limitations, is the evidence that that structural effect actually converted into a physiologic effect. So, and, as was pointed out, the, the problem is the coefficient of variation for the immuno-blots were so great that there was very little correlation or evidence of benefit in functional outcomes, either in the nonclinical or the clinical realms. And I think those issues, plus the fact that there were other explanations for differences between the four to five year old group and the six to seven year old group that could include age, I think those were limitations that diminished my enthusiasm.

Dr. Ahsan: Thanks, Raj. Buddy, did you want to go?

Mr. Cassidy: Yes. Hi. Can I ask for a quick clarification from Sarepta?

Dr. Ahsan: Sure. Sure. Would the sponsor please be ready to reply. Go ahead.

Mr. Cassidy: Do you have, did you also, in your studies, collect patient reported outcomes or findings? Because I imagine they could give us a good idea of, like, qualitative data and observation and maybe some indication about how this benefits quality of life. So are there, is there patient reported outcomes data, and was this submitted to the FDA?

Dr. Rodino-Klapac: I'd like to ask Dr. Stefanie Mason to address.

Dr. Mason: Stefanie Mason, Sarepta Therapeutics. We did administer some caregiver proxy measures called the PROMIS, or Patient Reported Outcome Measurement Information System, in the 102 trial. However, these were intended to be exploratory, and we used the trends in those outcomes to inform our design in the larger 301 study where we will be administering the PROMIS to all of the patient caregivers, as well as a measurement directly to the patients who are aged eight and older during the study.

Dr. Rodino-Klapac: Thank you.

Mr. Cassidy: Okay. Thank you. I was just asking because I do know that in terms of FDA's guidelines to industry for Duchenne, it does mention potentially looking at patient reported outcomes to assess clinical meaningfulness. I guess what I'm concerned, what I'm concerned about here is that, in terms of the, the investigative report, we're talking about accelerated approval process for a relative disease. And it doesn't seem to me like there's much of a place or room for a discussion of qualitative changes outside of the clinical setting. And I'd, I'd like to stress, as the patient representative, that these things are so important and meaningful to patients. And I would just like to stress that qualitative observation is indeed scientific, and it is not to be conflated with anecdotal evidence.

Again, this, I think quality of life is very important here, and we need to seriously take into account what we're seeing in the videos. In terms of the Gower's sign, there are actually documented instances of patients no longer using the Gower maneuver to get up. And I can speak from personal experience that having had to use the Gower maneuver myself, which would put me at about a one on that NSAA evaluation to a zero, not being able to get up on my own at all. And that's not just significant, but almost miraculous, that we don't, we as Duchenne patients, in terms of the natural history, in terms of lived experience, don't get better. We don't

improve. Right? So to not do that anymore is, to me, nothing short of miraculous. And even just stabilization across three, four years, I can't tell you how meaningful that is as a patient. I, what I wouldn't give for another four years to just maintain the level of strength I have now. So I just, I just wanted to bring that to bear. Thank you.

Dr. Pavlakis: Thanks. And you're right.

Dr. Ahsan: Thank you, Buddy. Up next up would be Kathleen, please.

Dr. O'Sullivan: Hi. Yes. You know, I think there is data there that suggests that, that micro-dystrophin is a good proxy measurement. And I think there's the CK levels, there's the data that came that Dr. Mason shared about the NSAA scores improving. I think, you know, it's, it's a variable disease. It's a, this genetic mutation will, has many different mutations, and it will express itself differently among patient to patient. So we're not going to get that, that, that neat and tidy, wrap it in a bow. This is perfect. Check this box, then it goes directly to this box. We're not ever going to be able, this is not the kind of disorder that's going to be able to be solved with using those old tools that work for the generic diseases that you have a very predictable disease outcome. But similar to what Buddy was stressing, what I was taken with is that not only do we have data that shows improvement, which I think is, to echo his words, nothing short of miraculous, but also that stabilization is kind of, you know, waved away certainly by our FDA team in, in what they think is a meaningful clinical endpoint. And I want to be sure as a other, as someone who represents and is a patient advocate for a different monogenetic X-linked disorder, that, that is so important.

And then, you know, I would completely discount the concerns about blinding and the variability in, or coaching involved in the NSAA scores. Those kids are not faking their NSAA because they wished it, because they hoped it. Otherwise, every single DMD patient would be

better instantly because everyone is hoping, and their clinicians are hoping for a better outcome. So I think that's borderline offensive to continue to bring up that, you know, that somehow slight variabilities in scoring would lead to any disrepute of that data. But I just want to remind people that, you know, part of our job is to make sure that we're not only, you know, it would be great if we were adding years to their lives, but we want to add life to their years. And we have, I, I feel optimistic we have an opportunity here, and I'm hoping that people will step away from genuflecting to statistical rigor and box checking and actually pay attention to the whole holistic breadth of data and evidence that's been produced here today by the community and by the sponsor. Thank you.

Dr. Ahsan: Thank you, Kathleen. Caleb, would you like to go?

Dr. Alexander:Yeah. I mean the, listen this is an incredible amount of science, so it's really, you know, an incredible amount of synthesis. And the fact that we're here at all is, is pretty incredible, frankly, because it's based on decades of work by thousands of people and, and remarkable discoveries. I, I guess let's just make a, a few notes. The, the first, just because the last speaker mentioned it, I don't know that the FDA or the sponsor suggested CK as a means of assessing the suitability of the surrogate. I think the FDA specifically noted that assessment of CK values, which only occurred in one study, was inconclusive due to the frequency of, of missing data and high variability in the individual animal data. But, you know, and I guess the, the preclinical data's mixed. I mean, there, there's, I already noted that there's fairly different interpretations by the FDA and the sponsor. My read is that the sponsor argues that the mouse data showed correlations that were highly statistically significant. I think the FDA noted that they were post hoc and produced using immunofluorescence, but not Western blot, which is a more reliable or valid method.

The sponsor executive summary was silent on the rat studies, the FDA noted that those studies yielded similar declines among treatment and, and the vehicle controls, I believe. You know, the real money is in study 102, part one. And, by the way, it's not that the, I don't think anyone's suggesting that, that people would try to fake the NSAA. The NSAA is a highly regarded, extensively validated tool. But I think we saw data presented by the FDA that indicated the basis for concern about open label and bias that could be introduced using such. So I'd be interested in the sponsor's interpretation of that, that figure, that shows increasing magnitudes of change in the NSAA across groups when you go from blinded to unblinded groups. But, you know, I think the real money is in study 102, part one. It failed in the primary endpoint. And there were a number of post hoc analyses performed. And those are interesting. They're provocative. But they're not, they're useful for hypothesis generations.

So, you know, on the one hand, it was curious that the higher dosed groups didn't do better. In fact, they did worse than the lower dosed groups based on this, you know, inadvertent, missed dosing. But, you know, one can't conclude too much about that because that's a post hoc, non-prespecified subgroup analysis. And it has to be interpreted with caution. And so similarly, the age, that the age groups and the fact that younger people appear to do better, perhaps, than older people. So, you know, there's always interest in these settings in the subgroups that do really well. In the case of Adam Plurson (phonetic) five years ago or so, it was, what I think people talked about and referred to as super responders. You know, a year and a half ago, is Aducanumab. And, there again, there was discussion and focus on this, this small group of people despite negative overall top line results that appear to really have profound improvements. And I think there's, it's understandable, they had a real interest and desire to learn

from them and try to understand, you know, what's going on with them, but it doesn't change the fact that the primary results were, were not statistically significant.

So I think there's just a lot of uncertainty. I mean, that's what I feel. And it's too bad that the doses were so varied in study 102, part one, and I'm especially struck by the really profound variation in micro-dystrophin expression across individuals. A number of people have noted it, and we've looked at figures that represent it. But that's really striking to me, and it makes it more difficult for me, I guess, for all of us, because there's no clear, I guess there's no clear level, target level that is being sought. And it's also hard when one can't see any evidence of or assess for any evidence of a relationship between the magnitude of expression and the clinical outcome. Thank you.

Dr. Ahsan: Great. Thank you. I do want to remind people we have several topics, so let's stay focused on this topic of the surrogate endpoint. I did want to, I'm going to take a little of a liberty and follow-up on Caleb, which is one of the issues with study 102, part on, is the fact that when you don't have a nice span of data on your outcome measure, it is very hard to then establish the correlation of your surrogate endpoint. And because of that, there's some challenges in creating that correlation. And so, specifically to this point about whether that's a valid surrogate endpoint, that becomes very challenging when you don't see that outcome in the clinical outcome changes based on the treatment as well. Okay. So, next up is Nirali.

Dr. Shah: Hi. This might be a very basic question, but going to the issue of it being a surrogate marker, my question is, wouldn't the expectation be that if you received this therapy, that you will have measurement of micro-dystrophin? I didn't see any data about what percentage of patients who received this therapy did not have measurable micro-dystrophin. And so I think that, to me, questions how you're able to use it as a surrogate endpoint.

Dr. Ahsan: Perhaps the sponsor could speak to that, as to whether or not you had lack of signal in any of your treated patients.

Dr. Rodino-Klapac: All patients showed transduction of the micro-dystrophin.

Dr. Shah: So I guess my follow-up would be that if every patient who gets the therapy is able to show the measurement, it sort of piggybacks on the follow-up question that there's not really a level because essentially every patient who gets the therapy is going to achieve it; is that correct?

Dr. Rodino-Klapac: Let me just, to clarify your question, what exactly, you're looking for a threshold level or you're looking for a range of expression? Just, no, I'm just clarify.

Dr. Shah: No, I'm just clarifying that every patient who receives this gene therapy would express the micro-dystrophin.

Dr. Rodino-Klapac: That's correct. Correct. And we shot, we saw improvements using the external control regardless of the amount of expression given.

Dr. Shah: Thank you.

Dr. Ahsan: I think that goes back to my previous comment, which is if the variables don't span the space, it is very hard to make strong correlations. Um, Eric.

Dr. Crombez: Thank you. Yeah, and for me, you know, it really begins and ends with reasonably likely. And I think reflecting on the slide that the FDA presented earlier and just touching on, you know, two of them, the biologic plausibility. I mean, I think in rare disease, you know, we are used to replacing exactly what's missing, whether that's enzyme replacement therapy, messenger RNA, DNA, or messenger RNA, but, you know, that's not common for a lot of diseases. So, you know, I accept the argument that it is different. It needed to be modified to fit into the AAV capsid, but, by and large, it is replaced exactly what's missing. I know we

reviewed some data today, but there's limitation given the time. There's additional data in the briefing books.

But over the years, you know, I've seen a lot of additional data published on this, and I do think there's biologic plausibility there. And then, again, reasonably likely in tying to the clinical work, you know, there's been a lot of discussion on the limitation of North Star, and I think we do have to recognize that there are limitations. But it is by far the most established, I don't want to use a technical term as validated, but it really is the most understood, the best used tool. It is what we have today, even given those limitations. And then, again, I know we've touched on it with other people who have spoken before me, but it's the totality of the data. And, again, we can only look at a subset of that data, given the limitations here today. But there are additional data in the briefing books, and then I know that there was a great deal of information uploaded to the docket, you know, including caregiver experience, videos, and interviews.

So, again, looking at the totality of the data that is available for us to review, I do see, you know, reasonable likelihood, and that's the bar here. And I also, I understand that it's tempting to wait, and I know we'll have this discussion later. But it's not just getting to June, it's then analyzing all that data, you know, getting these regulatory packages, getting back to the FDA. So it is a very long, it can be a long period of time. And then if this indication is for ambulatory patients, there are a cohort of boys who will lose that ability, and then their opportunity is lost forever.

Dr. Ahsan: Yes. Thanks, Eric. That will be great to reiterate the later discussion points as well. Susan.

Dr. Ellenberg: Yes. So I want to comment, I want to comment on the primary analysis for showing the correlation between the marker and the, and the clinical outcome. The NSAA, most

of the people in that two-thirds of it, as the FDA pointed out, were from the uncontrolled studies. And while the NSAA may be validated and may have been shown to be, you know, to have good interrater reliability and all of that, that doesn't mean that, that it's, people aren't going to, it's not going to, it's not going to be susceptible to the kinds of things that we worry about in uncontrolled studies. And some of those things are hard to explain, but it's been well documented in a variety of settings.

And I, I would like to give one particular example that I think is most relevant to what we have here. There was a surgeon in Italy that developed a procedure to treat multiple sclerosis, which is also a disease that, that has, you know, people decline in their functionality. And there's a, there's a score that's used to evaluate people's changes in functionality in multiple sclerosis. And he reported a case series where the changes seemed to be remarkable. And some of the patients talked about how dramatically their life had changed. It was amazing.

Then they did a randomized clinical trial, double blind, sham controlled, and they found no difference whatsoever between the people who had this new surgery and those who got the sham control. So, you know, the fact that this is a functional outcome and it's well validated, doesn't mean it's not susceptible to the, to the problems that you have when you do an uncontrolled study. It has nothing to do with people faking or cheating or anything else. We're all, we're human beings, and this kind of thing happens. And so I feel like that primary analysis showing that there's this correlation is not very persuasive.

Dr. Ahsan: Thank you, Susan. Just a reminder, if your comment is not going to be on, on this topic, maybe you can hold it off for a more appropriate discussion topic because we are very much behind and I want to make sure that we discuss all the, all the points that the FDA needs guidance on. So, Anthony.

Dr. Amato: Yeah, again, I think there's evidence that, you know, that this micro-dystrophin is expressed, you know, on Western blot. It's on immune-labeling and it's going to the sarcolemma. The CKs dropped. That's biological evidence. And it, it's not the study we would like to see in the results. There could have been better, but I did like the, you know, in the, in the second study, in the early cases, I, early onset group, it looked like there was improvement. In terms of the North Star, the invariable, that, that's the importance of doing the propensity studies. So, yes, you know, it's not that people are faking it, but there's always a placebo effect. We always see it. But the propensity studies being done on, on patients like in the, in the four DMD study, in the synergy studies, where, again, participants were, were randomized to placebo-controlled trials, you know, and you're looking at the changes, again, that, that helps get rid of it. It's not as good as a randomized trial. But I thought that was supportive data.

You know, as a clinician that's seeing, seeing kids with Duchenne, you don't go from having to do a Gower's or having tremendous difficulty with stairs to being able to run up, run up and down steps. Now, I don't know that those boys got placebo or they, whether they got the, they got the drug, but I suspect that they got the drug. And, again, the other convincing, this, this isn't an Italian surgeon doing MS, which is a variable. I mean, the doctors that we heard from are the world's leaders in Duchenne. They are Mendell, Connolly, McDonald, and these are very experienced clinicians. I don't think they're guns for hire. If they're convinced that they're seeing in a population what they haven't seen in the past, that, that does, that's very supportive, at least to me.

Dr. Ahsan: Thank you. Yeah. So I think we'll take one final comment about the strengths and limitations of the surrogate endpoint. So, Buddy Cassidy.

Mr. Cassidy: Yes. So I'm still not convinced by the FDA's explanation as to why they question or are skeptical about the, the validity in certain areas of the North Star Ambulatory Assessment. Certainly open label conditions would have an impact on any kind of performance evaluation measure. So that would be like for perform, that stands for performance evaluation in general, not the NSAA in particular. And so, I mean, you can't really get, you can't make it perfect, but you can only mitigate influence of suggestive bias. And the literature shows it's well documented for the, for the NSAA does a remarkably good job in creating protocols to guard against bias. And, again, this is well established in the literature.

So it's, and this is, I mean, the problem of open label conditions influencing things would be problematic across the board for this mode of evaluation. But we need to look at the NSAA in particular. And, in fact, in the NSAA evaluation, this would be less of a concern than it would be with, than with other permits evaluation criteria. And, again, this is well documented by a number of different scholars, Ricotti (phonetic), Henrickson (phonetic), Drong (phonetic), and these names are in the sponsor data. And I'm just seeing industry guidelines in the FDA investigative report. So I would say that certainly open label conditions are a concern, but the NSAA is constructed to guard well against subjected, subjective bias.

Dr. Ahsan: Great. Thank you. So I think I'm going to take a couple of minutes to summarize where we are on our discussion on this point. So I think overall there's been this variability in how people interpret the data, both on the Western blot side, as well as the NSAA. There have been some people who have said that those metrics are flawed. Others have mentioned that that might be the best that we have. There was some discussion about CK, but that was not offered as a surrogate marker by the sponsor.

So let's think about some of the strengths. I think there were co, there were comments that were made that some patients might be getting better, perhaps a subset. And there was some emphasis that it's not just about the clinical metrics, but the quality of life; and some nonclinical quality parameters and improvements are very meaningful and impactful to the patients. And so there was some thought that maybe we should look at the patient holistically and the benefits that they're getting. On the more specific side, it was discussed that DMD is a heterogeneous population, and its efficiency of treatment or the efficacy of treatment might be dependent on multiple factors, such as age, but also delivery and others. And because of that, maybe we don't get the predictable disease outcome, in the case of DMD, that we may get in others.

There were folks that thought that the external controls were quite compelling and helpful to interpret the data that they saw from the clinical trials. There was also some comment that the, there was, they were able to effectively show that there was a structural effect of the micro-dystrophin. But the concern is that potentially the structural effects is not physiologically meaningful. In terms of thinking about the surrogate, there were, there was some discussion that there is not a very strong correlation. A lot of the emphasis was put on the study 102, part one, which was double blinded versus the open studies. And there was quite a bit of discussion as to the value of data from the open, open studies. There was also a concern about the distribution of the shortened micro-dystrophin in different tissues and whether that's actually reflective of physiologic import and also that the shortened micro-dystrophin is not the same as it is on the exon-skipping and in the natural progression of the mild aversion of DMD.

In terms of the nonclinical data, there were a lot of different perspectives on the value and the interpretation of that data. Some, what was put forth by the sponsor versus what was put forth by the FDA very much led you down to different lines of thinking about how being a reasonable

predictor of clinical outcome. There was also, again, some discussion about whether strong correlations can be made if all patients that are treated are seeing transduction and whether that actually allows us to create these clinical correlations. And I think that I've captured holistically what was discussed. Were there any points that I failed to recapitulate in the summary that was specific to this discussion topic?

Okay. And so, Dr. Witten, did you get a robust discussion on topic one?

Dr. Witten: Yes. Thank you.

Dr. Ahsan: Okay. Let's move forward to discussion topic two. Part one of study 102 was the only randomized, double-blind, placebo-controlled clinical study for which data currently are available. The study failed to demonstrate a statistically significant effect of treatment with SRP-9001 versus placebo on the primary clinical outcome measure, change in the North Star Ambulatory Assessment (NSAA) total score from baseline to year one. Exploratory subgroup analyses suggest that the SRP-9001 group may have had a better NSAA outcome compared to the placebo group among ambulatory patients between four to five years of age. However, among ambulatory patients between six to seven years of age, there appeared to be no difference between the SRP-9001 group and the placebo group, and the SRP-9001 group showed no improvement from baseline. Please discuss the clinical significance of these findings.

And the first discussant on this will be Dr. Susan Ellenberg. Susan, if you could go ahead and go on camera and unmute yourself.

Dr. Ellenberg: Yes. Okay. Yes. Well, subgroup analyses always raise the potential for false positive findings. The more ways one looks at the data, the greater the probability of getting something positive just by chance. The FDA tells us that this subgroup analysis was not pre-specified within a hypothesis testing framework. And thus, and there's, there's no indication, at

least I haven't heard any, that there was a prior thought that the younger boys would do better. They, you know, well, so if the older ones had done better, that's what we would've been focusing on. So what, what we worry about is that, is that there, maybe there were other subgroups that were looked at, and we're just seeing the one where we see something positive. I don't know about that. Without pre-specification, it's really impossible to statistically adjust for the multiple comparisons. And the p-value that we saw, the 0.017, in the younger age group can't be taken as a reliable statement of probability. And even if the two subgroups were the only ones of potential interest, then the statistical significance would be lost if we adjusted for the three comparisons, the overall, the younger, and the older.

And actually there's another endpoint relating to the marker expression. So even if we just adjusted for those, we would lose, we would lose significance. Given all that, however, the functional trajectory for boys with DMD status do start to shift downward at about the age of six. So this does seem to be a logical subgroup analysis to do. In my view, the findings in this group have to be considered suggestive, but the numbers are very small, 10 or maybe fewer in each arm. The confidence intervals are very wide, and actually get wider over time, perhaps reflecting dropout or missed visits. Maybe they were even fewer than that at the week 48 endpoint. But I, and so it seems like a change in even one value could be enough to move the p-value away from statistical significance. It’s hard to know because we're looking at means, and a mean is very susceptible to one very high value. And it could, it could make everything, it could make the overall, the overall result look quite different if, if that value had been somewhat lower.

So I think these results are pretty unstable. I think, again, I think they're, they're suggestive. It would've been interesting to see the individual values at each point to have a better feel for the variability. So, overall, I'd say these results are encouraging, without a doubt. But

given the small numbers and the difficulty in interpreting the p-value in the younger group, it's hard to be very confident about what we're going to see when the, when we have the results from the, from the more definitive 301 study. That's it.

Dr. Ahsan: Great. Thank you, Susan. That was very, very helpful. Donald, would you like to comment?

Dr. Kohn: Yes, thank you. Yeah, I think one of the factors that we're struggling with is that it's only a one-year endpoint. And I think with the variability of disease and the, you know, not rapid regression, progression like an SMA, it's hard to see a difference. And it probably, in the six to seven year old, it's even harder to see that. But the, you know, the very compelling videos and the testimonials from the clinicians were mainly boys who were out four years, and there the delta from them in the natural history becomes more apparent. And so I, I think, you know, obviously the company wants to do it as quickly as possible. The patients want to get it approved as possible. And I think, you know, it is just a limitation when, when you have a one-year endpoint for disease that has a variable course and, you know, it's not, it's not super rapid. It's, it's too rapid as it is, but it's, it's hard to see. And so, you know, I don't know the answer to it because this is the study that was done, but I think, you know, I would say that those videos, anecdotal as they are, and the, and the comments from the clinicians, you know, are, although anecdotal, I think they're, they're, what's the phrase, substantial evidence of effectiveness.

Dr. Ahsan: Great. Thank you, Donald. Next up is Eric.

Dr. Crombez: Yes, thank you. I trained in pediatrics and genetic. I've spent the entirety of my academic and industry time working on rare diseases. And in my experience, younger patients always do better, at least from a clinical trial perspective, they can do more. And, therefore, it's, it's easier to detect a signal there. And I think, you know, that very well may be playing an

important role here in what we're seeing in the four to five year olds, versus the six to seven year olds. I think, you know, also the sponsor did spend a lot of time talking about that imbalance between the groups and the six to seven years of age. And I do think that's important. And, again, that is a limitation with these rare disease trials. We can't enroll, you know, a thousand patients in these studies. That's just not possible. And I think, you know, with the clinical significance, it's, it's why we're talking about a conditional approval here. I mean, I think, you know, if you know the data, if they hit the primary endpoint in the other study, maybe this would be a conversation on full approval. But that's why the bar goes back to reasonably likely to predict. And, again, I think that that clear signal we're seeing, in the four to five year olds, it's important.

Dr. Ahsan: Great. Thank you. Raj.

Dr. Ratan: I would just comment that I think that from the, that the NSAA seems like a series of tests where there could be lots of compensations in, depending on which muscles are affected. And it, it's, it is interesting to me that manual muscle testing isn't done in some of these kids as a way of adding maybe a more sensitive marker. But I think when, when people are talking about, you know, placebo effect, it may reflect things that enable kids to compensate. And I think that, while this is a very well accepted measure, it has many domains and doesn't really measure muscle strength in its final analysis. I would just make that comment.

Dr. Ahsan: Great. Thank you. I had virtually or, in my mind, raised my hand after Raj. So the one comment I would like to make is that for me, the external controls, they're, they're challenging for me to interpret. So when you see the natural progression, the nice curve that is the mean of all of that, is different than the way the FDA put it, that there were four clusters of different cascades happening. And so that smooths it out. And so the idea that the placebo group should stay constant is, is unclear to me that, that that would be a default expectation, even if

they're at the crest of the curve. And so that, that to me is a little bit problematic when we stratify based on age and, afterwards, after we've already seen the results. But it doesn't negate what, seems to me, that there is some positive effect that we're seeing in the, in, in the younger patients. So I'm of two minds there, but it's a point that does not leave me with a lot of confidence in, in either direction. Okay. So, let's see. Next up is Buddy. Sorry, Buddy. Were you going to speak?

Mr. Cassidy: Yes. One second. Let me just.

Dr. Ahsan: Sure. No problem.

Mr. Cassidy: Okay. So I'm, I'm a bit puzzled about the question itself and that it directs us specifically to part one of study 102, regarding that it was the only randomized, double-blind, placebo-controlled clinical study. And I, I don't understand what's wrong with part two, in that this looks like a crossover design to me. And crossover design is increasingly prevalent in measuring the efficacy of drugs for rare diseases. And Sarepta characterizes this as crossover design in their report. However, the FDA team refers to it as just an unblinded study. And, again, I don't, there seems to be a conflict in terminology here because it doesn't look just like an unblinded study. It looks like crossover design. And the FDA investigative team noted that crossover design would be used in trial 301. So I don't understand, in that 102, part two, it was unblinded and not crossover design, but in 301, it would be considered crossover design. And that seems to be a, a real inconsistency there.

Dr. Ahsan: Buddy, are you pointing that out, or would you actually like the FDA to make a comment on that?

Mr. Cassidy: If the FDA cares to comment, I'm, I'm just curious as to this, what seems like an inconsistency in terms of terminology.

Dr. Ahsan: Okay, great. Yeah, I think that that is an, that is an interesting point that the term crossover was used for one study and not the other. If the FDA could make a quick comment about that.

Dr. Witten: Perhaps Mike would want to, but, or, yeah.

Dr. Singer: Thank you. This is Mike Singer. Yeah, so, so it's the crossover, the term, you're correct that it does apply to both, both the trials. And the issue in both is that there, that at that crossover point, then, you know, everybody knows that, at that point, everybody, all the, the patients will have received the active treatment, whether they received it in the part one or whether they received after the crossover. So that part two, and that's true both for the study 102 and also for the study 301, there'd be, you know, so, so that issue of the, the described as, you know, functionally open label is, refers to, to that, that at the part two for both of those studies, then everybody is aware that all the patients have received, at that point, the active treatment. So it's, so the, the, the part two in both of these studies have that different characteristic, than the part one in, in both of these studies.

Dr. Ahsan: Great. Thank you, Dr. Singer. Um, Richard.

Dr. Kryscio: Okay. I'm trying to get the, my screen open here. Sorry about that. Yes.

Dr. Ahsan: Perfect.

Dr. Kryscio: First of all, a crossover study is a little bit different. One assumption that has to be made in a two-treatment, two-period crossover design is equal carrier effects. And I don't think you're going to have, I don't think you'll meet that assumption in this particular case. So it's kind of a misnomer to call it a crossover. It's a, it looks to me like people are being moved in the second period to the open label. So I think the FDA has a point there, but it is not being analyzed as a true two-treatment, two-peer crossover design simply because of, of the fact that the, there's

probably an unequal carrier effect from of, of whatever treatment you get in the first period into the second period.

I guess I wanted to talk a little bit about the point of stabilization, you know, that was pointed out that that might actually be a good outcome. And I, I wouldn't disagree with that, but, you know, you still need the placebo group because I, if the placebo group is also stable, then what's the point of the treatment? So I, I really think the problem here, in this particular case, is that people are being crossed over after 48 weeks. And I can see how that helps recruitment because you tell people, you know, you tell patients and parents that you're going to get the, you're going to get the drug no matter what. You'll either get it right away or a year later, and it probably wouldn't make a big difference. But, you know, I just feel that if stability for the older children is an issue, then you need a much longer period of time so that the placebo arm could actually decline. And with that, I'll be quiet.

Dr. Ahsan: Great. Thank you, Richard. Caleb.

Dr. Alexander: Yeah, just, first, one point, I think someone mentioned conditional approval. That's, I think I, this, this isn't what we're discussing, and I just wanted to be sure it was clear that conditional approval is different from, from accelerated approval. But we're fortunate to have such a well-designed study. I mean, listen, when we, when we reviewed at Plurson (phonetic), there were 14, we looked at data on 14 boys, if I recall correctly, with historical controls alone. So, you know, the, this trial is tremendous in terms of the, the commitment of the participants, the sponsor, and the sites, the investigators, everybody that, that made this possible.

You know, we're asked what the basis is for this exploratory post-hoc subgroup analysis. And the answer is, I don't know. I mean, I think the FDA has given us a number of potential possibilities and, correct me if I'm wrong, but I, I don't think we can know. So one is

that the product is ineffective. Another is that it's due to baseline imbalance. Another is that the product only works among young children. I mean, that would be important to know when you're labeling this, right? Another is that, that the differences are result just a small sample size, and some combination of these factors. Maybe not one of these is operative. Or maybe there are other factors and maybe someone wants to add to my list, but, but I, I don't think one can know. So I think the important thing here is just not to, you know, that, that, that, just to recognize that we can speculate and that's fine and may be important. But that's different than doing hypothesis testing. Thank you.

Dr. Ahsan: Thanks. Okay. Buddy's the last comment, and then we really need to move on to the next topic.

Mr. Cassidy: I would just like to say as the, the patient representative, I understand the, the need and the desire to have patients on the placebo longer, but I have to say that given the progression of the disease, there really isn't time. There really isn't time. And to leave patients without a chance on the placebo any longer, I think, would be, or would be a real ethical concern. And I, I appreciate, I strongly appreciate the ethical concerns about patient welfare on the part of Sarepta.

I do fear that, that part, well, I understand that there's some frowning on 102, part two, and on 301, part two. But it doesn't seem to me to be motivated by a lack of rigor. It appears to me to be motivated by ethical concerns and that while this disease is heterogeneous, it progresses fast. A year or two could mean the difference between walking and being in a wheelchair. So I, I just wanted to point that out.

Dr. Ahsan: Thank you so much. Great. So I think I'm going to try to summarize this and, if I missed something, please let me know. So, first, in terms of the study itself, there seems to be

potentially some, some different perspectives on the terminology regarding study 102, part one, whether it's a crossover study, whether it has the proper carryover effect, if not for this crossover study. So there's some thought about generally how the study is thought about. In terms of the subgroup analysis, right, I think it was mentioned by the biostatisticians that there is an increase in the chance of seeing a finding, right? And that's always problematic. And also, without this pre-specification, it's challenging to adjust for the p- value. And then thinking about the metric, the metric itself, right? So there's still concerns about the NSAA and whether that is an assessment that is a clean measure of what we're trying to establish. But yet others were mentioning that the video and the clinical statements, they may be anecdotal, but they're still quite important.

In terms of the results themselves, it was mentioned that often younger patients are, are observed to do better in trials of various sorts. So that, that was not surprising. And there was a mention from the biostatistician as well as to whether or not that younger cohort was presupposed to have done better and whether that would've, that impacts the way we're observing these findings. But still, it was mentioned that based on the data and the natural history, that age six might be an appropriate cutoff to be applied to this subgroup analysis. The other discussion, major discussion point, was about the one-year endpoint. Some thought that it, that's problematic. It does not allow you, for the progressions of both the treatment and the placebo, to advance far enough to see the signal between the two groups. But then it was also raised that there might be some ethical concerns about allowing the placebo group to go on much longer past one year, and that that is a real concern.

So I think with that, the overall sentiment was that it is hard to interpret the clinical significance of these findings. There's many qualifying statements that you need to

apply, whether it's based on the age or how the data was measured or how the data was analyzed. So I think that there was a lot of good discussion, but not clarity as to exactly a precise way to interpret the clinical significance of these findings. Okay. So unless the FDA has some more points of clarity, we should move on to discussion topic number three.

Dr. Witten: Thank you.

Dr. Ahsan: All right, great. So if we could advance to the next slide. Thank you. So this next topic is please discuss the potential benefits, risks, and uncertainties that may be associated with administration of SRP-9001 for treatment of ambulatory patients with DMD with a confirmed mutation in the DMD gene. And so our first discussant is going to be, Dr. Nirali Shah.

Dr. Shah: Thank you. So the risk of the therapy, in particular, related to gene therapy, is not only in isolation, and it has to be taken into account of the risk related to the underlying disease and the potential of benefit of the therapy that is proposed. There is no doubt that DMD is a devastating disease and that months matter and the stabilization of disease is a benefit to individual patients and families. Based on the safety data presented by Sarepta, the risk to date associated with the use of this novel gene therapy are generally overall well tolerated and or treatable. And while no long-term risk of insertional mutagenesis with the use of the AAV vector has been seen, this will be closely monitored over time. Specific risks that have been reviewed by both the company and the FDA include immunogenicity against the AAV, the potential implications of that for additional therapy, and then specific adverse events include the potential of liver injury and some complication with the ability to assess those immune mediated myositis and cardiac toxicities.

While the clinical benefit through videos, open discussion, expert input, and those presented by all are compelling, the ability to assess risk and benefit is primarily based on use of

a product process that we do not have data from through a randomized trial and is not, but will be moving forward. As the product process can have a major impact on both toxicity and outcome and additional data would be contingent on the completion of the currently enrolling phase three study, it is noted that that study could be at risk of not being completed with an accelerated approval. While we're all acutely aware that this is a case where several months may matter, given the uncertain outcomes of the product that will ultimately be what is commercialized or made available, awaiting the readout of a confirmatory trial, given the potential implications on safety, toxicity and efficacy, may be prudent. An additional comment is that having the results based on balanced proof enrollment by NSAA functional status would provide an important insight into when you would initiate therapy and how early you would do so as, as another consideration for risk benefit.

Dr. Ahsan: Great. Thank you, very much. If people want to raise their hands to comment on this topic. Buddy, if you want to go ahead.

Mr. Cassidy: Okay. So I feel compelled to weigh in as patient representative, and I see my task, first and foremost, is to carefully weigh the benefit risk profile and have extensively read about all the adverse effects and see, severe adverse effects in terms of the safety profile and benefit risk analysis. I as a patient am exceedingly pleased. I am exceedingly pleased, and I am well aware of the risks of AAV gene therapies as a class. Again, I'm, if you know anything about me, I'm, I'm well versed in this. And so this is something you want to be evaluating when dealing with this particular class of drugs. But I would say that it was, from what we see in the studies, some of these usual effects of AAV were seen, but the incidents of them was comparatively low when looking at the rate of incidents in other AAV based therapies and for, I would say, in fact, remarkably low.

I was thoroughly impressed by Sarepta's post-hoc analysis of all the adverse effects encountered. They looked at them thoroughly and went through plausible explanations, seriously considered the dangers of the drug, and to each they responded with developing a set of protocols to monitor for this in the future and further mitigate the already very low risk of AEs, and that level of attentiveness is impressive, that not only does it seem very safe, but further protocols are set up in the future to, to further mitigate any issues.

I will say in terms of, of risks of adverse effects of mortality, if you look closely at the patient preference studies applied, I mean, sorry, supplied to us by PPMD, Parent Project Muscular Dystrophy, in terms of the patient preference studies, the plausibility of adverse effects or mortality, it's still very much within acceptable range. Safety profile looks good to me.

Dr. Ahsan: Thank you, Buddy. Kathleen.

Dr. O'Sullivan: I just wanted to echo Buddy's sentiments. You know, I don't want to make light of the adverse effects that patients bravely suffered as part of a trial, but, you know, fever and vomit cannot be the worst things that, short-term fever and vomit cannot be the worst things that have happened to DMD patients. And we have to remember that they are our consumer. This is not to be judged against generic perfectly healthy people. Would they put up with, with some of these outcomes? You know, we're dealing with folks that are, are suffering in, are on a known trajectory to additional suffering and hardship.

They can all be monitored, you know, liver levels, platelets, et cetera. They're measurable. They seem to, the data showed them to be mild to moderate and resolvable or treatable. And there was no death. There was no cancer. I appreciate that the FDA put up a special slide showing known AAV side effects from different versions of the AAV vector, although none were shown certainly through this data. Yeah, there was a risk of cardiac damage,

but that, without opportunity to take the benefit of this treatment, that is part of the natural history that's coming for patients without intervention.

So, and with respect to the risk about one bite of the Apple, AAV, you know, taking one AAV treatment and being blocked from others, I think it's been brought up previously that there are more vectors to try that, that that won't fall into that case, and someone will come up with a way, perhaps, to mediate that risk as well in the future. But, you know, if we're protect, if part of our job as a body is to ensure that safe and effective treatments can get through the pipeline and to the patients for their benefit, you know, I, as a fellow rare disease patient and mother, I don't have any significant concerns about the safety profile here.

Dr. Ahsan: Great. Thank you, Kathleen. Jay?

Dr. Chiorini: Yeah. With respect to the anti AAV antibodies, as they pointed out, that only was around for a year. Then it, it's not clear what the T-cell response is and whether that would prevent, permanently, re-administration or receiving any other AAV vectors. But just from an antibody standpoint for one year, I, I'm not so concerned about it. And I, I had a little bit of pause with the increase in the risk associated with the myositis and the scores dropping from 23 to 17, I think, in one of the patients. But as Kathleen pointed out, that's sort of the natural course of the disease.

Dr. Ahsan: Great. Thank you. Raj?

Dr. Ratan: Yeah, I mean, I think that, if those kids who we saw in videos today represent a subgroup of patients who really do have remarkable benefit, then I think there's huge potential benefit in a, a treatment that really has the potential to fill a void right now. I think the uncertainty though is whether any of the studies that are currently being done or are planned would have a way of actually identifying that group and differentiating what, what allows them

to have such benefit. The other, the risk that concerned me was the, the potential risk of the promoter that's being used, which seems to have, at least there's some data that it has high expression in the heart and lower expression in skeletal muscle and some expression in the liver. I mean, the heterologous expression of dystrophin in cells that shouldn't have it, seems like it, it could open up a potential risk in addition to the risks that were already mentioned.

Dr. Ahsan: Great. Thank you, Raj. Donald?

Dr. Kohn: Yeah. I just wanted a clarification of the speaker one ago that said that, it was said that the antibodies are gone at one year. Can we ask the sponsor? Is that, is that I, I'm not sure if that's what they said, that it's gone after a year. I thought they stick around longer than that. And so could we ask Sarepta if they can comment? Do they have –

Dr. Ahsan: Sure.

Dr. Kohn: -- serologies after, after that period?

Dr. Ahsan: Absolutely. Happy to get that confirmatory bit of information. Can Sarepta please answer that?

Dr. Rodino-Klapac: Yes, the antibodies do stay on beyond a year. That was the one-year time point. So that's what I showed. But they do stay beyond that. Just to, and one clarification on the MHTK7 promoter, it expresses well in both heart and skeletal muscle. We did not see any toxicity in the heart based on expression with MHTK7 promoter. We saw trace levels in the, in the liver in some experiments, but not all, these are trace. Thank you.

Dr. Kohn: Thank you.

Dr. Ahsan: Great. Thank you.

Dr. Chiorini: Yes. Thank you for clarifying that point.

Dr. Ahsan: Anyone else want to make a comment before I summarize for this topic?

Great. So there was a few things that were discussed. Overall, it seems like the risk, the risk is well tolerated and aspects of the risk are treatable. It was mentioned that, you know, nausea and low-grade fever, they're relatively mild compared to the disease progression. And so that taking that into account in terms of the risk to benefit profile is important. I, I think that the patient representative was quite pleased with the data regarding adverse events and is happy to see that mitigation plans are being put into place after some in-depth analysis of these events and so appreciates that from the sponsor.

There was some discussion about the anti AAV antibodies and, and the opportunity cost if you are treated with this therapy, as opposed to a future and, and then foregoing any future AAV. There was discussion about the antibody persisting, not just one year, but longer. But also thoughts about whether that is a realistic sacrifice is unknown given that it's, there's not a lot of clarity on what other therapies are emerging over the next few years. Additionally, there was a, a concern about the promoter, and that was discussed in terms of where it's expressed and whether there's cytotoxicity in those tissues. The sponsor seemed to indicate that that was not so much of an issue. And then, finally, the other risk that was mentioned was about the manufacturing process and that moving forward we're using process B. But much of the data that was used so far has been based on process A, and there's a very different level of impurities of empty capsids in process B. So it seems like there' s monitoring that really should be taking place about product quality as we move forward. That is my summary. Was there anything that I missed that people would like to add?

Okay. And, Dr. Witten, that suits your purpose?

Dr. Witten: Thank you so much.

Dr. Ahsan: So discussion topic four, if we could get that slide up. Great. If SRP-9001 were to be approved under accelerated approval provisions, the applicant proposes that part one of study 301, the phase 3 randomized, double blind, placebo-controlled 52-week crossover clinical study, may serve as the required post marketing confirmatory trial to verify and describe clinical benefit. Please note that the last patient last clinical visit for the 52-week primary endpoint is expected to be completed by the end of September 2023. Please discuss the potential impact of marketing approval on completion of part one of study 301.

At this point, I'll take some latitude and ask the first question, which is a repeat of what I asked before, but if the sponsor could describe for us the design, could iterate the design for us and describe for us the power and whether or not this would truly function as a confirmatory study based on what we're looking to approve.

Dr. Rodino-Klapac: Absolutely. I'll ask Mr. Mullen to comment.

Mr. Mullen: Chris Mullen. So, 301 is designed, as noted, as a randomized study. The sample size is based on 120 subjects. That is intended to provide a 90% power, assuming a dropout rate, actually, of 10% for an effect size of about 0.63. That's based on a mean difference between groups and the NSAA's changed score from baseline of 2.2 points.

Dr. Ahsan: Great. Thank you. And was that going to be, that's going to be stratified based on age, right? And, if you can, discuss that and then also NSAA.

Mr. Mullen: My apologies. Yeah. The, the intent was to try to have 50% of the patients in the four to less than six age group by design. And I'm, I missed the second part of your question. I'm sorry.

Dr. Ahsan: And then are you doing any binning based on NSAA score?

Mr. Mullen: I can't recall that off the top of my head. But we are, my colleagues tell me we are.

Dr. Ahsan: Okay. Yes. I do believe you're going from 16 to 22 and 22 to 29. Is that correct?

Dr. Rodino-Klapac: That's correct.

Dr. Ahsan: Okay. Great. All right. So with that, perhaps we could, right, Susan, I was just going to throw it to you if you could comment, you and Richard, if you could comment on the biostatistics part, portion of this.

Dr. Ellenberg: Well, I, the way the question is written, I don't really see that it has a biostatistical component. My comment was I've heard so much about how desperate people are and how the time is so important. And, you know, even a few months means that some, some boys, you know, will not have, will not be able to benefit from this treatment. And yet I've heard great confidence expressed by the sponsor that everybody's going to stay in the study, even if the drug became available. So I, I'm not sure I quite understand that. And if, if those people are willing to stay in the study, then I'm thinking about maybe the community is willing to wait for the more definitive evidence that's going to come from this study to make sure that the benefits are actually going to outweigh the risks.

Dr. Ahsan: Great. Thank you, Susan. Yes, that's, I think, on point, the discussion of whether the patients that are currently enrolled in that study would stay on or would want to pull out in a, in order to understand if they've been treated and part of the placebo group. So that's a very good point of discussion as well. Richard?

Dr. Kryscio: Yes, just one, one point I wanted to ask Chris, if I understood the power analysis, it's based on an end of 120, but that's really not the end for part one of study 301. Or did I misread that?

Mr. Mullen: Sorry. Chris Mullan. Sorry. Can you hear me? Thank you. Yeah. Chris Mullen. It was for the power for the part one hypothesis test. That is correct. Does that answer your question?

Dr. Kryscio: Yes. Thank you.

Mr. Mullen: Thank you.

Dr. Ahsan: Great. Thank you. Next up is Lisa.

Dr. Lee: I can't seem to start my video, but I will speak. I initially was asked to, to open up some comments to this discussion topic, so I'd like.

Dr. Ahsan: I apologize. My bad. I just missed the process. Please, of course.

Dr. Lee: Yeah. Yeah. It's fine. I just want to, I have a few things that I think I would like to put out on the, on the table. And so just setting aside or, or pivoting from the harms related to the trials themselves, I really want to focus my brief comments here on the risks associated with an accelerated approval. So I, as I see the two potential harms, one of those being completion phase three trial, and the second being the one we've been talking about with patients getting one chance at a gene-based therapy. So, the first, with respect to completing the phase three trial, I, I just want to make a couple of comments about, you know, so far we're zero for four on the completion of previously accelerated approvals from this group. So that's concerning to me. This would also end up being the first trial where we're looking at process B. So I think its completion is absolutely essential for approval since that will be with the product, the process by which the product will be made, the product that will be for, on market.

More importantly for this approval, though, we've heard a lot about time is muscle. This has been expressed a number of times today, and I, I think that the question here is really what is the motivation for parents to keep their children in the trial? And here I'm speaking about subjects

obviously who are awaiting their, their dosing in September. So why would parents wait and, ethically speaking, insisting that they do is, you know, potentially amounts to a trial, causing a trial that will cause harm by withholding available treatment, again, with this idea that time is muscle. So in the case of this disease, I think it would be extremely ethically challenging to support that kind of question. So that, I think, is, those are critical issues related to completing this phase three trial.

For the second issue, with respect to patients getting one chance at this therapy, I, I think the risk here is that if a product is approved in an accelerated manner with, that has unconvincing efficacy data, patients will, who, who use a potentially ineffective gene therapy with the associated risks, including liver and cardiac problems, would be doing so risking those things without the benefit but also, and importantly, closing the door for use of subsequent developed, subsequently developed effective ones. So even if there are innovative methods on the horizon or in the pipeline, all of the patients who take a potentially ineffective, accelerated approved AAV based gene therapy in the short term will be unable to take advantage of any improved therapies, even an improved version of this one, for the short and medium midterm future. So, again, since time is of essence with DMD, I think we have to weigh here the potential harm against the uncertain benefit.

Finally, when I'm thinking about risk here, I'm thinking both about the severity of harm, as well as the probability of that harm occurring. In this case, severity of harm, that is the removal of this future opportunity, will likely vary by perspective. It depends who, who you ask, whether that's a parent, a patient, or someone else. But the probability of this harm seems to be very close to one. So the fundamental question, as I see it, is that we must weigh whether a month, a month's long, maybe a year long delay for the results of trial 301, which will mean

functional decline for, for patients, for current patients, must weigh that against the accelerated approval of a single opportunity treatment that has an, you know, so far uncompelling benefit, which might remove the opportunity for a beneficial treatment some time, especially for these patients existing cohort, in the near future. So those are the couple of things I'd like for us to, to take a look at.

Dr. Ahsan: Great. Thank you for setting us up. I think next we had was Anthony.

Dr. Amato: Yeah. And I was going to echo what's been said, and I brought this up. One of the first things I said in the first section, you know, is would this have an impact? It's fully enrolled. That's good. And, you know, so the risk is having patients who are already enrolled in the trial, potentially drop out. The questions that I would ask is, when is the FDA meeting to make a decision? Also, if, you know, the decision is a positive to allow for approval, how quick would Sarepta be able to ramp up production and get it to the hospitals for infusion? And, remember, it just doesn't occur overnight too because every single hospital system is going to have to have something like this go on there where they discuss whether the, you know, to put it on the hospital formulary. So that takes time.

I want, I wonder too whether the sponsor has already looked into this proactively, because as soon as an announcement, if there is an announcement of an approval, you're going to have to inform all the subjects and you're going to have to offer them to drop off. That's a, any ethical hiring board is going to insist that you, that you just can't go and you're, you're making the case of time is muscle. You're going to have to make, you're going to have to say, well, time is muscle for everybody else that's not in the study, but it's, but it's not for the people who are already in the study. And we heard testimonies from family members of people, of sons who got better, but how about testimonies for sons who hadn't gotten better or, or were declining and

would they want to know? And, you know, if it was two months, I mean, again, I, what is the impact?

I, getting the drug and, and approving it at September 203 eliminates two, 2023 eliminates that possibility because all the patient subjects that are. In the study can know there won't be a part, part two of the study, but that's not as relevant to me. But have you, have you gone on and actually asked the subjects who are currently enrolled in the study and what they would do and what the families would do? If, because that would be easy to do is, is have the, you know, have the site investigators ask their subjects and document how many would want, would want to drop off to get the drug. If it's truly time is money, that's what's going to be in the consent form too. And that'll have to go to a, to a letter that's already scripted. Do you already have a prepared scripted letter or phone script that you're going to have the site investigators tell the subjects?

I just was wondering, again, when, when might the study be approved and, and what's the timeline from your, or, or if the FDA says it's approved, the timeline to get it through to sites and, and approved at local P and T committees? You know, if it's after September, 2023, that's not going to be an issue.

Dr. Ahsan: Right. So let's, let's allow the sponsor to give a very brief response. And then if the FDA wants to speak, then they can as well.

Dr. Rodino-Klapac: Thank you. We have a timeline slide that we can put up to help facilitate.

Dr. Ahsan: Great.

Mr. O'Malley: Patrick O'Malley, Sarepta. I also wanted to just share, there's a lot of, I think, confusion about the timeline and, as you say, time is muscle. We can have a slide up which

shows in detail the patients in the US who are remaining to get to the crossover point of September. Okay. Thank you. Okay. Can we see that now? Yeah. So you can see –

Dr. Ahsan: We don't see it. Looks like it's coming up. Here we go.

Mr. O'Malley: Okay. So I, the references to the yellow section, you can see by month, we start in June. If, if the product would, is approved according to PDUFA, that, that would be the end of this month. Then at that point, for each successive month, those numbers in yellow would be the patients remaining in the US to crossover. So you can see that by September, all of the patients would crossover. And to the point about access to an approved product, as you may know, for a gene therapy, that process to get the product to the patients is, can be quite timely. And so we don't envision any patient possibly getting the product earlier than eight weeks. More likely it takes about four months to get through all of the processes to, to make that product available commercially.

I think, in the case of the trials, these boys are guaranteed treatment, so all of them in succession up through September. So I think we would definitely notify the patients of the approval, and they would also have a choice to understand whether the option of trying to get commercial access or stay in the trial and get the guaranteed treatment. And that's all within the period of, of four months. And so the other point is that the, they're not guaranteed to get commercial product. There, there are a number of steps that they would have to go through to do that.

Dr. Amato: Well, that, that delete, that's my concern and alleviates my concern is you're going to have part one finished by September '23. But going through all the processes, most of these, these boys will have been done with part A. So the concern of a dropout, you know, isn't that high of a concern then, at least to me.

Dr. Rodino-Klapac: Correct.

Dr. Ahsan: Great. Great. Thank you. Buddy, did you have a comment? Oh, I'm sorry. Actually, before we go to Buddy, I think I was going to allow the FDA to make a comment as well. I see that Celia has her hand up.

Dr. Witten: Yes. Actually, I don't have a comment as much as a question, which is, I appreciate the sponsor outlining their plans and what would happen to the patients in the US versus, you know, and, and how that would be viewed. So I just would appreciate a, if there are any comments, from Lisa Lee on that, would that, you know, from an ethical perspective, be a reasonable way to proceed?

Dr. Lee: Mm-hmm. Well, again, I think, you know, we're, we're talking hypothetical timelines here, so I, you know, I, I think we would need to map that out, and it would need to be something that, you know, we, we actually calculated how many of those in that yellow, highlighted yellow box would still be, you know, not yet crossed over. And, you know, by the date, I, you know, again, this timeline is, is critical. The other piece about it with respect to somebody's suggestion that we ask parents, you know, would you, would you pull your kid and, and try, your child and try to get a commercially available, I, I think, you know, that, that seems to me is kind of a, not a viable option with respect to the difference between a, a parent's intention in a hypothetical situation and their actual choice when they're facing it. Those are two very different things.

A lot of us intend to do things, and then when we're faced with the choice, we, we don't end up doing them or we do, do them when we say we won't. So I think that's challenging. But with respect to the transition from those without treatment to treatment, again, if we leave here today and the timeline is, you know, parents, you know, really clamoring to get it and, and

dropping out of the trial so they can, will 5 or 10 or 15 patients in the trial reduce the power enough to make the results, you know, not, not interpretable. So all of that stuff would need to be calculated through before I could really comment on whether that would be a feasible solution to this.

Mr. O'Malley: Yeah. If, if I could, I think it's important to be very clear here that those timelines are, are not hypothetical. Those are the actual timelines scheduled in the study, and those timelines that I mentioned for access to commercial product are real. Those timelines have been experienced with other gene therapy products, including our exon-skipping. The process to get from approval to treatment is, is likely to be at least four months. And those timelines for those patients reaching that milestone are absolute.

Dr. Lee: Yeah.

Mr. O'Malley: They're not hypothetical. I want to be clear.

Dr. Lee: Yeah, no. No. I didn't mean that you, what you were saying was hypothetical. I meant the approval time being hypothetical. You had mentioned somewhere between, you know, eight weeks and four months. So I, you know, just to line that up would need to be something we would, we would need to take a look at.

Mr. O'Malley: I, I also just want to clarify that the September time point is not an, it's not an approval time point. There would be a, an additional process to finalize the results of part one and submit them to FDA and, and ultimately have them reviewed. Thank you.

Dr. Lee: Thank you.

Dr. Ahsan: So let's see if we can go, next is Buddy.

Mr. Cassidy: Hi. Yes. To begin with, if I can ask everyone to please take their hands away from their keyboards and put their arms down at their sides just for now while I talk. I promise this

will make sense. First of all, I would just like to say, in terms of time, I cannot stress enough that I, I do agree that time is muscle. Time equals quality of life. I cannot stress that enough. And there, just focus on time. There is no yes but or yes and. There isn't, in terms of not being able to take any other therapies eventually, my being part of the community and having sort of read the pulse of the community, honestly, we don't care. It's a risk that we are willing to take. In terms of post-market approval for the anti oligo nucleotides, that seems to me to be immaterial and irrelevant to the discussion at hand. Those are different therapies, and they have a different mechanism of function. And as far as I can see, that really shouldn't come into our calculus as we're discussing this particular drug.

And, finally, I just want to stress what Sarepta noted is the commitment of the DMD community to clinical trials. We are serious, and we are going to see through to the end of these trials. I can vouch for my community. This isn't a subjective thing. This I know to be true. And the thing is, we're not getting an immediate cure now, but you know why we stay in these studies? For future generations, for other people. So they might not have as hard of a time. I probably won't be able to benefit from this, but I'll be damned if another generation goes by that isn't able to get some kind of treatment. So now, what I would like you to do, in terms of thinking about quality of life, what you can do, what that means, look down at your arms, at your side. Guess what? You can't lift them. You can't lift up your arms. You can't move your hands. You can't put your hands up at your keyboard. You're stuck. Okay. That's how it is for me. Okay.

And you want to, I want you to look around the room. Is there anyone else in there or in earshot that you can call to put up your hands on that keyboard? So take a look around. I'll give you a second. And, you know, maybe there's no one there, and you're stuck. Well, yeah, that sucks. The other thing is, maybe there is someone there that you can call for help, but then,

again, you don't really want to call for help because you feel a little weird, a little self-conscious that you don't have dignity, that you can't do it on your own. It's these kinds of things that SRP-9001 will make a difference for, right? Being able to lift your hands up to your keyboard without assistance for another year sounds pretty good to me. Thank you.

Dr. Ahsan: Great. Thank you, Buddy. Next is Eric.

Dr. Crombez: All right. Thanks. And when I originally raised my hand, I wanted to comment on the timeline to access. And I appreciate the clarification there because, in my mind, it was very clear that the, the fastest way for these patients in the clinical trial to gain access to this drug is by staying in the clinical trial. And I appreciate that clarification. Then I wanted to comment on the patient community and how educated they are. And, you know, if this was approved, you wouldn't need to notify anyone. They would know immediately. But I think Buddy said that best. So I just have a question then for the sponsor because we've been talking a lot about these videos, and it came up earlier in this, in this discussion topic. So I guess that's the question. Are these videos that we're seeing here today and that have been posted to the Federal Register, are they representative or are they outliers?

Dr. Rodino-Klapac: Sure. Dr. McDonald can address.

Dr. McDonald: Craig McDonald.

Dr. Ahsan: So, briefly, we really need to get to the vote, please.

Dr. McDonald: Craig McDonald from University of California. These, these videos are not outliers. They really demonstrate profound benefit. There are multiple videos from the investigators. They're posted on the Federal Registry site. Dr. Proud, Dr. Zeidman, Dr. Mendell and myself, we've shared multiple videos with the FDA. The patient that I showed the video on

had a North Star of 25, and subsequently now he's got a North Star, two years later, of 31 with really quite profound durable effect that we just don't see in Duchenne Muscular Dystrophy.

Dr. Ahsan: Okay. Thank you. And then final comments by Kathleen, and then I'll wrap up.

Dr. O'Sullivan: Hi. I just wanted to remind people that we've had plenty of testimony today during open public hearing of parents of kids, you know, Mason's dad, Luke's dad and others, you know, Hawken's mom, who said the community is basically galvanized around making sure this happens. I just don't want people to, I get it, right? And people are desperate and time is muscle. And ethically you want to make sure people can go and make the right decision for their child. But given the timelines that have been set out and trusting this community to do the best thing, not only for themselves but for all the others who are currently blocked from this treatment because 103 is fully enrolled, that dragging our heels seems like it's doing harm. So I would not worry about this coming to fruition. I would just get to the matter at hand. Thanks.

Dr. Ahsan: Great. Thank you. So let me summarize pretty quickly. So there was a little bit of discussion about the power of the study in terms of trying to determine the value of what that completion of that study would be in terms of the accelerated approval. It was mapped out that there's a couple of issues here, right, with the idea that time is muscle. The question is whether folks would remain on the confirmatory trial or come off, but then the timeline seems to support the fact that their quickest way to treatment is actually to remain on the trial. And so that puts another view on that. And that helps to, to think about the ethical challenges for completing, for, for staying on the trial.

The other aspect is whether or not the treatment with this, which may, let's say, be ineffective and the cost of weighing that versus the opportunity cost of a future treatment, in

terms of the fact that you can only do the single AAV treatment or, or the thought around that at the moment. And so those seem to be the biggest issues, he, the opportunity cost if you treat it now with this treatment versus a future AAV based treatment, and whether or not the people that are currently on the confirmatory trial would actually stay on. There seemed to be some good discussion about the timeline and the rest of it supporting the fact that people would likely stay on, but it was raised and, and can never be understated, that what we think that people would do and what will, what they will do in the actual situation are quite different.

It looks like Nirali has a comment. Maybe I missed something. Nirali, if you want to add, but the one thing before you go on was, I was going to say that the other aspect is whether the process b material in this confirmatory trial is, and the role it plays in making sure that we have done our due diligence before we get to the accelerated approval. Nirali, do you want to make a statement?

Dr. Shah: No. I just have a general FDA question. Would that be okay?

Dr. Ahsan: Sure, if we can be quick about it. Yep.

Dr. Shah: What is, what happens if this is, if there is an accelerated approval and the confirmatory studies don't get completed? What, what happens then?

Dr. Ahsan: Dr. Witten, if you could speak to that.

Dr. Witten: If the confirmatory studies don't get completed, well, we work with the sponsor to try to get them completed, but, obviously, that is sometimes a problem that we, we do face. But I, you know, we, we try to make sure to minimize that chance. And the sponsor in this case does have a trial that's fully enrolled.

Dr. Ahsan: And was that different for, I think it was mentioned there we're 0 for 4 on the other ones. Was that different for those confirmatory trials that those were not completely enrolled?

Dr. Witten: I, I don't really know, but I, I think, in general, the one, the confirmatory trials that have struggled haven't been, but perhaps someone else knows the answer to that.

Dr. Ahsan: Okay. Donald, did you have one quick comment?

Dr. Kohn: Yes, sorry. Just along those lines, the other question is what happens if we give accelerated approval and then the confirmatory study gets completed and it doesn't show efficacy? What happens to the, to the approval? If Dr. Witten could address that, I think she did earlier before, but –

Dr. Ahsan: Yeah. Dr. Witten, if you could, reiterate that outcome.

Dr. Witten: Yeah, so we would look at the study to try to understand it and what we learned from it. And then if, if it seemed that the product didn't, you know, deserve approval any longer, we would either work towards withdrawing it or we would see whether the sponsor wanted to withdraw it, which has sometimes happened.

Dr. Ahsan: Okay. Great. Thank you very much. So now we're going to bring up the voting question or the, discussing the text around the voting question. If we can bring that up and have a short discussion around that. Can we go to the next slide, please? Right. So I do want to make clear that we're not voting at this point. Your options are going to be yes, no, and abstain. Right now what we're going to do is, I'm going to read this off. We're going to have a little bit of discussion with Caleb starting us as the first discussant. and then we will roll into the formal voting. So at this point, there's no voting to be made. And then I do want to iterate or reiterate

that when we get to the discussion point on this, that we should not state how we are going to vote. We can discuss our thoughts but not exactly how we would vote.

So the question at hand: Do the overall considerations of benefit and risk, taking into account the existing uncertainties, support accelerated approval of SRP-9001 - using as a surrogate endpoint expression of Sarepta's micro-dystrophin at week 12 after administration of SRP-9001 - for the treatment of ambulatory patients with Duchenne Muscular Dystrophy with a confirmed mutation in the DMD gene? So, Caleb, if you could start us off, that would be great.

Dr. Alexander:Sure. And I will try to be brief, you know, clear potential benefits with profound unmet need, very strong family and caregiver buy-in and support, non-trivial effects suggested by the analyses with external controls, and a setting where there's a very small, minimally important clinical difference. We've talked about risks. I, I think the big wild card here is the manufacturing processes. You know, as was noted, the, the study 301 that's, that's underway is the only one using manufacturing, it's the only trial using manufacturing process B, and I think that's a pretty big wild card. And I, I am, have some trouble. I see sort of mixed evidence regarding how concerned I, I feel like I should be about the risks that may be introduced by the difference in manufacturing processes.

You know, accelerated approval was based on the, these three factors that we heard: biologic plausibility, empiric evidence, clinical studies. The plausibility, there's uncertainty. I mean, we heard evidence, both of the similarity of functional domains between micro-dystrophin and wild type, but also the potential for important differences such as the absence of nitric oxide or alpha syntrophin binding sites in Sarepta's micro-dystrophin. So that's the biologic plausibility. Empiric evidence, we don't have it as, as the FDA pointed out, because this isn't a naturally occurring protein. We don't have epidemiologic or pathophysiologic or therapeutic or

pharmacologic data that we might otherwise have to support accelerated approval. The preclinical data we discussed extensively. You know, there's, I think I would characterize it as mixed. And, you know, concerns not only in the absence of that, the, that of regarding the absence of strong evidence in and of itself, but also the translation of animal models to humans.

So then we have the clinical data. We discuss the null top line results, the exploratory post-hoc findings. And, again, we don't, that trial that we discussed wasn't with manufacturing process B. We have correlation analyses, which in my mind are, are really important in understanding whether something is a valid surrogate. The primary correlation analyses between micro-dystrophin expression and change in NSAA failed to achieve statistical significance. After the inclusion of additional study data, two-thirds of which was open label, there was a suggestion of a correlation there. You know, the last two comments, one about external controls and one about substantial evidence.

So it would be one thing if study 102, part one, showed clear efficacy and the external controls did not. But that's not the situation that we have. We have the opposite situation. And, you know, as was pointed out, the use of external controls is complicated, where modest effects are expected. And whereas with propensity scores, you know, they depend on, on, on unverifiable assumptions. So, you know, external controls are maybe a piece of the puzzle, but I think it's why the, it's the FDA's position that these analyses can only serve as, as exploratory.

So I'll just close with, you know, the, the issue, which is that substantial evidence has to be met, that evidentiary threshold, whether or not a product is being considered for, for accelerated approval or standard approval. And so we were reminded that typically double-blind, placebo-controlled trials are preferred. And we were also reminded of settings where single arm, open-label clinical studies may suffice. Unfortunately, in this setting, it's not a setting where the

disease course is highly predictable at an individual level. We've talked about the NSAA as a measure that's, and seen data supporting the assertion that it is process and effort dependent. And this isn't a setting where we expect a necessarily large treatment effect and where we know that, that a study population and external controls are suitably comparable. So I think, you know, I think these are sort of contextual factors that have to be considered in, in thinking about this question. Thank you.

Dr. Ahsan: Thanks. That was a wonderful summary.

Dr. Rodino-Klapac: Clarify the discussion.

Dr. Ahsan: Yes, And I know that the sponsor wants to make a, probably a quick clarification related.

Dr. Rodino-Klapac: Yes. Quick clarification around process B. Process, our intended commercial process was used in study 103, as well as 301. 110 patients, 120 patients have been dosed with process B. 110 have passed the 90-day windows. So I just really wanted to clarify that process B is used in both studies. Thank you.

Dr. Ahsan: Okay. Great. Thank you. Next up is Buddy.

Mr. Cassidy: So I, I would just like to stress this here, that it says considerations of benefit and risk. I've talked about the benefit risk profile today. There is a benefit risk profile in the sponsor data from Sarepta. I'm a bit puzzled as to why there isn't much in the way of a benefit risk analysis in the FDA investigative report. So I think in evaluating this question, we need to take seriously this notion of benefit and risk here. Again, I would like to stress and reiterate that the four AON therapies, in terms of the post-market approval data, again, this is the voting question and that has absolutely no bearing on this, and these are not the drugs at hand we are discussing. So it's not relevant here.

Finally, I would just like to say that science is ultimately about observation, and we have that from the beginnings with Francis Bacon. And qualitative data is gathered through observation. It is data. It is science. It cannot be summarily dismissed altogether and called anecdote. So it is worth taking into consideration. Thank you.

Dr. Ahsan: Thank you, Buddy. Lisa?

Dr. Lee: Quick question, clarification from the sponsor, process B was, she stated was used in 102. Was this during the blinded phase or the open phase?

Dr. Ahsan: It was used in 103.

Dr. Lee: Oh, 103. I'm sorry. Okay. So in the open phase?

Dr. Ahsan: Yep.

Dr. Lee: Okay. So my, my comment earlier about it being only the, this 301 being the only study that's going to have a, a blinded use of this, so a real place where we can see results with, without any potential bias.

Dr. Rodino-Klapac: Correct. But we have –

Dr. Ahsan: 103 was not blinded. Right? Sponsor, if you –

Dr. Rodino-Klapac: That's correct, but 301 blinded safety data is, has been submitted. Yes.

Dr. Lee: Thank you. So, so it. Yeah. All right.

Dr. Ahsan: Does anyone else want to make comments? Oh, I see Dr. Marks.

Dr. Marks: Hi. I just want to reiterate something that Dr. Witten mentioned because it, it is a difference now than perhaps during previous approvals that were done. As part of the FDA, the, our User Fee Act, the FDA Reform Act of 2022, there were provisions to put some more teeth into our, our ability to make sure that sponsors were held accountable for completing, essentially, post-approval requirements, in this case, a confirmatory study for an accelerated approval. And

so, I think it, it, it, it goes without saying that we would obviously want to work collaboratively with the sponsor and the community to make sure this gets done. But we are very serious that we will need, if this were to receive an accelerated approval, it would need to have confirmatory data from a, a clinical trial to support continued approval. So that would be obviously, potentially, coming. You know, if, if that was not completed, obviously, as Dr. Witten noted, we would initially work with the sponsor. But if necessary, it could involve ultimately coming back to an advisory committee to have further discussions. So that is the process that has been laid out. Just wanted to make sure that we stress that the agency, understands the importance of getting these post-approval commitments, in this case, the confirmatory trial answered.

Dr. Ahsan: Thank you, Dr. Marks. It, maybe I can ask a question and, and bear with me if this isn't perfectly well posed. If this were to move forward with the accelerated approval, and while we are waiting for the confirmatory study, it sounds like there is a delay before between approval and access, is there a sense of how many patients would be treated with the approved product prior to receiving the confirmatory results?

Dr. Rodino-Klapac: Mr. O'Malley can comment. Thanks.

Mr. O'Malley: Yeah, you're, you're asking from approval to completion of part one of study 301, which is four months?

Dr. Ahsan: No. What I'm saying is, if you were to, if it were to be moved forward that there was accelerated approval, right, you're saying four months before, you know, the commercial access to patients. When is, I know in September is when you're getting your final data, but when is that confirmatory study going to be complete, just so I can understand the delta and time and how many patients would be treated?

Mr. O'Malley: So let me just put up the timeline that, get the slide up. Just remember, so the study part one completes, or the last visits, are in September, and then we have to go through a period of, as you know, verifying all of that data and doing proper quality checks. And then we're estimating top line results in December, a complete study report for part one in Q1, and then we would give that report to FDA. And then what happens from that point forward is, is with FDA to decide the, the time if we apply the priority review, that would put us, you know, longer than a year from now to have the final decision on the trial.

Dr. Ahsan: Yeah. If, if it were going that way. I guess my question is, in six months, if you were to get accelerated approval now, in the first six months of availability, how many patients would you treat?

Mr. O'Malley: I, it's probably very difficult to answer that. Very few, I think. It's not because we wouldn't be trying to treat as many as possible, but the process itself has some limitations to make the, the product available.

Dr. Ahsan: Okay. Thank you.

Mr. O'Malley: Just an estimation of maybe 100 or less, is our best guess.

Dr. Ahsan: So smaller than the size of the enrollment for the confirmatory trial?

Mr. O'Malley: Correct.

Dr. Ahsan: Okay. Looks like, Buddy, you have your hand up.

Mr. Cassidy: Yes. I just wanted to clarify one last thing in regard to the North Star Ambulatory Assessment. In the FDA investigative report, it says that NSAA in particular is susceptible to increased bias when evaluated under open label conditions because it is process dependent and effort dependent. And I understand that. However, again, as I pointed out before, these are effort dependent and process dependent or issues that are just by definition problematic for

performance evaluations. But the phrasing in this report makes it sound like these are a particular concern for the North Star Ambulatory Assessment. And in terms, it seems to me that the FDA has not adequately shown that there's reason for inordinate concern about these biases coming up in the North Star Ambulatory Assessment. And again, the North Star Ambulatory Assessment is specifically referred to, not performative evaluation generally. And it doesn't seem to me to be adequately grounded in the scholarly literature out there on the problem of bias and how it's mitigated in the North Star Ambulatory Assessment. So it's not quite what the report says.

Dr. Ahsan: Great. Thank you. Anyone else have any comments? I don't see any hands up, but I'll give everyone one more moment. Okay. So I think for this portion a summary is not necessary since the inherent discussion is a summary. So we can move forward towards the formal voting procedure. And so I'll hand the meeting over to Christina Vert, who will manage the voting process.

Vote

Ms. Vert: Hello. Thank you. Great. Thank you, Dr. Ahsan. I am Christina Vert, backup DFO, and I will be conducting the vote. Next slide. And next slide. Only our four regular members and 10 temporary voting members, a total of 14, will be voting in today's meeting. With regards to the voting process,

Dr. Ahsan will read the voting question for the record, and afterwards, all voting members and temporary voting members will cast their vote by selecting one of the voting options, which include yes, no, or abstain.

You'll have one minute to cast your vote after the question is read. Once the poll has closed, all votes will be considered final. And once all of the votes have been placed, we will

display the results and read the individual votes out loud for the record. Does anyone have any questions?

Unknown speaker: Where, where would we be voting? I'm sorry.

Ms. Vert: So a voting poll will appear later. It'll be visible on your screen, and you just have to click the choice, yes, no, or abstain.

Unknown speaker: Okay. Great. Thank you.

Ms. Vert: Okay. Next slide. Okay, Dr. Ahsan, can you please read the voting question number one for the record?

Dr. Ahsan: Of course. Do the overall considerations of benefit and risk, taking into account the existing uncertainties, support accelerated approval of SRP-9001 – using a surrogate endpoint expression of Sarepta's micro-dystrophin at week 12 after administration of SRP-9001 - for the treatment of ambulatory patients with Duchenne Muscular Dystrophy with a confirmed mutation in the DMD gene?

Ms. Vert: Thank you. Next slide. Okay. We now need to prepare the zoom room for the vote. Voting members and temporary voting members, please stay present. At this point, our AV will move all non-voting members out of the main room. And for those non-voting members, please do not log out of Zoom. We will move you back to the main zoom room in a few minutes.

Vote Results

Ms. Vert: Okay. All right. There are 14 total voting members for today's meeting, and we have eight yes votes, six no votes, and zero abstain votes. And I, let's see. And here are all the voting responses of each voting member, and I will read them out loud for the public record. Richard Kryscio, no. Donald Kohn, yes. John Chiorini, yes. Steven Pavlakis, yes. Caleb Alexander, no. Kathleen O'Sullivan, yes. Anthony Amato, yes. Rajiv Ratan, no. Taby Ahsan,

yes. Raymond Roos, yes. Christopher "Buddy" Cassidy, yes. Nirali Shah, no. Susan Ellenberg, no. Lisa Lee, no.

This concludes the, voting portion of today's meeting, and I want to make sure we're on the right slides. And thank you. Uh, can you pull up the slides? Okay. And so this does conclude the voting portion of the meeting, and I will now hand the meeting over to Dr. Ahsan.

Dr. Ahsan: So we'll go through the virtual table, and everyone can speak to their vote. Now that the non-voting members are in, I've lost my list a bit, but I think I'll be able to do it this way. If I can start, I'll, I'll start on this list that I have, which is from the bottom up. So, Dr. Nirali Shah, can you comment on your vote?

Dr. Shah: Yes. So I don't have any real concerns about the risk of therapy. I think that's well-tolerated, but I do remain quite concerned about the actual benefit and whether that has been adequately demonstrated without a study that is going to be using the commercialized product. I think that's really my primary concern. Coming from a field of gene therapy, you know, the product is the process. And I think that the confirmatory study needs to be completed. I, these patients deserve the best. And there is an incredible impact on patient hope and the ability to complete the confirmatory study. I, I would feel better knowing that we were, they, benefit was able to be shown using the product that patients were ultimately going to be receiving.

Dr. Ahsan: Great. Thank you. Dr. Raymond Roos?

Dr. Roos: Yes. I, I voted yes. My vote, yes, included the results of the study that's going to end in September, 2023. I think that the downside of the gene therapy here is relatively small compared to whether it really helps the patient, and for this reason I voted yes.

Dr. Ahsan: Thank you. Dr. Rajiv Ratan.

Dr. Ratan: I voted no. I was not convinced, either by the nonclinical or the clinical data, that an effect on the primary endpoint functional endpoints, really provided plausibility that this, the expression of the, the micro-dystrophin would predict clinical outcome.

Dr. Ahsan: Thank you. Dr. Steven Pavlakis.

Dr. Pavlakis: I voted yes. I was, I don't think the biomarker micro-dystrophin has proven to work for the study, and I also was a little disappointed with the clinical data because it, it's not statistically effective. The reason I voted yes, though, is I, and this was, I decided that there's, there's some very good clinicians here that, you know, think it, think it really does work. And that's how we do a lot of clinical science. And I think the study that's going to be done now is going to help with this. So I'm looking forward to that.

Dr. Ahsan: Thank you. Ms. Kathleen O'Sullivan.

Ms. O'Sullivan: Hi. I voted yes, partially because I think our main directive is to protect and to serve patient need, and there's, there's clearly unmet patient need. I thought that the sponsor did a good job showing that the, you know, the protein gets there. The protein does something. And then we have all this observable data in addition to different groups are going to, both sides are going to, are go seem to look at the existing clinical data with different lenses. So, at the end of the day, giving people a chance, the risk of one chance versus no chance and no help on the horizon, I think we owe it to the patients to help them intervene. And, and we can trust that patients and clinicians are going to be educated enough to make good decisions and what's right for their child. And I just want to say in the public comment docket, someone put it the best, Elizabeth Elliot's mom said, Do not let perfection be the enemy of the greater good. And that's why my vote is yes.

Dr. Ahsan: Thank you. Dr. Lisa Lee.

Dr. Lee: Thank you. I, my vote was no. I, I do want to acknowledge and express my appreciation for the compelling narratives of the families. There is no doubt that this is an extremely challenging condition that is in definite need of excellent treatments. And while the risks are low, there was no evidence of benefit. And without some data showing benefit, we're basically, I, I feel like we're basically asking families to shut off any future short or, or midterm possibilities for treatment. Finally, even without an accelerated approval, we will have confirmatory data to better guide this decision in a relatively short period.

Dr. Ahsan: Thank you. Dr. Richard Kryscio.

Dr. Kryscio: It's Richard Kryscio, University of Kentucky. I voted no because it was very hard to interpret the findings here as it related to clinical efficacy.

Dr. Ahsan: Okay. Donald Kohn.

Dr. Kohn: Yes. I voted yes. You know, I, I think maybe the most compelling efficacy he did is the, the four year follow up on the first four patients who have stable scores over that time. That's, and those are presumably some of the patients we saw. And, you know, voting, giving accelerated approval will give patients access to this over the next year, while the results from the definitive study are, are being analyzed. So, I, I think, again, as Kathleen said so well, we need to err on the side of giving patients the benefit of, of access.

Dr. Ahsan: Dr. Susan Ellenberg.

Dr. Ellenberg: I voted no. I felt that there were just too many uncertainties with these data right now, and we will have more definitive results soon that will allow parents to make more informed decisions about therapies. There are a number of other, I'm sure there are other companies developing therapies and I really hate the idea of people going with something that may or may not be effective and, and then not having a chance for something else. I've seen too

many studies over the years, including in my 12 years at CBER at the FDA, at seeing therapies that look very promising in early studies, including for some for really bad diseases, that ultimately failed to show any benefit.

Dr. Ahsan: Thank you, Dr. Jay Chiorini.

Dr. Chiorini: Yes. So I was not convinced of the surrogate data. But that said, the risk to benefit ratio seemed favorable, and I was convinced by the long-term data from the original patients that there was stability. And I think waiting is not going to be beneficial to the patients.

Dr. Ahsan: Great. Thank you. Mr. Buddy Cassidy.

Mr. Cassidy: Yes, so I, in fact, found Sarepta's analysis of the data quite convincing and compelling. And it was particular, what I, I thought was particularly convincing was their external controls based on natural history data. I thought they did some impressive work there, turning the natural history data into an external control. And I would also just like to note we're talking about accelerated approval today and factors that would be considered in that, so the FDA industry guidance from DMD drug development. And also it's important to note that in the case of the rare disease space, going on for 20, I mean, sorry, 10 years now, the FDA has, it's documented that they're willing to permit and accept regulatory flexibility, adaptive trial design on the use of natural history data for a control like we see today, given the rarity on severity of rare diseases and unmet needs.

And we've seen the FDA take these things into account in February for a drug for Friedrich, a treatment for Friedrich's Ataxia; and in April a drug for ALS. And so these were things were seriously taken into account when discussing the approval of those drugs. And I think given that this is yet another rare disease, these things should be taken into consideration. And I would stress things like regulatory flexibility, adaptive trial design, and use of natural

history data for control is not permitting laxity or a lack of rigor, but rather adjustments that must be made and acknowledgement of the reality of things to be ethical. And so with that, I am pretty thoroughly convinced of the efficacy of this drug. And I realize that sometimes what might look small and, like small and insignificant improvements to those outside of the community, like I demonstrated with a hand exercise, for myself as patient representative and those within my community, these things look significant. Thank you.

Dr. Ahsan: Thank you. Dr. Caleb Alexander.

Dr. Alexander: Caleb Alexander, Johns Hopkins. I also want to thank the sponsor and FDA and DMD community for what, you know, these, these, we've reviewed what science that has taken an extraordinary amount of work over many, many years to put together. So I'm grateful for that. You know, I agree that the videos were compelling and there are good clinicians here that think this product works and that the first four patients are, are compelling as well. But, as we heard, accelerated approval is based on more than that. And, you know, the, the threshold of substantial evidence has to be met whether or not a product is being approved under the standard pathway or accelerated pathways.

So we heard about settings where single arm, open label clinical studies and external controls may suffice. And this, this isn't one where, unfortunately, that's really ideally suited for that. So, you know, the decision that the FDA has to make is not, doesn't just affect the patients in study 301, it affects the entire field of drug development for Duchenne's. And there's a reason why our, our regulatory framework is regarded as the gold standard around the world. And it's because of the, the careful science and careful work that the FDA and sponsors do working together, you know, to bring new products to market. So I think the totality of evidence in this,

that we've reviewed today and that we reviewed in the briefing, simply doesn't rise to the threshold of substantial evidence that's required for accelerated approval. Thank you.

Dr. Ahsan: Thank you. Dr. Anthony Amato.

Dr. Amato: Thank you. I know there were pluses and minuses in, in this study, but, again, I thought there was compelling evidence that there is an effect. Again, my eyes looking at videos and taking care of people with muscular dystrophy for over 30 years, you don't get these benefits. It's not a placebo response. And I also trust my colleagues that were site investigators who, who also relayed and echoed that the improvements seen in their boys that were in a trial were not something that they had typically appreciated. And I, I take that into considerable consideration of weighing the risks and benefits and, and knowing that we're, the pivotal phase three study is going to be completed pretty soon. Again, I, I voted approving, approving the drug.

Dr. Ahsan: Thank you. And I think I'm the last person to comment. I also was very much on the edge of one way or the other. I ended up voting yes given that we are so deep into the confirmatory trial that is going to be very influential, I think, moving forward, and, but thinking about the risk level being quite low and that it's highly, it's well tolerated, that there was some benefit in this time is muscle concept to move forward for what would end up being a, a small cohort that had access to the commercial product before we got the confirmatory trial results back.

So with that, I think we've run through everyone. Is there any, any voting member that did not support their vote? Okay. Great. I think everyone has, has discussed. And so with that, I will move it over to Dr. Marks who will be making some closing remarks for the meeting.

Closing Remarks — Dr. Peter Marks

Dr. Marks: Great. Thanks very much. So I first want to just say some thank yous, first of all, to the sponsor and to the public commenters, the really an incredibly, incredible amount of work went into those presentations. I want to thank our, our advisory committee members and you as chair. I also want to thank the incredible effort of our FDA staff and the office of therapeutic products, as well as the office of biostatistics and pharmacovigilance and others who worked on the scientific presentation in our advisory committee group that had to do a lot of logistics in a rapid amount of time to get this meeting together. And I also, importantly, want to thank the patients and their families who participated in the trials that were presented today. I, the hour's late, and I just want to say thank you for all of the input today.

What I really hear coming out of this is that we still are in an area where there is a lot of uncertainty but which there is a feeling, the small majority felt that there was enough evidence here that was compelling to them, and with a confirmatory trial ongoing, that provided that was completed, that they felt comfortable moving forward. Obviously, we will now take this back and, and do something that we have to do every day at FDA. And it's something that I'm pretty used to doing over the past several years, which is that we have to manage through the uncertainty here. And we will work with the sponsor, and our staff will work through that in, in, in the coming weeks. So just to say thank you for the incredibly great discussion today, and really appreciate everyone's contributions here. It really was incredibly helpful. So thank you very much to all.

Ms. DeGregorio: So thank you – go ahead, Dr. Ahsan.

Dr. Ahsan: I just wanted to reiterate Dr. Marks' comments about thanking everyone for their time. It was a long day. I think it was a robust discussion, and hopefully we served our purpose

to give the FDA some sub points to think about to help inform their decision making. And so with that, I'll pass that over to Marie and thank you everyone.

Adjournment

Ms. DeGregorio: Okay. Thank you, Dr. Ahsan, for closing comments. I want to thank this committee and CBER staff for working so hard to make this meeting a successful one. I now call this meeting officially adjourned at 6:22 PM Eastern Time. Have a wonderful evening.