



STN: BL 125781/0

**LATE-CYCLE
MEETING MEMORANDUM**

April 12, 2023

Sarepta Therapeutics, Inc.
Attention: Patrick O'Malley
215 First St.
Cambridge, MA 02142

Dear Mr. O'Malley:

Attached is a copy of the memorandum summarizing your March 13, 2023, Late-Cycle teleconference with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Rachel Duddy at Rachel.Duddy@fda.hhs.gov.

Sincerely,

Ramani Sista, PhD
Director
Division of Review Management and Regulatory Review 1
Office of Review Management and Regulatory Review
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: Monday, March 13, 2023, 9:30 AM-11:00 AM ET
Meeting Location: Zoom
Application Number: BLA 125781/0
Product Name: delandistrogene moxeparvovec (ELEVIDYS)
Proposed Indications: Treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene
Applicant Name: Sarepta Therapeutics, Inc.
Meeting Chair: Emmanuel Adu-Gyamfi, PhD
RPM: Rachel Duddy, MS

FDA ATTENDEES

Emmanuel Adu-Gyamfi, PhD, CBER/OTP/OGT
Atul Bhattaram, CDER/OTS/OCP/DPM
Lilia Bi, PhD, CBER/OTP/OGT
Wilson Bryan, MD, CBER/OTP/AS
Theresa Chen, PhD, CBER/OTP/OPT
Elin Cho, MS, CBER/OBPV/DB
Benjamin Cyge, CBER/OCBQ/DCM/APLB
Brendan Day, MD, MPH, CBER/OBPV/DPV/PB2
Maureen DeMar, BSN, RN, CBER/OCBQ/DMPQ/ARB
Rachel Duddy, MS, CBER/OTP/ORMRR
Varsha Garnepudi, MS, CBER/OCBQ/DBSQC
Denise Gavin, PhD, CBER/OTP/OGT
Leila Hann, CBER/OTP
Andrew Harmon, PhD, CBER/OTP/OGT
Christopher Jason, MD, CBER/OBPV/DPV/PB
George Kastanis, MS, CBER/OCBQ/DBSQC
Simleen Kaur, MSc, CBER/OCBQ/DBSQC
Larissa Lapteva, MD, MHS, MBA, CBER/OTP/OCE
Shiowjen Lee, PhD, CBER/OBPV/DB
Wei Liang, PhD, CBER/OTP
Heather Lombardi, PhD, CBER/OTP/OCTHT
Olivia Ou Ma, PhD, CBER/OCBQ/DMPQ/MRB2
Tyree Newman, MDiv, CBER/OTP/ORMRR
Steven Oh, PhD, CBER/OTP/OCTHT
Tao Pan, PhD, CBER/OCBQ/DBSQC
Tejashri Purohit-Sheth, MD, CBER/OTP/OCE
Rong Rong, MD, PhD, CDRH/OPEQ/OHTVII/DIHD/HB
Christopher Saeui, PhD, CBER/OTP/OPT
Kimberly Schultz, PhD, CBER/OTP/OGT
John Scott, PhD, MA, CBER/OBPV/DB
Anurag Sharma, PhD, CBER/OTP/OGT
Abigail Shearin, MD, PhD, CBER/OTP/OPT

Rosa Sherafat-Kazemzadeh, MD, CBER/OTP/OCE
Mike A. Singer, MD, PhD, CBER/OTP/OCE
Ramani Sista, PhD, CBER/OTP/ORMRR
Sukyoung Sohn, PhD, CBER/OTP/OGT
Brian Stultz, MS, CBER/OTP/OGT
Natasha Thorne, PhD, CDRH/OPEQ/OHTV/DIHD/HB
Triet M Tran, PharmD, CBER/OCBQ/DIS/BMB
Ramjay Vatsan, PhD, CBER/OTP/OGT
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Nadia Whitt, MS, CBER/OTP/ORMRR
Iwen Wu, PhD, CBER/OTP/OPT
Min Wu, PhD, CDRH/OPEQ/OHTV/DIHD/HB
Lei Xu, MD, PhD, CBER/OTP/OCE
Boguang Zhen, PhD, CBER/OBPV/DB

APPLICANT ATTENDEES

Patrick O'Malley – Executive Director, Regulatory Affairs
Sharon Standerwick – Chief Regulatory Officer
Doug Ingram – President and CEO
Louise Rodino-Klapac – Executive Vice President, Head of R&D
Dr. Jake Elkins – Chief Medical Officer
Dr. Teji Singh – Vice President, Head of Clinical Development
Dr. Stefanie Mason – Senior Medical Director, Clinical Development
Dr. James Richardson – Executive Director, Global Program Team Lead
Lilly East – Vice President, Clinical and Quantitative Pharmacology
Rachael Potter – Vice President, Head of Gene Therapy Research
Lixin Han – Vice President, Biometrics
Na Cai – Senior Director, Biostatistics
Meghan Brown – Vice President, Global Regulatory CMC
(b) (4) – Regulatory Affairs Lead, (b) (4) collaboration

BACKGROUND

BLA 125781/0 was submitted on September 28, 2022, for delandistrogene moxeparvovec (ELEVIDYS).

Proposed indication: Treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.

PDUFA goal date: May 26th, 2023

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on March 6, 2023.

DISCUSSION

1. Discussion of Substantive Review Issues

a. Chemistry, Manufacturing and Controls (CMC)

FDA acknowledged the additional CMC information submitted. FDA stated that the CMC information is currently under review.

The Applicant clarified that the proposed Post Marketing Commitment (PMC) milestone date of April 21, 2023, is not a milestone date, but the date they plan to submit the milestone dates on the E&L study.

b. Clinical

FDA presented the substantive clinical issues that were provided in the agenda. The Applicant acknowledged that the explanation that was given in the agenda is in line with their previous Type C meeting; however, the Applicant requested further details regarding FDA concerns.

FDA acknowledges there seems to be a biological plausibility of SRP-9001 for the treatment of DMD. However, because the engineered protein expressed by SRP-9001 is not naturally occurring, epidemiologic data are not available. In addition, the effect of the protein expression on the pathophysiology of DMD is not known.

The Applicant requested more information on what FDA is looking for with respect to correlation. FDA responded that based on the Agency's assessment, there is not sufficient correlation between the biomarker (protein expression) and the clinical outcome data. The available clinical data are challenging to interpret in attempting to establish a correlation. FDA further stated that the correlation does not have to be linear but needs to be strong enough.

FDA also indicated that the nonclinical data evaluating micro-dystrophin protein expression and functionality in the murine model cannot establish clinical correlation. The variability in the nonclinical data is too high to establish a correlation between micro-dystrophin levels and functional improvement in mice. In addition, nonclinical functionality data cannot be directly translated to clinical functionality data due to the limitations of the weak functional phenotype of the DMD mouse model. Furthermore, while nonclinical data may help in identifying a potential surrogate endpoint to explore clinically, the appropriateness of a surrogate endpoint to reasonably likely predict clinical benefit should be supported by the clinical data.

FDA does not agree with the use of external controls to support the clinical benefit of SRP-9001 because a clinical outcome such as NSAA is effort- and

process-dependent and is likely biased when assessed in an open-label setting, and the study population and the external control population may not be comparable despite of the propensity score matching. The data from the randomized, double-blind, placebo controlled Part 1 of Study 102 indicate that there is not a significant difference in clinical outcome such as NSAA between the SRP-9001 and placebo groups. Exploratory subgroup analysis of the data for the 4–5 years old group suggests that the product might be of some benefit; however, subgroup analysis of the data for the 6–7 years old groups suggests that the product might be of no benefit as the product arm for this subgroup did worse than the placebo arm. FDA also stated that these subgroup analyses are more appropriate for hypothesis generation given the limited number of subjects in each subgroup, particularly in the context of a failed primary efficacy analysis on the endpoint of NSAA.

The Applicant requested clarification on whether there is a path to accelerated approval. FDA stated that the available data are challenging to interpret in support of a conclusion that the protein expressed by RP-9001 is reasonably likely to predict clinical benefit in ambulatory patients with DMD. The Phase 3 trial data will provide much clarity on the efficacy as well as additional safety of SRP-9001 manufactured by Process B. If the study is positive, it will provide evidence of effectiveness and safety to support traditional approval.

The Applicant inquired regarding other products approved via accelerated approval pathway. FDA stated they cannot comment on other programs which are not under OTP purview.

FDA reiterated that the Agency needs to take the benefit risk ratio into consideration. Although some serious adverse events that were observed in other AAV vector-based gene therapy products have not been observed in SRP-9001, the number of subjects being exposed to SRP-9001 is limited. In addition, there is evidence of cross-reactive humoral and T-cell response between different AAV serotypes. The latter will likely make any patient who does not benefit from SRP-9001 ineligible from receiving any other AAV-based gene therapy product that could be effective for DMD.

2. Additional Applicant Data

The Applicant indicated that they do not expect to submit additional data for review.

3. Information Requests

A Clinical Information Request (IR) was sent to the Applicant on March 8th regarding preexisting antibody titers. The response is due by 5pm on Monday, March 13, 2023. The Applicant confirmed that the IR response will be submitted by the deadline.

As our review continues, new information requests will be conveyed as needed.

4. Discussion of Upcoming Advisory Committee Meeting

An Advisory Committee (AC) meeting is tentatively scheduled for late July based on AC member availability. FDA will notify the Applicant once the AC meeting date is scheduled.

The Applicant inquired if the FDA knew what questions would be asked at the AC. FDA stated that the questions are not finalized until a few days prior to the meeting and the issues will be similar to what have been discussed at this late cycle meeting.

5. Postmarketing Requirements/Postmarketing Commitments

FDA does not anticipate any PMR/PMC issues at this time. The review is ongoing.

The Applicant inquired about their proposed PMRs. Because of the substantive issues identified, it is premature to comment on the Applicant's proposed PMRs.

6. Major Labeling Issues

There is no anticipation of major labeling issues identified at this time. The Applicant did not have any questions.

7. Review Plans

Review is ongoing. FDA will provide the Applicant the final date of the scheduled Advisory Committee (AC) meeting as soon as possible.

Inspections are still ongoing. FDA has not identified any issues related to risk management and does not believe that a risk management action is needed at this time. The Applicant did not have any questions.

8. Applicant Questions

The Applicant inquired if there will be any additional inspections other than the ones currently scheduled.

There are no additional planned inspections for manufacturing or clinical investigator sites. FDA will be sending inspection details for the upcoming March 20th inspection.

9. Wrap-up and Action Items

The Applicant does not plan to submit any additional data.

The meeting summary will be sent within 30 days of this meeting.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.