

SUMMARY OF INFORMAL TELECONFERENCE WITH APPLICANT
[For Internal Purposes Only]

Submission: BLA 125781/0

Office: OTP

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Applicant: Sarepta Therapeutics, Inc.

Meeting Date/Time: Monday, May 22, 2023, from 10:30am-11:30am ET

FDA Attendees

Emmanuel Adu-Gyamfi, PhD, CBER/OTP/OGT

Rachel Duddy, MS, CBER/OTP/ORMRR

Denise Gavin, PhD, CBER/OTP/OGT

Phillip Kurs, JD, CBER/OD

Sherry Lard, PhD, CBER/OD

Peter Marks, MD, PhD, CBER/OD

Mara Miller, MA, CBER/OTP/ORMRR

Tyree Newman, MDiv, CBER/OTP/ORMRR

Rosa Sherafat-Kazemzadeh, MD, CBER/OTP/OCE

Mike A. Singer, MD, PhD, CBER/OTP/OCE

Ramani Sista, PhD, CBER/OTP/ORMRR

Lori Tull, CBER/OTP/ORMRR

Nadia Whitt, MS, CBER/OTP/ORMRR

Lei Xu, MD, PhD, CBER/OTP/OCE

Applicant Attendees

Patrick O'Malley – Vice President, Regulatory Affairs

Louise Rodino-Klapac, PhD - Executive Vice President, Head of R&D

Doug Ingram – CEO

Jake Elkins, MD – Chief Medical Officer

Eddie Darton, MD - Executive Medical Director, Safety Evaluation & Risk Management

Stefanie Mason, MD - Senior Medical Director, Clinical Development

Sharon Standerwick, PhD – Chief Regulatory Officer

Meghan Brown, PhD – Vice President, Global Regulatory CMC

Ellen Wong, PharmD – Executive Director, Regulatory Labeling and Disclosures

James Richardson, MD - Executive Director, Global Program Team

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Summary:

The purpose of this informal teleconference was to provide a review status update to the Applicant for BLA 125781/0.

Dr. Marks started by conveying the following key points:

1. We appreciate the information submitted in the BLA for SRP-9001 along with the significant serious unmet medical need in Duchenne's Muscular Dystrophy, along with the input of patients, providers, and advisory committee members at the recent CTGT Advisory Committee meeting held on May 12th, 2023.
2. To be transparent, there are challenges in the data provided in this BLA which in large part relate to the uncertainty in the data without having the results of Study 301 in hand as we move forward.
3. The challenges include 1) remaining questions about how SRP-9001 microdystrophin compares to full length and other truncated dystrophins, 2) challenges with the use of external controls, and 3) the discrepancy between the finding seen in study 102 Part 1 in the 4- to 5-year-old group and the 6- to 7-year-old group.
4. FDA would like to take the opportunity on this teleconference to lay out what the Agency sees as the path forward over the next several weeks.
 - a. FDA needs to miss the PDUFA goal date to engage in adequate labeling negotiations for SRP-9001. Because of this, FDA is proposing a revised action due date of June 22, 2023. FDA will try to move this up, but the Agency cannot promise anything at this time.
 - b. Moving forward, the labeling negotiations will focus on consideration of the efficacy data from the 4- and 5-years old subset of study 102 and the overall safety data set. FDA is already aware that you may not agree with this parsing of the study data, but please work with the Agency on this, as the larger population of ambulatory patients is not under consideration for labeling at this time pending the results of Study 301.
5. Although it is obvious that older patients potentially have more urgent therapeutic need, there are plausible explanations why micro-dystrophin expression might not predict clinical benefit in these individuals, particularly in the setting of the negative results from study 102 Part 1.
6. FDA must also look at the potential issues with treating older children with a therapy that has not clearly demonstrated the likelihood of efficacy, and that also may preclude treatment in the near future with any one of a number of the several other gene therapies in development.

7. In the context of the lack of clinical evidence of benefit in the 6 and 7 year old children, as the team has discussed with the applicant previously, FDA again urged the applicant to consider modifying the ongoing Study 301 trial to be powered for demonstrating efficacy in the 4 to 5 year old subset, or to be prepared to have to conduct an additional study if study 301 fails its primary endpoint yet indicates likely efficacy in 4 and 5 year old subgroup. Though FDA hopes that this will not be the case, FDA owes it to the patients to work through the potential contingency situations.
8. FDA has considered all the issues, has discussed them very carefully and has briefed senior leadership in the agency, including Dr. Woodcock.

Based on the discussions at this meeting, the press release submitted to the BLA will need to be revised.

The applicant shared their concern about limiting the indication to only 4- to 5-year-old patients with DMD, including whether efficacy of SRP-9001 needs to be demonstrated in all age groups.

FDA reiterated that the Agency does not know whether SRP-9001 is likely beneficial to the 6-7 years old subgroup based on available data. FDA hopes Study 301 will provide more clear answer. Study 301 is only powered for the overall population of 4 to 7 years old patients and the primary endpoint will be tested solely on the overall population. If the study fails in the overall population but wins in the younger age subgroup of 4 to 5 years old, and if the applicant does not specify an inferential subgroup analysis, the applicant won't be able to proceed with testing the subgroup effect following a failed test of the overall population. FDA continues recommending the applicant pre-specify the inferential age subgroup analysis based on findings of Study 102 Part 1. This means that the subgroup analysis needs to be pre-specified with adequate power and proper alpha control. Ultimately, whether data from Study 301 would support an indication broader than the 4-5 years old ambulatory patients with DMD will be a review issue. It is premature to comment in the absence of data.

Dr. Marks made it clear that FDA's position is not up for negotiation. If the applicant does not agree with FDA's position, please let FDA know within the next day. The applicant agreed to follow up with any concerns within the next day.

END