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Cellular, Tissue, and Gene Therapies Advisory Committee

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

Applicant: Sarepta Therapeutics, Inc.

Advisory Committee Planning Working Group
Office of Therapeutic Products
Center for Biologics Evaluation and Research, FDA

May 12, 2023
Duchenne Muscular Dystrophy: Serious, Progressive Condition

• X-linked monogenic disorder

• Affects ~1 in 3,300 boys

• Progressive muscle weakness

• Standard of care: long-term corticosteroid treatment

• Loss of ambulation by age ~12 years

• Death typically by young adulthood, due to cardiomyopathy or respiratory insufficiency
Urgent Unmet Medical Need

• Even with improved standard of care and available therapies
  – Estimated that for every 1,000 patients age 20-25 years with DMD, 86 lose their lives each year\textsuperscript{1}
  – Estimated life expectancy for patients with DMD receiving ventilatory support is ~ 30 years\textsuperscript{2}

• Since 2016, four exon-skipping drugs have received FDA approval via Accelerated Approval pathway
  – For only a subset of patients, with specific mutations in \textit{DMD} gene
  – Clinical benefit for all four drugs remains to be verified

\textsuperscript{1}Broomfield J. (2021) Life expectancy in Duchenne muscular dystrophy. \textit{Neurology} 97:e2304-e2314
Product Overview: SRP-9001

- cDNA for normal dystrophin ~14 kb
- AAV vector can carry only ~4.7 kb DNA genome
- SRP-9001 encodes a protein designed to include only certain domains of normal dystrophin
- Intended to be expressed in skeletal and cardiac muscle
- Genome packaged in AAV vector (serotype rh74)
Regulatory Flexibility and Concerns

- Regulatory flexibility enables faster delivery of safe and effective drugs – small-molecule drugs as well as biologics, such as gene therapies
- Accelerated Approval: uncertainty regarding clinical benefit
- Many shortened forms of dystrophin exist, but with very different properties → each must be assessed on its own merits
- Sarepta's micro-dystrophin differs fundamentally from the shortened forms of dystrophin in BMD patients and with exon-skipping drugs
- Evidence for whether Sarepta’s micro-dystrophin is “reasonably likely predict clinical benefit” is only available from SRP-9001 clinical program
- Gene therapy carries unique risks not present for small-molecule drugs
Concerns Related to SRP-9001

• Manufacturing and Nonclinical
• Surrogate Endpoint
• Safety
• Confirmatory Study
Terminology Differences

**Sarepta**
- SRP-9001 dystrophin
- percent dystrophin positive fibers
- percent normal expression in Western blot
- Prespecified subgroup analysis

**FDA**
- Sarepta’s micro-dystrophin
- Percent Sarepta’s micro-dystrophin positive fibers
- Expression of Sarepta’s micro-dystrophin measured on Western blot, compared to control
- Not statistically rigorous analysis: not prespecified for hypothesis testing, and did not use a prespecified multiplicity adjustment strategy
Manufacturing Concerns
SRP-9001 Manufacturing Changes: Lower Purity of Process B (To-Be-Marketed) Product

• Major changes in manufacturing process affected purity
  – Initial nonclinical and clinical studies used SRP-9001 made by Process A → higher percentage of full capsids
  – Subsequent nonclinical and clinical studies used SRP-9001 made by Process B → lower percentage of full capsids → lower purity
Nonclinical Concerns

Theresa Chen, PhD
Office of Pharmacology/Toxicology, OTP, CBER
Nonclinical Data: $Dmd^{mdx}$ Mice

- $Dmd^{mdx}$ mice have phenotype that is less severe than that of patients with DMD.
- Administration of SRP-9001 in 4-8 week old $Dmd^{mdx}$ mice resulted in:
  - Expression of Sarepta’s micro-dystrophin: heart (supraphysiological levels compared to normal dystrophin) > skeletal muscles > liver
  - Partial improvement in specific force and in muscle pathology
- No correlation between specific force and expression of Sarepta’s micro-dystrophin (measured by Western blot)

The expression profile and functionality of Sarepta’s micro-dystrophin differs from that of normal dystrophin expressed from the endogenous $DMD$ gene.
Nonclinical Data: $Dmd^{mdx}$ Rats

- $Dmd^{mdx}$ rats have a more severe phenotype than $Dmd^{mdx}$ mice, with reduction in spontaneous motor activity at 3 months old\(^1\)
- Administration of SRP-9001 in 3-4 week old $Dmd^{mdx}$ rats resulted in
  - Expression of Sarepta’s micro-dystrophin protein
  - Increased spontaneous activity and reduced dystrophic pathology in skeletal muscles
- Administration of SRP-9001 did not result in similar improvement in 3-5 month old $Dmd^{mdx}$ rats despite robust expression of Sarepta’s micro-dystrophin

Expression of Sarepta’s micro-dystrophin did not predict functional response in these studies, since motor function improvement was observed in younger but not in older rats.

Challenges in Translation of Nonclinical Data

- Limitations due to species-specific differences
  - Disease pathophysiology
  - Compensatory mechanisms
  - Regenerative capacity of muscle fibers
  - Physiology of skeletal and cardiac muscles

- Limitations due to study design
  - Robustness
  - Potential for bias
  - Missing data/documentation

These studies formed the basis for clinical development of SRP-9001, but were not designed to help determine adequacy of the candidate surrogate endpoint.
Surrogate Endpoint Concerns

Emmanuel Adu-Gyamfi, PhD
Office of Gene Therapy, OTP, CBER
What Makes a Surrogate Endpoint “Reasonably Likely to Predict Clinical Benefit”?

- Judgment is made on a case-by-case basis

- Predicts an effect on a clinical endpoint (direct measure of whether patient feels or functions better, or survives longer)

- Support
  - Biological plausibility
  - Empirical evidence
  - Clinical studies
Biological Plausibility
Sarepta’s Micro-dystrophin is Structurally Distinct from Normal Dystrophin

Sarepta’s micro-dystrophin
(138 kDa)

Normal dystrophin
(427 kDa)

Sarepta's micro-dystrophin lacks multiple functional domains present in normal dystrophin.
BMD Patient’s Shortened Dystrophin and Sarepta’s Micro-dystrophin are Structurally Different

- Sarepta’s micro-dystrophin was designed based on a mutated, shortened dystrophin found in a patient with Becker muscular dystrophy with relatively mild symptoms.
- Sarepta’s micro-dystrophin lacks multiple protein-interaction domains.
Sarepta's micro-dystrophin

Normal dystrophin

BMD patient
England et al. 1990
Passos-Bueno 1994
Morandi 1993
Koenig 1989

Images modified from: Applicant; Nelson and Ervasti 2021
20

Sarepta’s micro-dystrophin

BMD patient
England et al. 1990

Images modified from: Applicant; Nelson and Ervasti 2021
Is Sarepta’s Micro-dystrophin Sufficient to Retain Essential Function of Normal Dystrophin?

• There are important differences in the structure of Sarepta’s micro-dystrophin compared to normal dystrophin
  – Sarepta's micro-dystrophin lacks multiple functional domains

• Sarepta’s micro-dystrophin also differs from shortened dystrophins produced in patients with BMD

• It is unclear whether Sarepta’s micro-dystrophin can function in humans sufficiently similarly either to normal dystrophin, or to the shortened dystrophins produced in patients with BMD or treated with exon-skipping drugs
Empirical Evidence

Mike Singer, MD, PhD
Office of Clinical Evaluation, OTP, CBER
Lack of Empirical Evidence for Sarepta’s Micro-dystrophin

- Epidemiology
- Pathophysiology
- Therapeutic
- Pharmacologic
Clinical Studies

Mike Singer, MD, PhD
Xiaofei Wang, PhD
Office of Clinical Evaluation, OTP, CBER
North Star Ambulatory Assessment (NSAA) Score is Effort-Dependent and Process-Dependent

- Effort-dependent
  - Affected by motivation and effort of patient
  - Affected by coaching/encouragement from family members, caregivers, and medical staff
  - Results of open-label studies are difficult to interpret

- Process-dependent
  - Affected by consistency of administration
  - Comparison of results from different sources/studies are not reliable
DMD Progression is Heterogeneous and Nonlinear

- DMD progression for individual patients is quite heterogeneous
- Patients initially show improvement on standard-of-care treatment alone – in the age range in Applicant’s clinical studies – so it is crucial to distinguish that improvement from any effect of SRP-9001
Lower Purity of Process B  
(To-Be-Marketed) SRP-9001

• Initial clinical studies used Process A SRP-9001 → higher percentage of full capsids

• Subsequent clinical studies used Process B SRP-9001 → lower percentage of full capsids → lower purity

• Dose is based on vector genomes, so although the transgene is the same:
  – **Efficacy**: Empty capsids may interfere with transduction
  – **Safety**: More capsids → increased antigenic load → may increase risk of anti-capsid immune responses
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 (48 weeks)
  -_three different doses_
  - Part 2 (48 weeks)
  - functionally open-label

- Part 1 (48 weeks)
- Crossover study:
- Part 2 (48 weeks)

**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

Images: Modified from Applicant
Micro-dystrophin Expression ≠ Clinical Effect

Randomized, Double-Blind, Placebo-Controlled Studies are Necessary for SRP-9001

• Open-label, single-arm studies are interpretable when
  – Disease is homogeneous
  – Drug has large effect size
  – Clinical endpoint is objective

• But randomized, double-blind, placebo-controlled studies are needed in situations like this one
  – DMD progression is heterogeneous
  – Improvement occurs with standard of care alone
  – Any effect of SRP-9001 likely to be moderate
  – Clinical endpoint is effort-dependent and process-dependent
Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment

Guidance for Industry

Many functional endpoints in clinical trials for dystrophinopathies include tasks performed by a patient in a clinical setting according to instructions administered by a health care professional. Such endpoints can be affected by the effort of the patient and/or coaching or encouragement by a family member, caregiver, or medical staff so that blinding to treatment is critical.
Clinical Studies: Four Analyses

1. ΔNSAA Total Score for patients receiving SRP-9001 vs. placebo
   *Data from Study 102 Part 1*

2. ΔNSAA Total Score for SRP-9001 vs. external controls
   *Data from all patients who received intended dose of SRP-9001*

3. Is expression of Sarepta’s micro-dystrophin associated with ΔNSAA Total Score?
   *Data from Study 102 Part 1*

4. Is expression of Sarepta’s micro-dystrophin associated with ΔNSAA Total Score?
   *Pooled data from Study 102 and Study 103*
Analysis 1

ΔNSAA Total Score for SRP-9001 patients vs. placebo

Data from Study 102 Part 1
Study 102 Part 1: Treatment Effect Not Statistically Significant

Difference in ΔNSAA Total Score for SRP-9001 vs. placebo at Year 1 (48 weeks)

0.8 ± 0.9 (LSM ± SE)

This difference is not statistically significant

95% CI: -1.0, 2.7

p = 0.37

Source: FDA
Abbreviations: CI, confidence interval; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error
# Study 102 Part 1: No Clear Dose-Response Effect

<table>
<thead>
<tr>
<th>Dose (vg/kg)</th>
<th>Fraction of Intended Dose</th>
<th>SRP-9001 Group (n = 19)</th>
<th>Placebo Group (n = 21)</th>
<th>ΔNSAA for SRP-9001 vs. Placebo [LSM (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.29 x 10^{13}</td>
<td>0.5X</td>
<td>6</td>
<td>21</td>
<td>0.7 (-2.5, 4.0)</td>
</tr>
<tr>
<td>8.94 x 10^{13}</td>
<td>0.67X</td>
<td>5*</td>
<td>21</td>
<td>2.6 (-0.04, 5.3)</td>
</tr>
<tr>
<td>1.33 x 10^{14}</td>
<td>1.0X</td>
<td>8</td>
<td>21</td>
<td>-1.5 (-4.0, 1.0)</td>
</tr>
</tbody>
</table>

*One of the 6 patients who received this dose did not undergo NSAA testing at Week 48.

Source: FDA

Abbreviations: CI, confidence interval; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment

- The 95% confidence intervals of the mean for each dose include zero (no effect), and patients who received the intended dose had the \textit{poorest} outcome.
- Definite conclusions cannot be drawn from this analysis, due to small sample size for each dose and potential imbalance in baseline characteristics (e.g., age).
Subgroup Analysis Shows Inconsistent Results

4-5 year old patients
(39% of Study 102 patients)

<table>
<thead>
<tr>
<th>Study Week</th>
<th>SRP-9001 (LSM ± SE)</th>
<th>Placebo (LSM ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>4.3 ± 0.7</td>
<td>1.9 ± 0.7</td>
</tr>
</tbody>
</table>

6-7 year old patients
(61% of Study 102 patients)

<table>
<thead>
<tr>
<th>Study Week</th>
<th>SRP-9001 (LSM ± SE)</th>
<th>Placebo (LSM ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.5 ± 0.7</td>
<td>-0.2 ± 0.7</td>
</tr>
</tbody>
</table>

Source: FDA
Abbreviations: CI, confidence interval; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error
Does SRP-9001 Have an Effect on 4-5 Year Old Boys with DMD?

4-5 year old patients
(39% of Study 102 patients)

<table>
<thead>
<tr>
<th>Study Week</th>
<th>SRP-9001</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔNSAA Total Score (LSM ± SE)</td>
<td>ΔNSAA Total Score (LSM ± SE)</td>
</tr>
<tr>
<td>12</td>
<td>4.3 ± 0.7 (LSM ± SE)</td>
<td>1.9 ± 0.7 (LSM ± SE)</td>
</tr>
</tbody>
</table>

- Although the SRP-9001 group appears to show better outcome, the subgroup analysis is not statistically rigorous: not prespecified for hypothesis testing and no prespecified multiplicity adjustment strategy was used.
- Post hoc subgroup tests following an overall non-significant test in the study population as a whole can only be considered hypothesis-generating.

Source: FDA

Abbreviations: CI, confidence interval; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error
SRP-9001 Did Not Appear to Have an Effect on 6-7 Year Old Boys with DMD

6-7 year old patients (61% of Study 102 patients)

-0.2 ± 0.7 (LSM ± SE)
0.5 ± 0.7 (LSM ± SE)

• There was no difference between the SRP-9001 group and the placebo group
• Applicant’s explanation: imbalance in baseline NSAA Total Score for SRP-9001 and placebo groups
• But SRP-9001 group showed no improvement from baseline
• Other possible explanations: SRP-9001 ineffective, patients too old to benefit, too much muscle loss, small sample size, or some combination of factors?
Analysis 2

$\Delta$NSAA Total Score for SRP-9001 patients vs. external controls

Data from all patients who received intended dose of SRP-9001
Comparison to External Controls is Challenging to Interpret

• Applicant used propensity scores to compare $\Delta$NSAA Total Score for all patients who received intended dose, vs. external controls from
  – Cooperative International Neuromuscular Research Group Duchenne Natural History Study
  – Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD) Study
  – Placebo group of study conducted by Eli Lilly and Company

• Propensity model may not suitably account for influence of
  – Heterogeneity of DMD progression
  – Effort-driven and process-driven characteristics of NSAA
  – Unknown factors (in clinical study, would be balanced by randomization)
Analysis 3

Is expression of Sarepta’s micro-dystrophin associated with ΔNSAA Total Score?

Data from Study 102 Part 1

Xiaofei Wang, PhD
Office of Clinical Evaluation, OTP, CBER
SRP-9001 Key Biomarkers

Transduction Efficiency

Source: Modified from Applicant BLA
Abbreviations: DAPC, dystrophin-associated protein complex; PMDPF, percent Sarepta's micro-dystrophin positive fibers
FDA Used Western Blot Data to Quantify Expression of Sarepta’s Micro-dystrophin

- **Western blot assay**
  - Primary endpoint of Study 102 and Study 103
  - Measures absolute quantity of Sarepta’s micro-dystrophin (adjusted to muscle content)
  - Reported as percent (%) of control (i.e., relative to the quantity of normal dystrophin in normal muscle tissue)

- **Immunofluorescence**
  - Localizes Sarepta’s micro-dystrophin at sarcolemma membrane, and detects interaction with DAPC proteins
    - Fiber intensity
    - Percent Sarepta’s micro-dystrophin positive fibers (PMDPF)
  - PMDPF is not a fully quantitative assay
    - PMDPF does not clearly reflect expression of Sarepta’s micro-dystrophin
    - Level of Sarepta’s micro-dystrophin in muscle fibers can vary substantially
Study 102: Expression of Sarepta’s Micro-dystrophin Across Various Dose Levels

- Expression of Sarepta’s micro-dystrophin increased in a dose-dependent manner.

- High inter-subject variability was observed for the intended dose level (1.33 x 10^{14} \text{ vg/kg})

Source: FDA
No Clear Association Between Sarepta’s Micro-Dystrophin Expression and ΔNSAA Total Score

- The range of ΔNSAA Total Score at Year 1 (Week 48) was similar for SRP-9001 group (-3 to 6) and placebo group (-4 to 6)
- Limited data to evaluate the relationship between Sarepta’s micro-dystrophin and ΔNSAA Total Score
- No clear association between expression of Sarepta’s micro-dystrophin at Week 12 and ΔNSAA Total Score at Year 1

Note: *Adjusted for age and baseline NSAA Total Score
Source: FDA
Abbreviation: NSAA, North Star Ambulatory Assessment
No Clear Association Between Sarepta’s Micro-Dystrophin Expression and ΔNSAA Total Score

• At group level, there was also no clear association in Study 102 Part 1 between expression of Sarepta’s micro-dystrophin at Week 12 and ΔNSAA Total Score at Year 1.

• Limited data suggest improved ΔNSAA Total Score with increased micro-dystrophin expression in younger patients (4-5 years old). Because of limited data, results must be interpreted with caution.

Source: FDA

Abbreviations: NSAA, North Star Ambulatory Assessment; SE, standard error
Analysis 4

Is expression of Sarepta’s micro-dystrophin associated with ΔNSAA Total Score?

_Pooled data from Study 102 and Study 103_
Open-label Design May Affect ΔNSAA Total Score

- **Dataset:**
  - **Study 102 Part 1:** randomized, double-blind, placebo-controlled
  - **Study 102 Part 2 and Study 103:** open-label

- Available clinical data suggest that the impact of open-label design on ΔNSAA Total Score may not be ruled out
  - Open-label studies show higher ΔNSAA Total Score improvement compared to double-blind Study 102 Part 1

- Open-label design may drive association between Sarepta’s micro-dystrophin expression and ΔNSAA Total Score

Source: FDA
Abbreviations: NSAA, North Star Ambulatory Assessment
Open-label Design Without Concurrent Control May Confound Association of Micro-dystrophin and ΔNSAA Total Score

- Open-label design of Study 102 Part 2 and Study 103 without a concurrent control (e.g., placebo)
  - It is unclear if the ΔNSAA Total Score improvement was due to SRP-9001, or open-label design, or baseline characteristics, or some combination
  - It is challenging to interpret the correlation analysis results
- Sarepta’s micro-dystrophin accounts for 11% of variation in ΔNSAA Total Score after adjustment for baseline age and NSAA Total Score (i.e., $R^2 = 0.11$)
- The correlation is not sufficiently persuasive to consider expression of Sarepta’s micro-dystrophin “reasonably likely to predict clinical benefit”

Note: *Adjusted for age and baseline NSAA Total Score
Source: FDA
Abbreviation: NSAA, North Star Ambulatory Assessment
Summary of Relationship Between Sarepta’s Micro-dystrophin Expression and ΔNSAA Total Score

• Correlation analysis using only Study 102 Part 1 (randomized, double-blind, placebo-controlled study design)
  • Overall, no clear association was observed between Sarepta’s micro-dystrophin expression and ΔNSAA Total Score
  • Limited data suggest improved ΔNSAA Total Score with increased micro-dystrophin expression in younger patients (4-5 years), but must be interpreted with caution

• Correlation analysis using pooled datasets (Study 102 Part 1 & Part 2, and Study 103)
  • Open-label design without concurrent control (Study 102 Part 2 and Study 103) makes interpretation of correlation analysis results challenging
  • The correlation results indicate that Sarepta’s micro-dystrophin accounts for 11% of variation in ΔNSAA Total Score
  • Overall, 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 surrogate endpoint*

Concerns Related to SRP-9001

• Manufacturing and Nonclinical

• Surrogate Endpoint
  – Biological plausibility: Lacks important functional domains
  – Empirical evidence: None available
  – Clinical studies:
    ◦ Challenging to distinguish effect of SRP-9001 vs. standard of care
    ◦ Unclear which patients may benefit from SRP-9001
    ◦ No clear association of micro-dystrophin and ΔNSAA

• Safety
• Confirmatory Study
Safety

Mike Singer, MD, PhD
Office of Clinical Evaluation, OTP, CBER
Overall Safety Concerns

• Serious adverse events (SAEs) observed in clinical studies of SRP-9001
  – hepatotoxicity
  – myocarditis
  – immune-mediated myositis

• Possible cross-reactivity with other AAV vector-based gene therapy products

• Safety of AAV vector-based gene therapy products as a class
  – hepatotoxicity
  – thrombotic microangiopathy
• 85 patients with DMD in Studies 101, 102, 103
• Mean age 7.1 years (range 3.2 – 20.2 years)
• All exposed to one-time intravenous infusion of SRP-9001
  – Process A: n = 45
  – Process B: n = 40
• Median follow-up: 1.8 years (range 6 months – 4.8 years)
SRP-9001 Safety Overview

• No deaths

• Adverse reactions (incidence $\geq 5\%$)
  – Vomiting (61%)
  – Nausea (40%)
  – Acute liver injury (37%)
  – Pyrexia (24%)
  – Thrombocytopenia (12%)

• Adverse events of special interest
  – Hepatotoxicity
  – Cardiotoxicity: myocarditis and elevated troponin-I
  – Myositis

• Immunogenicity
Hepatotoxicity

- **Acute Liver Injury** – *defined as at least one of:*
  - Gamma-glutamyl transferase (GGT) > 3 x upper limit of normal range (ULN)
  - Glutamate dehydrogenase (GLDH) > 2.5 x ULN
  - Alkaline phosphatase (ALP) > 2 x ULN
  - Alanine transaminase (ALT) > 3 x baseline

- **Acute Serious Liver Injury** – *defined as*
  - Meets criteria for Acute Liver Injury and
  - Death, life-threatening event, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, or other important medical event

- Similar frequency of Acute Serious Liver Injury requiring hospitalization
  - Process A SRP-9001: 3 patients
  - Process B SRP-9001: 2 patients

- All events resolved without clinical sequelae
Cardiotoxicity: Myocarditis

Case 1 [age > 7 years]
– Received Process B SRP-9001
– Chest pain on Study Day 3
– Elevated troponin-I (peak > 40 ng/ml on Study Day 6)
– Resolved with residual changes on cardiac MRI
– Required addition of aldosterone and carvedilol to baseline regimen for chronic cardiomyopathy

Case 2 [age < 7 years]
– Received Process B SRP-9001 or placebo
– High fever, vomiting, seizure-like episode within 24 hours of treatment
– Elevated troponin-I (2,724 pg/mL, normal ≤ 45 pg/mL)
– Hypotension → Pediatric Intensive Care Unit (PICU)
– Treated with corticosteroids, antibiotics, and IV fluids
– Resolved without sequelae

Myocarditis was not observed in Process A SRP-9001 studies
Cardiotoxicity: Elevated Troponin-I

• Troponin-I > ULN: marker of heart muscle injury
• Study results
  – Study 101 and Study 102: Troponin-I not assessed
  – Study 103: Troponin-I > ULN in 4 patients (Process B SRP-9001)
• No clinical complications or acute cardiac imaging changes
• Unknown long-term effects on underlying DMD cardiomyopathy
Life-Threatening Immune-Mediated Myositis with Process B SRP-9001

- 8-year old patient in Study 103 with deletion of exons 3 – 43 in *DMD* gene

- Muscle weakness, dysphagia, dysphonia, difficulty sitting and walking about 1 month after receiving SRP-9001

- Muscle biopsy
  - Inflammatory myopathy, on background of chronic dystrophinopathy
Immunogenicity

• Used a clinical trial enzyme-linked immunosorbent assay (ELISA) to assess baseline pre-existing anti-AAVrh74 total binding antibodies

• Enrollment criterion: titer ≤ 1:400

• Four patients were excluded from clinical studies due to elevated titers (> 1:400)

• Only patients with titer ≤ 1:100 actually received SRP-9001

• High anti-AAVrh74 total binding antibody titers following SRP-9001 infusion
Potential Cross-Reactivity

- Antibodies against one AAV serotype can cross-react with capsids of other AAV serotypes
- Patients for whom SRP-9001 is ineffective likely will not be able to receive any future approved AAV vector-based gene therapy
## Serious Adverse Events Observed With AAV-Based Gene Therapies

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Serious Adverse Event</th>
<th>Vector Serotype</th>
<th>Indication</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
<td>Elevated liver enzymes</td>
<td>AAV5</td>
<td>• hemophilia</td>
<td>Intravenous</td>
</tr>
<tr>
<td></td>
<td>Liver failure</td>
<td>AAV8</td>
<td>• X-linked myotubular myopathy</td>
<td>Intravenous</td>
</tr>
<tr>
<td></td>
<td>Elevated liver enzymes, serious liver injury, liver failure and death</td>
<td>AAV9</td>
<td>• spinal muscular atrophy</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>Thrombocytopenia, hemolytic anemia, acute kidney injury</td>
<td>AAV9</td>
<td>• spinal muscular atrophy</td>
<td>Intravenous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Duchenne muscular dystrophy</td>
<td></td>
</tr>
</tbody>
</table>

Sources: FDA Briefing Document for Cellular, Tissue, and Gene Therapies Advisory Committee Meeting #70: Toxicity Risks of Adeno-Associated Virus Vectors for Gene Therapy (September 2021); Zolgensma U.S. Prescribing Information (2023)
Potential Impact of Accelerated Approval on Completion of Study 301
Study 301 (EMBARK Study)

• Study 301 design
  – Part 1: 52-week, randomized, double-blind, placebo-controlled period, with primary endpoint $\Delta$NSAA Total Score from baseline
  – Part 2: 52-week cross-over period

• Study 301 is fully enrolled
  – ~120 patients (~80 in US) age 4-7 years
  – 1:1 randomization to receive either SRP-9001 or placebo
Study 301 (EMBARK Study)

• 52-week outcome assessment for last patient in Part 1 expected at end of Q3 2023

• Topline results of Part 1 expected later this year (Q4 2023)

• Part 1 is proposed as confirmatory study if SRP-9001 receives Accelerated Approval

• Status of US patients by June 1, 2023
  – ~29 will cross over to Part 2
  – ~50 will still be in Part 1 follow-up period
  – ~25 (>1/3 of placebo arm) may not have received SRP-9001
Summary (I)

• Manufacturing and Nonclinical
  – Important purity differences in SRP-9001 manufactured by Process A vs. Process B
  – Results of nonclinical studies were inconsistent
  – Limitations in extrapolation from animal models to humans

• Surrogate Endpoint
  – Biological plausibility: Lacks important functional domains
  – Empirical evidence: None available
  – Clinical studies:
    ◦ Challenging to distinguish effect of SRP-9001 vs. standard of care
    ◦ Unclear which patients may benefit from SRP-9001
    ◦ No clear association of micro-dystrophin and ΔNSAA
Summary (II)

• Safety
  – Adverse events with SRP-9001, particularly Process B product
  – Potential cross-reactivity to future gene therapies
  – AAV-based gene therapy products as a class

• Confirmatory Study
  – Ability to complete Study 301 (EMBARK) to establish clinical efficacy of SRP-9001?
Summary (III)

• The uncertainties make it difficult to consider Sarepta’s micro-dystrophin a surrogate endpoint “reasonably likely to predict clinical benefit” in support of Accelerated Approval.

• Data from Phase 3 study will be available later this year, and should help clarify these issues.

• Patients likely have only one chance to receive an AAV vector-based gene therapy for DMD → critical that it is effective and safe.