Food and Drug Administration
Center for Biologics Evaluation and Research
Summary Minutes
74th Cellular, Tissue, and Gene Therapies Advisory Committee Meeting
May 12, 2023

Committee Members	**FDA Participants**
Tabassum (Taby) Ahsan, Ph.D. (Acting Chair) Marshall E. Bloom, M.D. + Christopher K., Breuer, M.D. + Eric Crombez, M.D. ** Donald B. Kohn, M.D. Wendy B. London, Ph.D. + Sean J. Morrison, Ph.D. + Kathleen O'Sullivan-Fortin, Esq. * Melanie Ott, M.D., Ph.D. + Nirali N. Shah M.D., M.H.Sc. Gil I. Wolfe, M.D. + Joseph Wu, M.D., Ph.D. + **Temporary Voting Members** G. Caleb Alexander, M.D., M.S. Anthony Amato, M.D. Christopher "Buddy" Cassidy, M.A. > John (Jay) Chiorini, Ph.D. Susan Ellenberg, Ph.D. Richard Kryscio, Ph.D. Lisa Lee, Ph.D. Steven Pavlakis, M.D. Rajiv R. Ratan, M.D., Ph.D. Raymond Roos, M.D. **Industry Representative** Eric Crombez, M.D. ** **Consumer Representative** Kathleen O'Sullivan-Fortin, Esq. * +Not Attending * Consumer Representative ** Industry Representative >Patient Representative	Peter W. Marks, M.D., Ph.D. (Speaker) Celia Witten, Ph.D., M.D. (Speaker) Leila P. Hann Emmanuel Adu-Gyamfi, Ph.D. (Speaker) Theresa Chen, Ph.D. (Speaker) Xiaofei Wang, Ph.D. (Speaker) Mike Singer, M.D., Ph.D. (Speaker) Rosa Sherafat-Kazemzadeh, M.D. (Speaker) **Designated Federal Officers (DFO)** Marie DeGregorio Christina Vert, M.S. (Alternate) **Committee Management Officer (CMO)** Joanne Lipkind, M.S. **Committee Management Specialist (CMS)** Tonica Burke, B.S. **DSAC Director** Prabhakara Atreya, Ph.D.

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These summary minutes for the May 12, 2023 meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) were approved on September 12, 2023.

I certify that I participated in the May 12, 2023 meeting of the CTGTAC meeting and that these minutes accurately reflect what transpired.

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Marie DeGregorio
Designated Federal Officer

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Tabassum (Taby) Ahsan, Ph.D.
Acting Chair

On May 12, 2023, the 74th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) took place in open session to discuss the biologics license application (BLA) 125781 from Sarepta Therapeutics, Inc. for delandistrogene moxeparvovec (SRP-9001). The applicant has requested an indication for the treatment of ambulatory patients with Duchenne Muscular Dystrophy (DMD) with a confirmed mutation in the *DMD* gene. Given the topic of this meeting, it was determined to be a Particular Matter Involving Specific Parties (PMISP).

On May 12, 2023 at 9:00 a.m. Eastern Daylight Time (EDT), Dr. Taby Ahsan, the Acting Chair, called the meeting to order. The DFO, Ms. Marie DeGregorio, made administrative remarks, conducted roll call, invited the CTGTAC members and consultants to introduce themselves, and read the Conflict of Interest (COI) statement into the public record. There were no conflict-of-interest waivers issued under 18 U.S. Code Section 208 in connection with this meeting. During the open session, the CTGTAC members, consultants, Applicant, FDA speakers and staff, and public speakers all participated via Zoom web conference.

Dr. Celia Witten, Deputy Director of CBER and also Acting Director of the Office of Therapeutic Products (OTP), provided FDA Opening Remarks followed by a brief Q & A.

Following the Q & A, Dr. Rosa Sherafat-Kazemzadeh, Clinical Team Lead in OTP, gave the FDA Overview entitled, "FDA Overview of BLA 125781, Application for Accelerated Approval of delandistrogene moxeparvovec (SRP-9001)."

Following the FDA Overview, time was allowed for clarifying questions and answers between the committee and Dr. Sherafat-Kazemzadeh. This was followed by a committee break.

Once the committee returned from the break, the Applicant team of speakers gave a presentation entitled, "SRP-9001 (delandistrogene moxeparvovec) for Treatment of Duchenne Muscular Dystrophy." The Applicant Presentations and Speakers were as follows:

- Introduction – Patrick O'Malley
- Disease Background and Unmet Need – Jerry Mendell, M.D.

- Evidence for Surrogacy – Louise Rodino-Klapac, Ph.D.
- Clinical Trial Results – Stefanie Mason, M.D.
- External Control Analyses – James Signorovitch, Ph.D.
- External Control Results – Craig M. McDonald, M.D.
- Summary of Safety – Eddie Darton, M.D.
- Clinical Perspective – Craig M. McDonald, M.D.

Following the Applicant presentation, time was allowed for clarifying questions and answers between the committee and the Applicant team of speakers listed above

The committee was released for a 45-minute lunch. Once the committee returned from lunch, a 60-minute Open Public Hearing (OPH) session was held from 12:30 p.m. to 1:30 p.m. in which 18 pre-registered public speakers gave PowerPoint presentations and/or made oral remarks. The names of OPH speakers and their remarks may be obtained from the transcript posted on the CTGTAC website.

Following the OPH session, there was a brief committee break. Once the committee returned from the break, FDA staff gave a presentation entitled, "BLA 125781 – Application for Accelerated Approval of delandistrogene moxeparvovec (SRP-9001) for Treatment of Ambulatory Patients with Duchenne Muscular Dystrophy with a Confirmed Mutation in the *DMD* Gene."

The FDA team of speakers were as follows:

- Dr. Mike Singer, Clinical Reviewer in OTP
- Dr. Emmanuel Adu-Gyamfi, Chemistry Manufacturing and Controls Reviewer in OTP
- Dr. Theresa Chen, Pharmacology/Toxicology Reviewer in OTP
- Dr. Xiaofei Wang, Clinical Pharmacology Reviewer in OTP

Following the FDA Speaker presentations, time was allowed for the committee to ask the FDA speakers some clarifying questions and receive answers , followed by a brief committee break.

The committee then started their discussion addressing the 4 discussion topics that were displayed, followed by the Alternate DFO, Christina Vert, conducting the voting process on a single voting question.

The following discussion topics and voting questions were presented to the committee:

Discussion Topics:

1. Please discuss the strengths and limitations of the available evidence supporting the use of measurement of Sarepta's micro-dystrophin, expressed through the 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.

Summary of Discussion: The Committee discussed the difficulty in assessing the clinical correlation between micro-dystrophin expression levels and clinical outcome data due to limitations of the metrics used, variability in the data, level of transduction observed, and differences in interpretation of the data. The panel stated that perhaps there was a subset of patients that might be getting better but DMD is a heterogenous population and the efficacy of the treatment might be dependent on multiple factors, such as age at the time of delivery. There was also discussion that although the micro-dystrophin may have a structural effect, it is unclear whether it's physiologically meaningful and there was concern regarding the differences between the SRP9001 micro-dystrophin and other shortened forms of dystrophin in both structure and tissue distribution.

2. Part 1 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 1.

   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 4 to 5 years of age; however, among ambulatory patients between 6 to 7 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.

   Summary of Discussion: The Committee noted that the clinical significance of the exploratory subgroup analysis data is difficult to interpret. Such analysis was not prespecified for hypothesis testing and no prespecified multiplicity adjustment strategy was employed. There was also discussion of NSAA that while it is a highly regarded tool for assessing patients, using it in an open label setting introduces challenges in interpreting the data. The panel noted there are many qualifying statements that may need to be applied, whether it's based on the age or how the data was measured or how the data was analyzed.

3. Please discuss the potential benefits, risks, and uncertainties that may be associated with administration of SRP-9001 for treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene.

   Summary of Discussion: Please discuss the potential benefits, risks, and uncertainties: The Committee thought that the most commonly identified safety events were manageable. There was discussion of persistence of anti-AAV antibodies developed after SRP-9001 infusion and the opportunity cost of foregoing any future AAV based treatment.

4. If SRP-9001 were to be approved under Accelerated Approval provisions, the Applicant proposes that Part 1 of Study 301 (the Phase 3 randomized, double-blind, placebo-controlled 52-week crossover clinical study) may serve as the required postmarketing 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 1 of Study 301.

   Summary of Discussion: The Committee noted that the data from Study 301 is critical as it will be the first controlled trial using product made with process B. There is a concern that, if approved, patients will drop out of the study to try and obtain commercially available product faster which would make the results of Study 301 hard to interpret. Without confirmatory evidence, there is a possibility that the product is ineffective, and the patients who have received SRP-9001 will not be able to take a future AAV-based treatment. There was a discussion about whether it would be ethical to keep patients who have not received SRP-9001 in the study until study completion after the product approval.

   Although Study 301 is currently fully enrolled, it may be difficult to predict whether patients who have not received SRP-9001 would continue the study because they may consider waiting until data from the confirmatory trial are available to ensure the treatment is effective considering that they can only receive a single AAV treatment. Some Committee members indicated that based on the current enrollment status, there may be a good chance that those patients will remain in the trial.

Discussion Question, Then Voting:

1. 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?

   a. Yes
   b. No
   c. Abstain

The committee voting results were as follows: 8 Yes; 6 No; 0 Abstain.

At the completion of the voting, while the voting results were displayed, the Alternate DFO, Christina Vert, read the voting results for the public record,

Following the vote, the Chair asked that all voting members explain their individual voting

decisions, which they provided.

After the Committee Discussion, Voting, and Vote Explanation, CBER Director Dr. Peter Marks thanked the committee and provided closing remarks.

The committee acting Chair Dr. Taby Ahsan then handed the meeting over to the DFO, Ms. Marie DeGregorio, who adjourned the meeting on May 12, 2023 at 6:22 p.m. EDT.

Additional meeting information and details may be obtained from the transcript, which may be viewed at:
https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-may-12-2023-meeting-announcement-05122023.

The recording of the webcast of the meeting may be viewed at:
https://youtube.com/live/k33d4h-CpGU.