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U.S. FOOD & DRUG ADMINISTRATION

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

FDA Overview of BLA 125781

Application for Accelerated Approval of delandistrogene moxeparvovec (SRP-9001)

Applicant: Sarepta Therapeutics, Inc.

Rosa Sherafat, MD
Office of Therapeutic Products
Center for Biologics Evaluation and Research, FDA

May 12, 2023

Outline

- Duchenne muscular dystrophy (DMD), a serious condition with ongoing unmet medical need
- Regulatory flexibility in approval of drugs & biological products
- Description of SRP-9001
- Overview of clinical studies submitted in support of Accelerated Approval of SRP-9001
- Overview of today's agenda
- Overview of discussion topics and voting questions for the Advisory Committee

Duchenne Muscular Dystrophy (DMD): A Progressive, Multisystem Disease

- Progressive, multisystem, heterogeneous disease
- Serious, life-threatening genetic disorder
- Urgent unmet medical need
- Affects ~1 in 3,300 boys
- Progressive proximal > distal muscle weakness, in legs then arms
- Loss of ambulation by age ~12 years
- Death often by early adulthood
  - Respiratory insufficiency or cardiomyopathy

Urgent Unmet Medical Need

- Standard of care: long-term corticosteroid treatment
  - Deflazacort (initial FDA approval 2017; expanded 2019): patients ≥ 2 years old with DMD
- Four exon-skipping drugs have received FDA approval via Accelerated Approval pathway
  - For only a subset of patients, with specific mutations in the *DMD* gene
  - Clinical benefit remains to be verified
- Even with improved standard of care and available therapies
  - Estimated that for every 1,000 patients 20 to 25 years old with DMD, 86 lose their lives each year[1]
  - Estimated life expectancy for patients with DMD receiving ventilatory support is ~ 30 years old[2]

[1]Broomfield J. (2021) Life expectancy in Duchenne muscular dystrophy. *Neurology* 97:e2304-e2314
[2]Landfeldt E. (2020) Life expectancy at birth in Duchenne muscular dystrophy: a systematic review and meta-analysis. *Eur J Epidemiol* 35:643–653

FDA Mission in Approval of New Therapeutics

- FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation

- For a new drug to be approved for marketing in the United States, FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling.

Section 505(d) of FD&C Act

Regulatory Requirements for Approval of New Drugs and Biological Products

- Approval of all drugs – for rare and common conditions – must be based on substantial evidence of effectiveness and sufficient evidence of safety.
- Evidence of effectiveness should be obtained from adequate and well-controlled studies.
- Certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases.
- FDA regulations provide flexibility in applying regulatory standards.

SRP-9001: Description

- SRP-9001 is an adeno-associated virus (AAV) vector-based gene therapy product encoding an engineered protein, Sarepta's micro-dystrophin

- SRP-9001 is prepared as a suspension of concentration of 1.33×10^{13} vector genomes per milliliter (vg/mL), and is supplied in a single-use, 10 mL vial for a single-dose, intravenous infusion

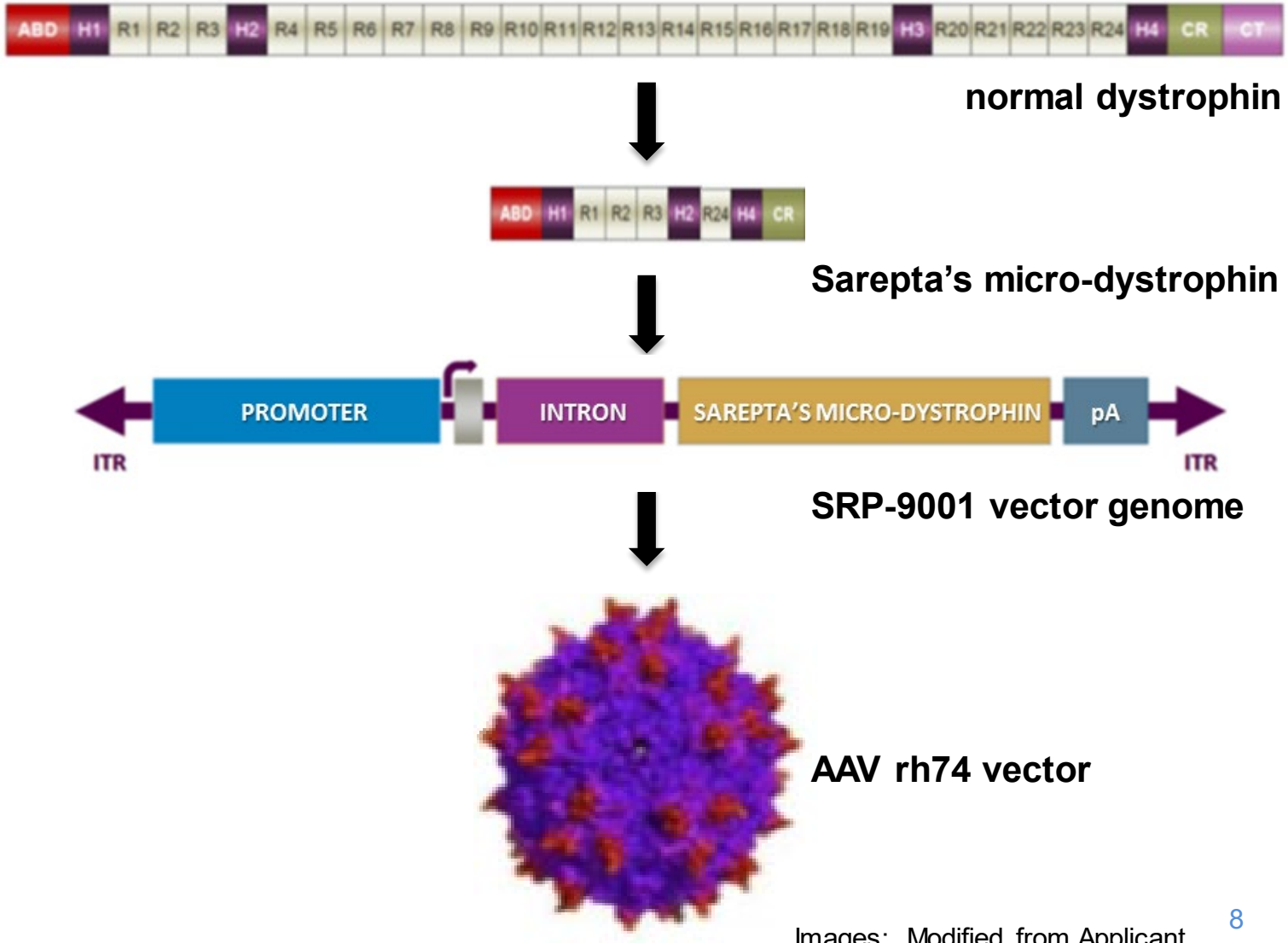
- Proposed dose
  - 1.33×10^{14} vg per kg of body weight (patients 10-70 kg)
  - 9.31×10^{15} vg total (patients ≥ 70 kg)

- **Proposed indication:**
  Treatment of ambulatory patients with Duchenne muscular dystrophy with a confirmed mutation in the DMD gene

- Applicant proposes that expression of Sarepta's micro-dystrophin serve as a surrogate endpoint "reasonably likely to predict clinical benefit"

SRP-9001 Product Overview

- cDNA for normal dystrophin ~ 14 kb
- AAV vector can carry only ~ 4.7 kb genome
- Sarepta's micro-dystrophin is engineered to include only certain domains of normal dystrophin
- Genome packaged in AAV vector (serotype rh74)
- Intended for expression in skeletal and cardiac muscle



Images: Modified from Applicant

FDA Commitment to Development of Safe & Effective Treatments for Patients With DMD

- Orphan Drug Designation
- Rare Pediatric Disease Designation
- Fast Track Designation
- BLA 125781, received on September 28, 2022 and was granted 8-month, BLA Priority Review Designation

BLA 125781 Clinical Studies

Study 101
4 subjects
First-in-human study
Open-label

- **Age 4-7 years**
- **Ambulatory**

Study 102
41 subjects
Randomized
double-blind
placebo-controlled
[Part 1]

- **Age 4-7 years**
- **Ambulatory**
- **Crossover study:**
  - **Part 1 (48 weeks)** ***three different doses***
  - **Part 2 (48 weeks)** ***functionally open-label***

Study 103
40 subjects
"Bridging" study
Open-label

- **20 ambulatory patients age 4-7 years**
- **7 ambulatory patients age 8-17 years**
- **6 non-ambulatory patients**
- **7 ambulatory patients, age ≥3 to <4 years**

Used Process A product **Used Process B product**

Images: Modified from Applicant

Overview of Today's Agenda

10:15 am	**Applicant Presentation: Sarepta Therapeutics, Inc. (90 min, including 15 min Q & A)**
11:45 am	**Lunch (45 min)**
12:30 pm	**Open Public Hearing (60 min)**
1:40 pm	**FDA Presentation (90 min, including 15 min Q & A)** BLA Review Team
3:20 pm	**Committee Discussion, Voting, and Vote Explanation (150 min)**
5:50 pm	**Closing Remarks (10 min)** Peter Marks, M.D., Ph.D. Director, CBER
6:00 pm	**Meeting Adjourned** Marie DeGregorio, B.A. Designated Federal Officer, FDA

Discussion Topic 1

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.

Discussion Topic 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.

Discussion Topic 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 with a confirmed mutation in the *DMD* gene.

Discussion Topic 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.

Discussion Question, Then Voting

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

Thank You!