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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 year¹
 - Estimated life expectancy for patients with DMD receiving ventilatory support is ~ 30 years²
- Since 2016, four exon-skipping drugs have received FDA approval via Accelerated Approval pathway
 - For only a subset of patients, with specific mutations in *DMD* gene
 - Clinical benefit for all four drugs remains to be verified

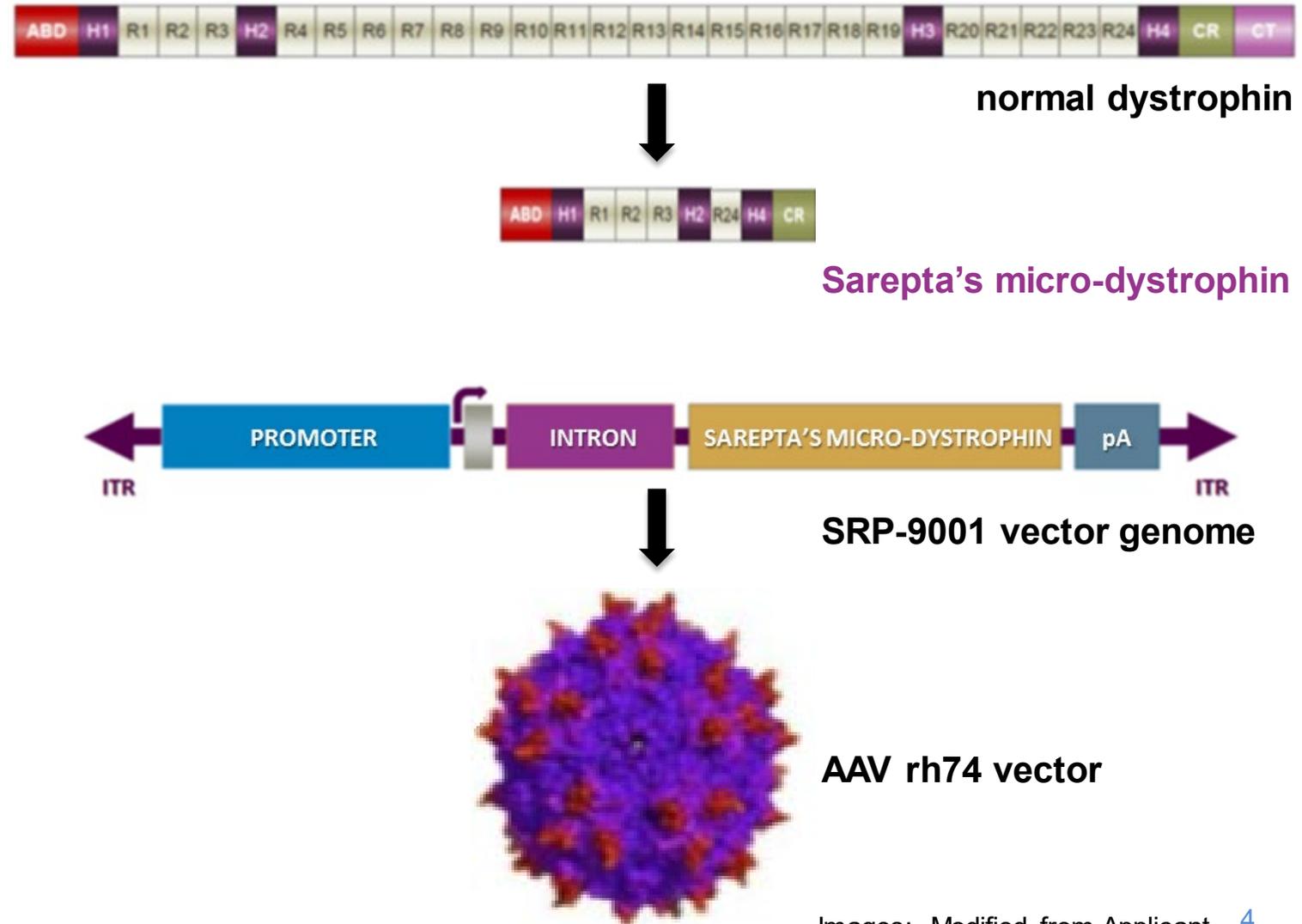
¹Broomfield J. (2021) Life expectancy in Duchenne muscular dystrophy. *Neurology* 97:e2304-e2314

²Landfeldt E. (2020) Life expectancy at birth in Duchenne muscular dystrophy: a systematic review and meta-analysis. *Eur J Epidemiol* 35:643–653

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**

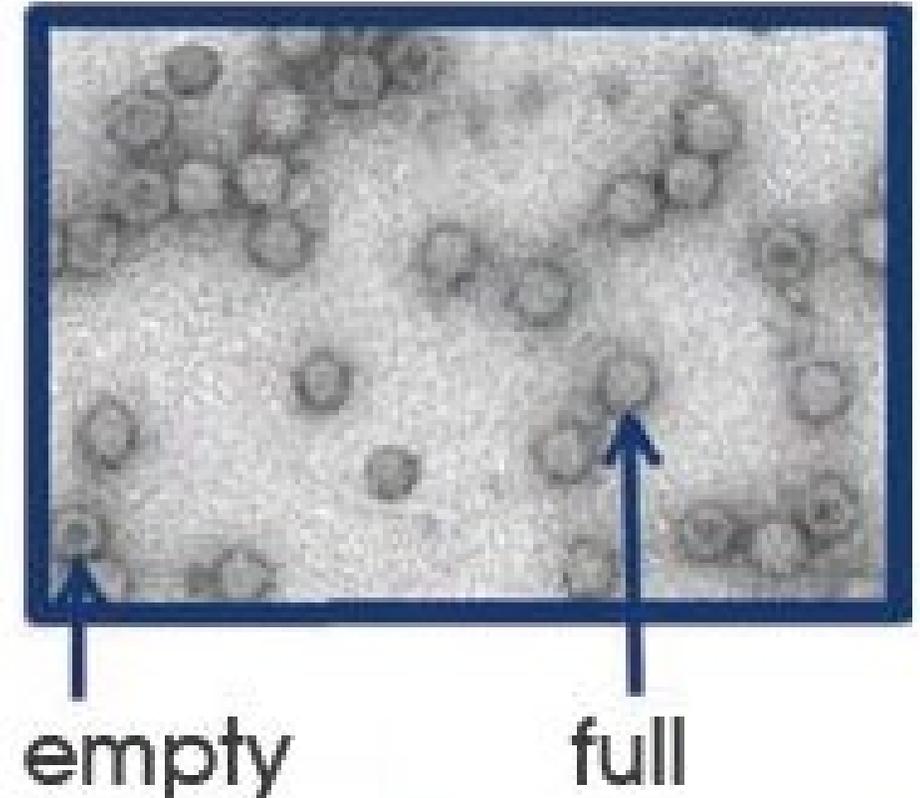


Image: www.2bscientific.com/getmedia/7a84110e-3faf-4b3c-aff3-a7185fdae455/AAV-ELISA.JPG

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 old¹
- 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.

¹Larcher T. et al (2014) *PLoS One* 9:e110371

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”?

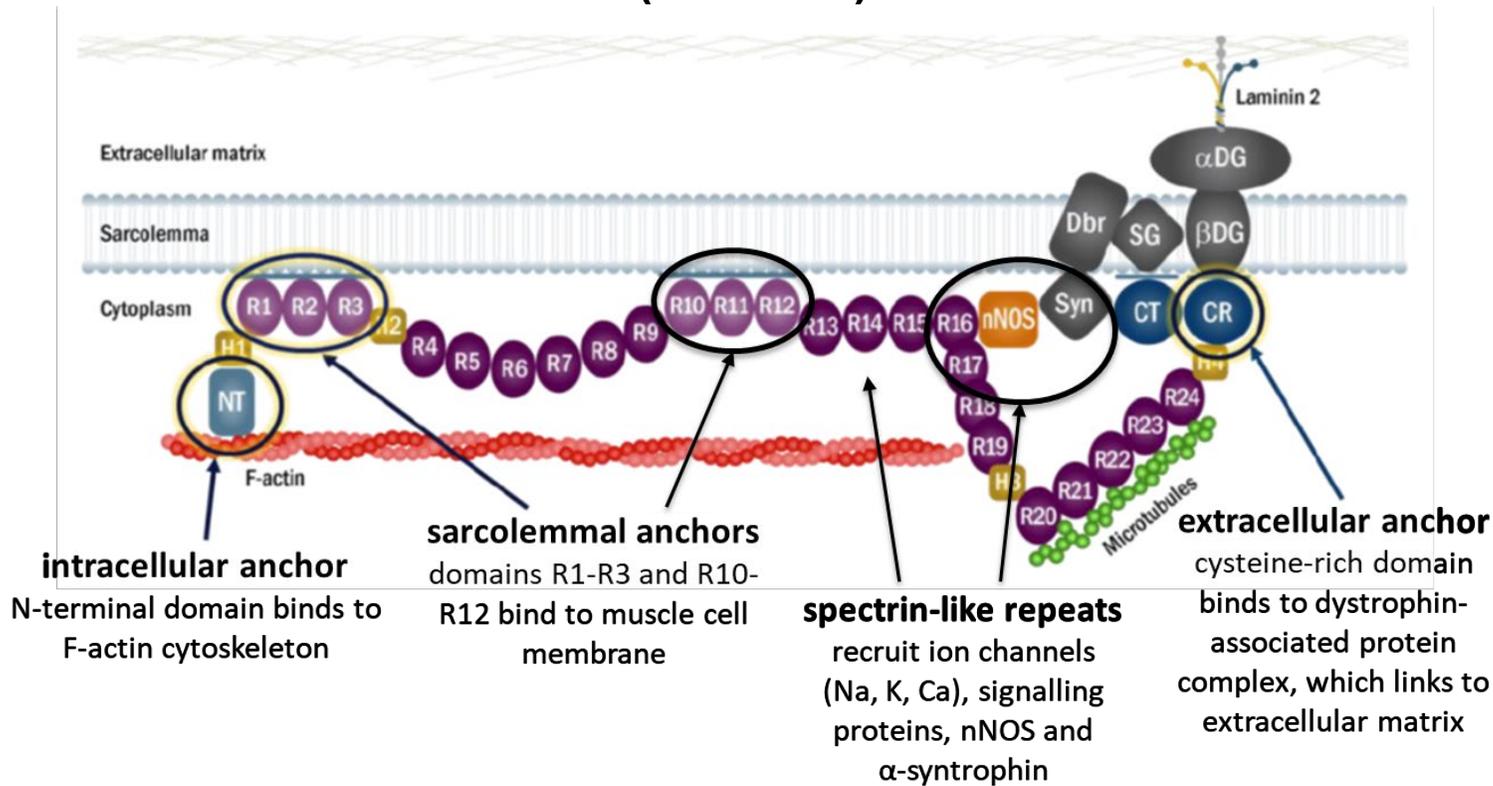
- Judgment is made on a case-by-case basis
- Predicts an effect on a clinical endpoint (direct measure of whether patient feels or functions better, or survives longer)
- Support
 - Biological plausibility
 - Empirical evidence
 - Clinical studies

Biological Plausibility

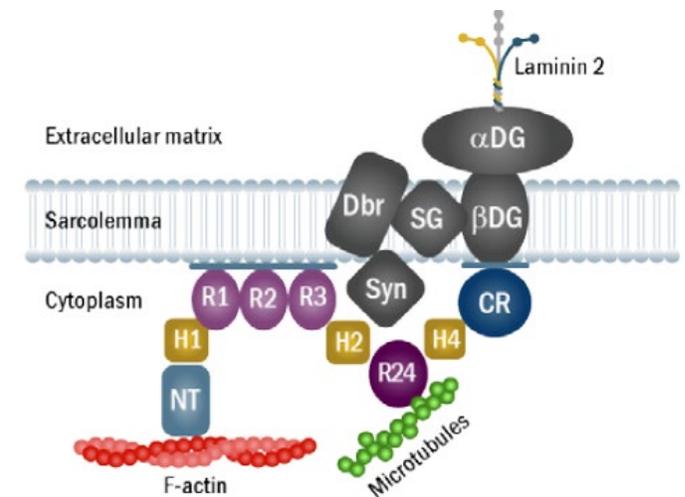
Sarepta's Micro-dystrophin is Structurally Distinct from Normal Dystrophin



normal dystrophin
(427 kDa)



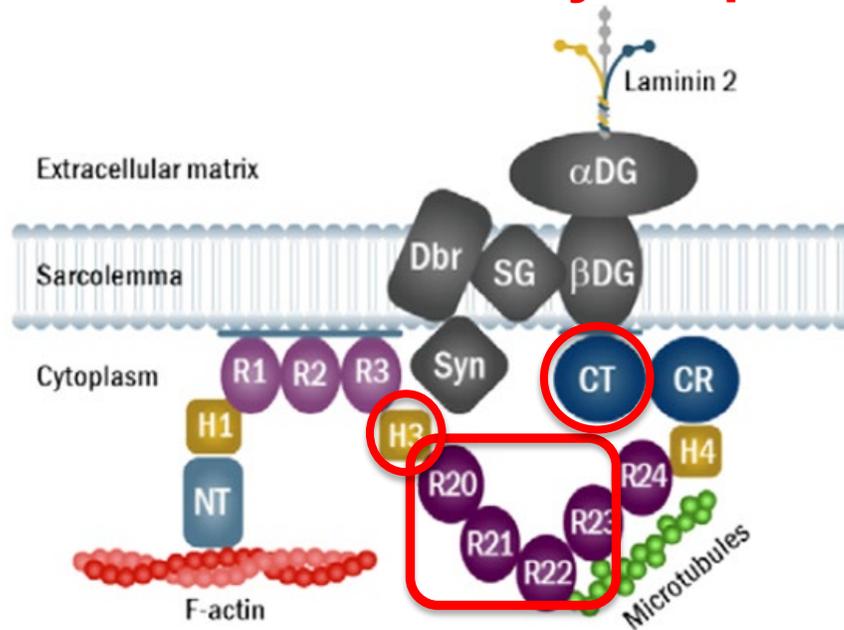
Sarepta's micro-dystrophin
(138 kDa)



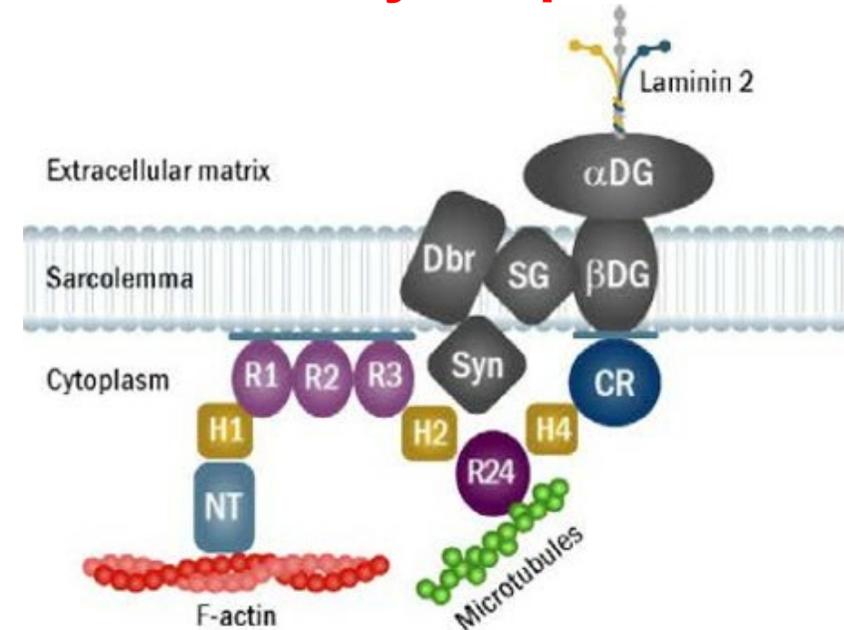
Sarepta's micro-dystrophin lacks multiple functional domains present in normal dystrophin

BMD Patient's Shortened Dystrophin and Sarepta's Micro-dystrophin are Structurally Different

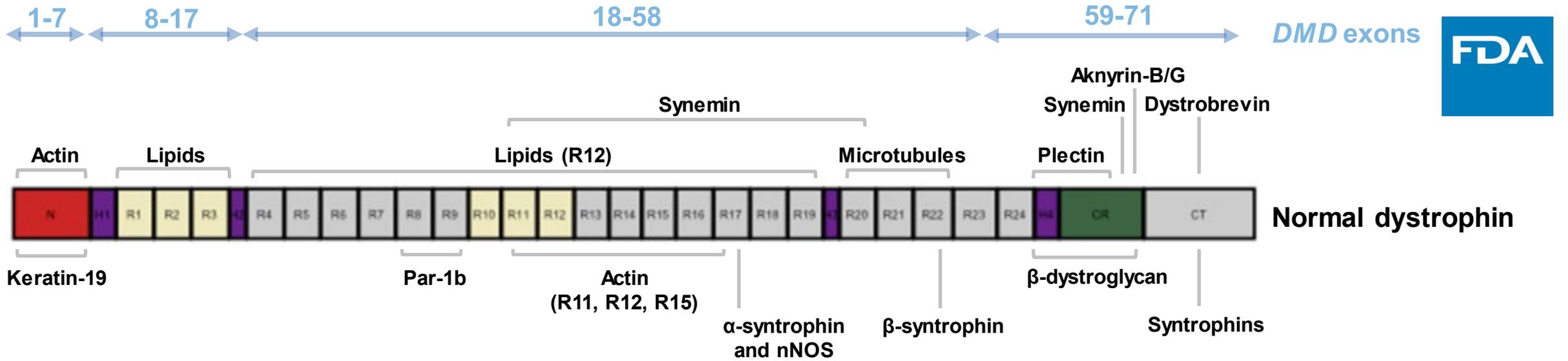
BMD patient's shortened dystrophin



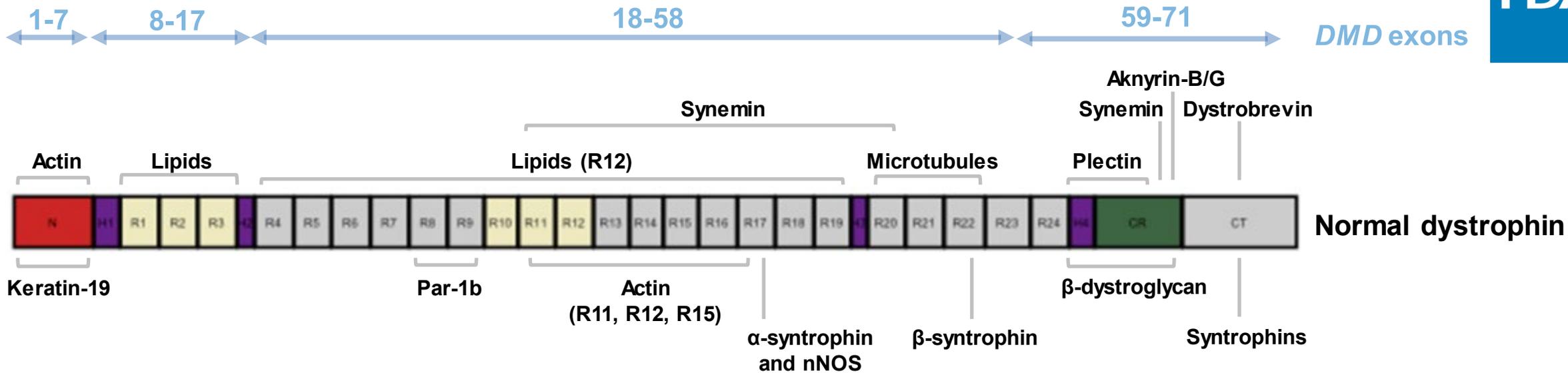
Sarepta's micro-dystrophin



- 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



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

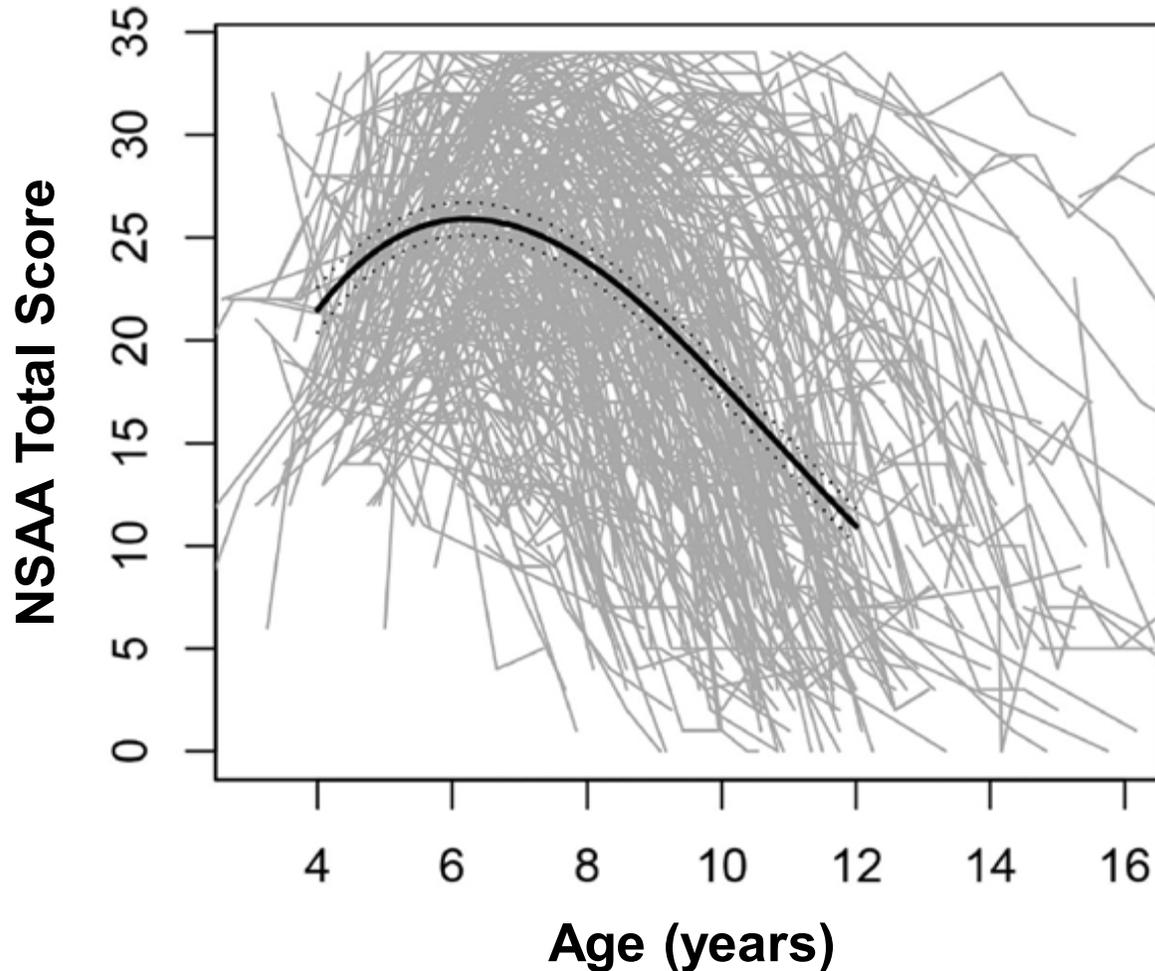
North Star Ambulatory Assessment (NSAA)

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]

- 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



Micro-dystrophin Expression \neq 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. Δ NSAA Total Score for patients receiving SRP-9001 vs. placebo
Data from Study 102 Part 1
2. Δ NSAA 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 Δ NSAA Total Score?
Data from Study 102 Part 1
4. Is expression of Sarepta's micro-dystrophin associated with Δ NSAA Total Score?
Pooled data from Study 102 and Study 103

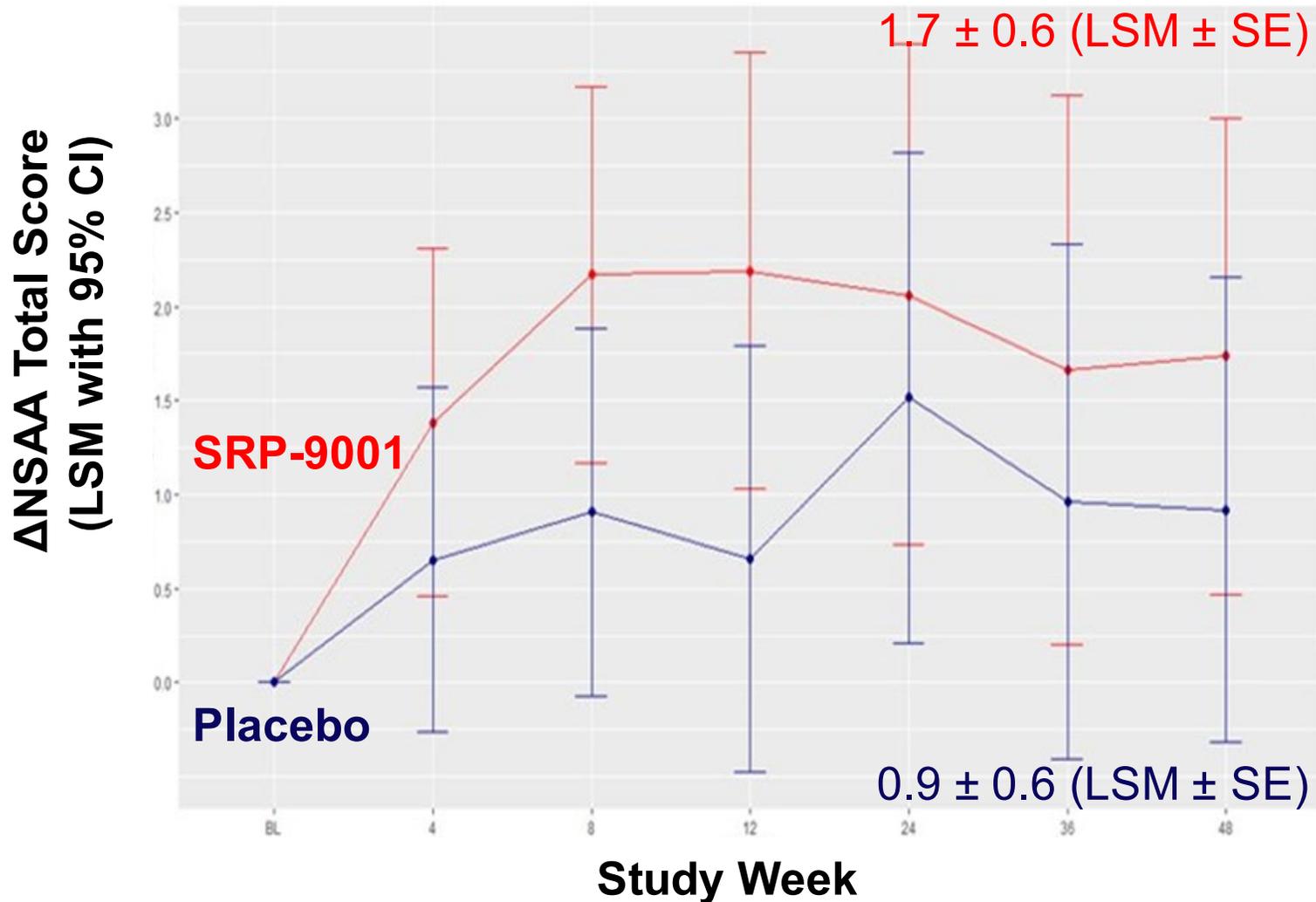
Analysis 1

Δ NSAA 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 \pm SE)

This difference is not statistically significant

95% CI: -1.0, 2.7

$p = 0.37$

Study 102 Part 1:



No Clear Dose-Response Effect

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

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

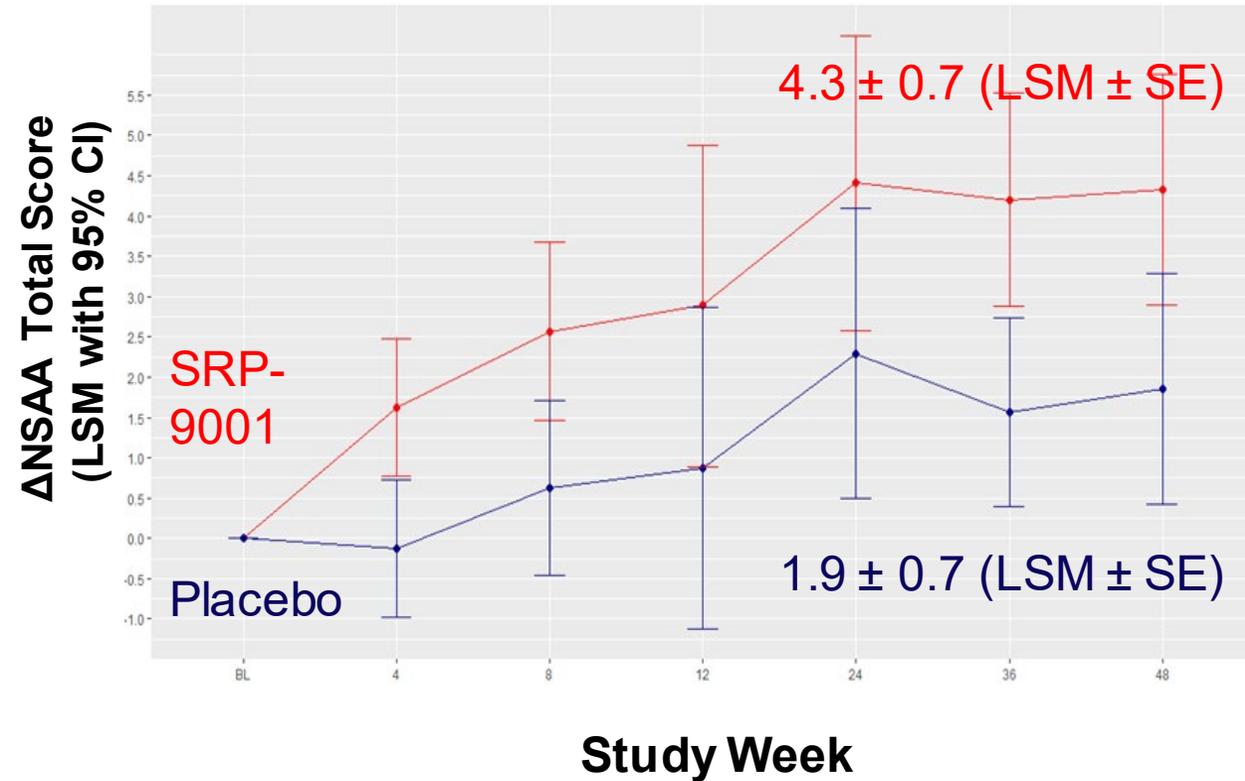
Source: FDA

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

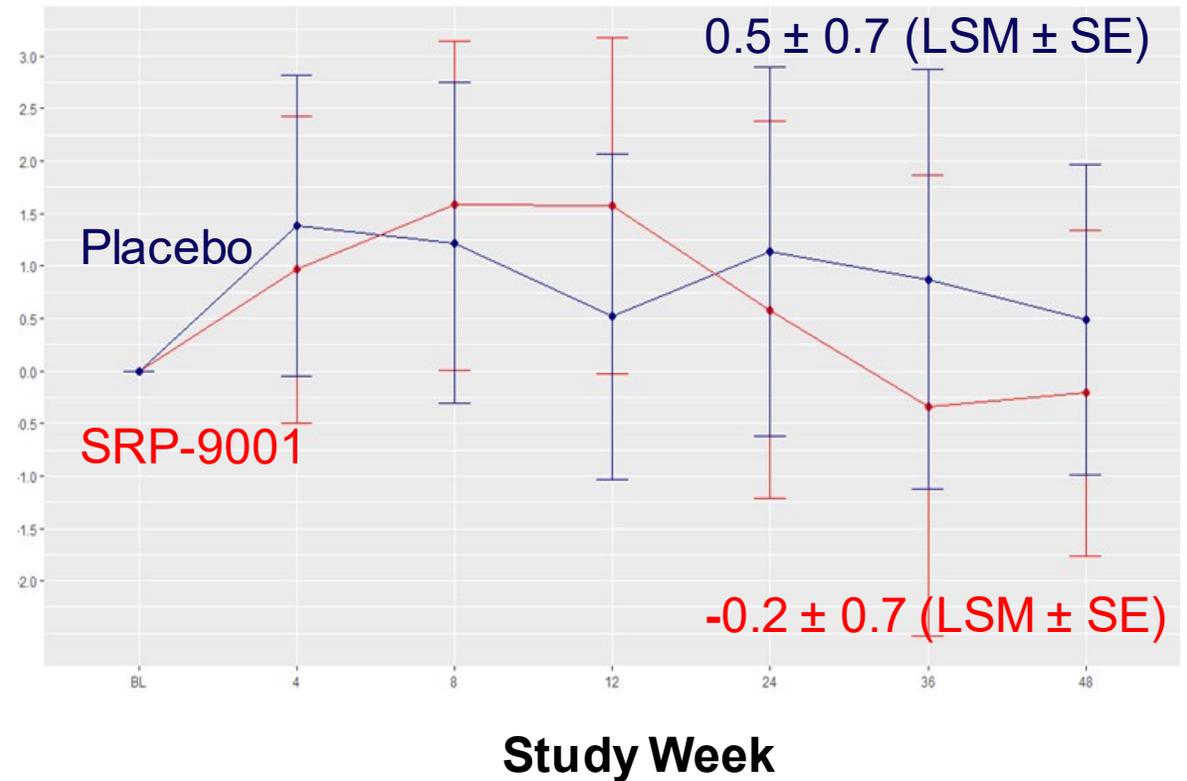
- The 95% confidence intervals of the mean for each dose include zero (no effect), and patients who received the intended dose had the *poorest* outcome
- Definite conclusions cannot be drawn from this analysis, due to small sample size for each dose and potential imbalance in baseline characteristics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

Subgroup Analysis Shows Inconsistent Results

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



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

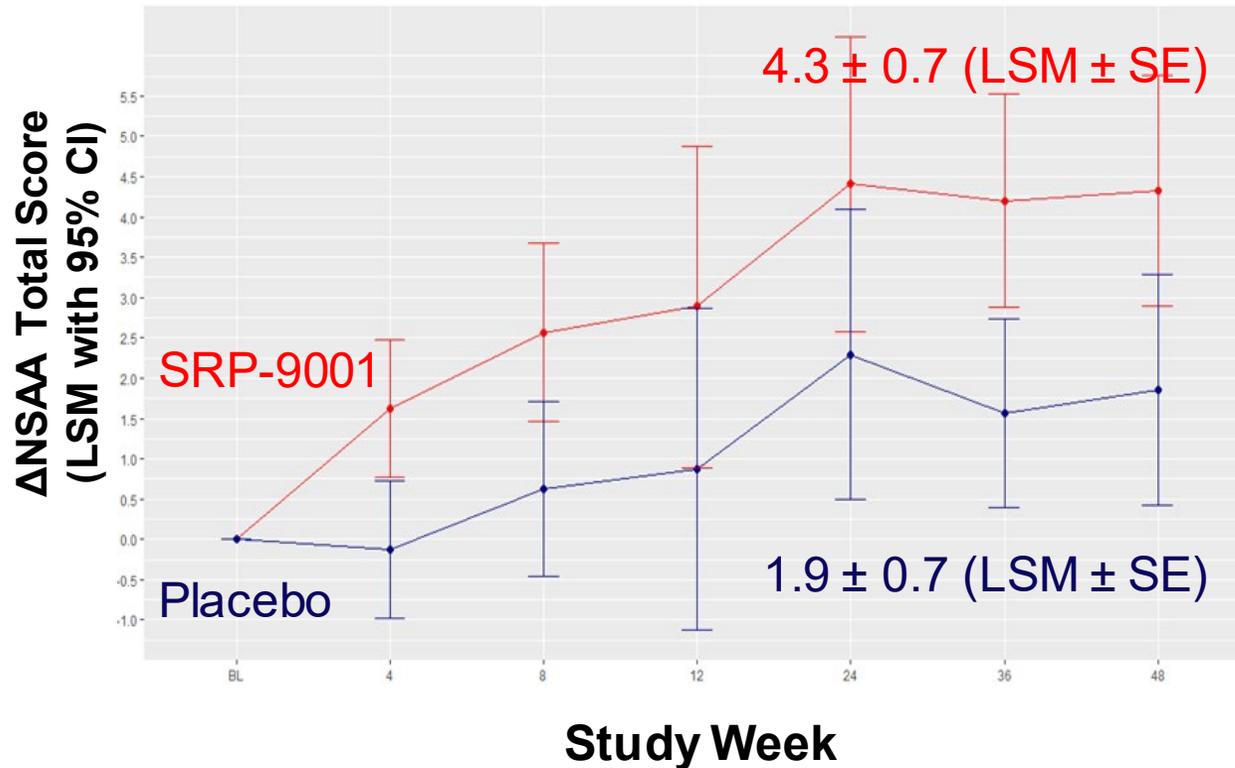


Source: FDA

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)



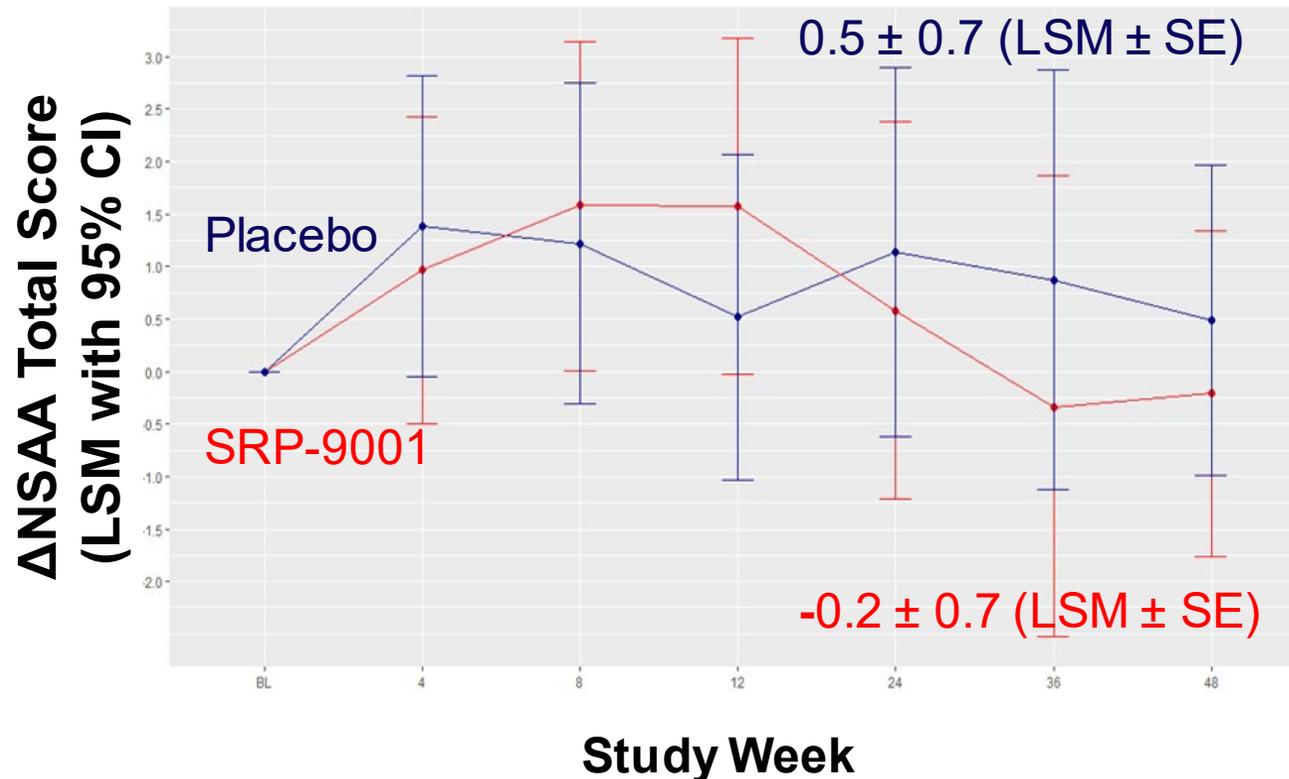
- Although the SRP-9001 group appears to show better outcome, the subgroup analysis is not statistically rigorous: not prespecified for hypothesis testing and no prespecified multiplicity adjustment strategy was used
- Post hoc subgroup tests following an overall non-significant test in the study population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



Source: FDA

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

- 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

Δ 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 Δ 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

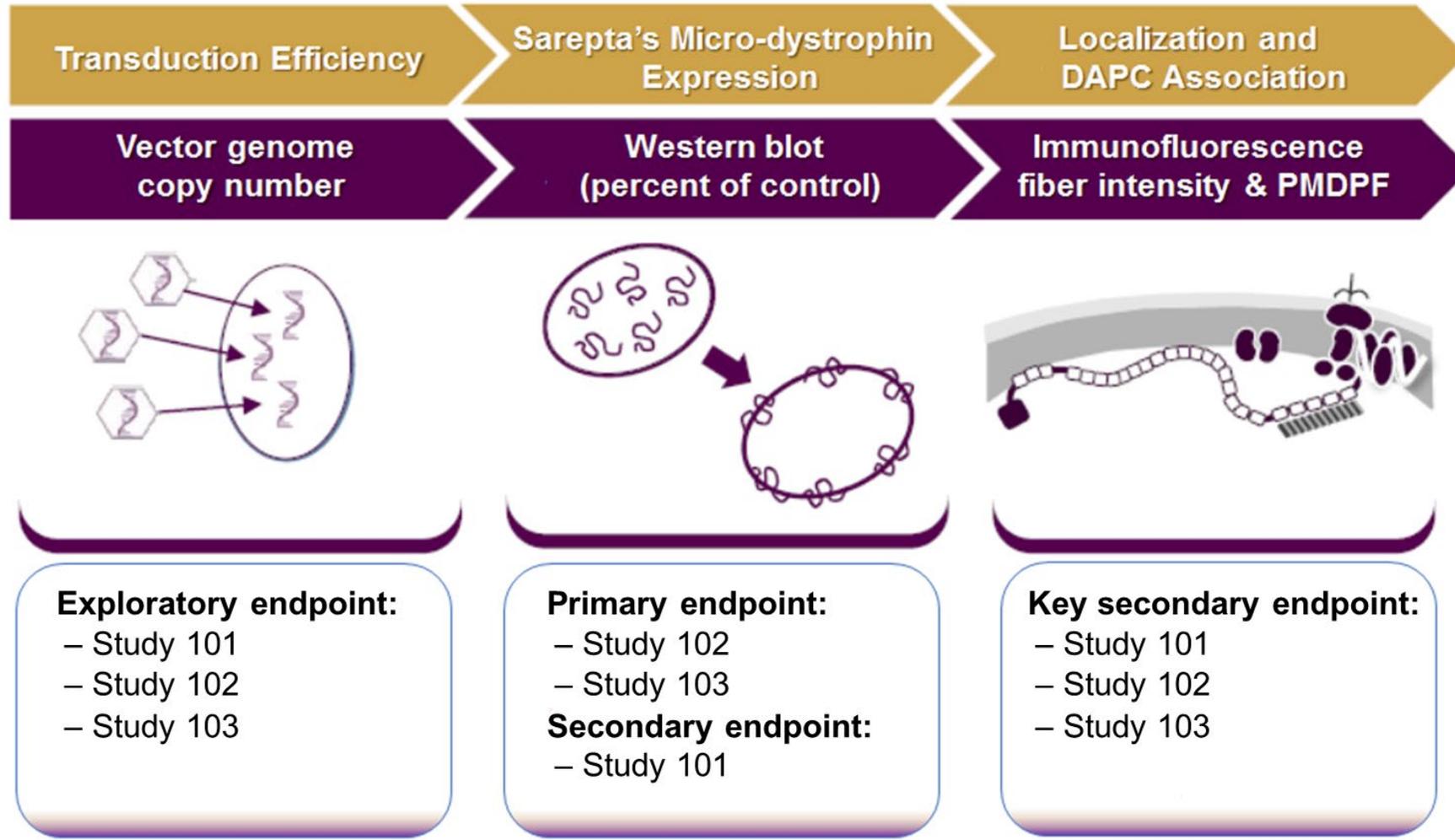
Is expression of Sarepta's micro-dystrophin associated with Δ NSAA Total Score?

Data from Study 102 Part 1

Xiaofei Wang, PhD

Office of Clinical Evaluation, OTP, CBER

SRP-9001 Key Biomarkers



WESTERN BLOT IS QUANTITATIVE

PMDPF IS NOT FULLY QUANTITATIVE

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)

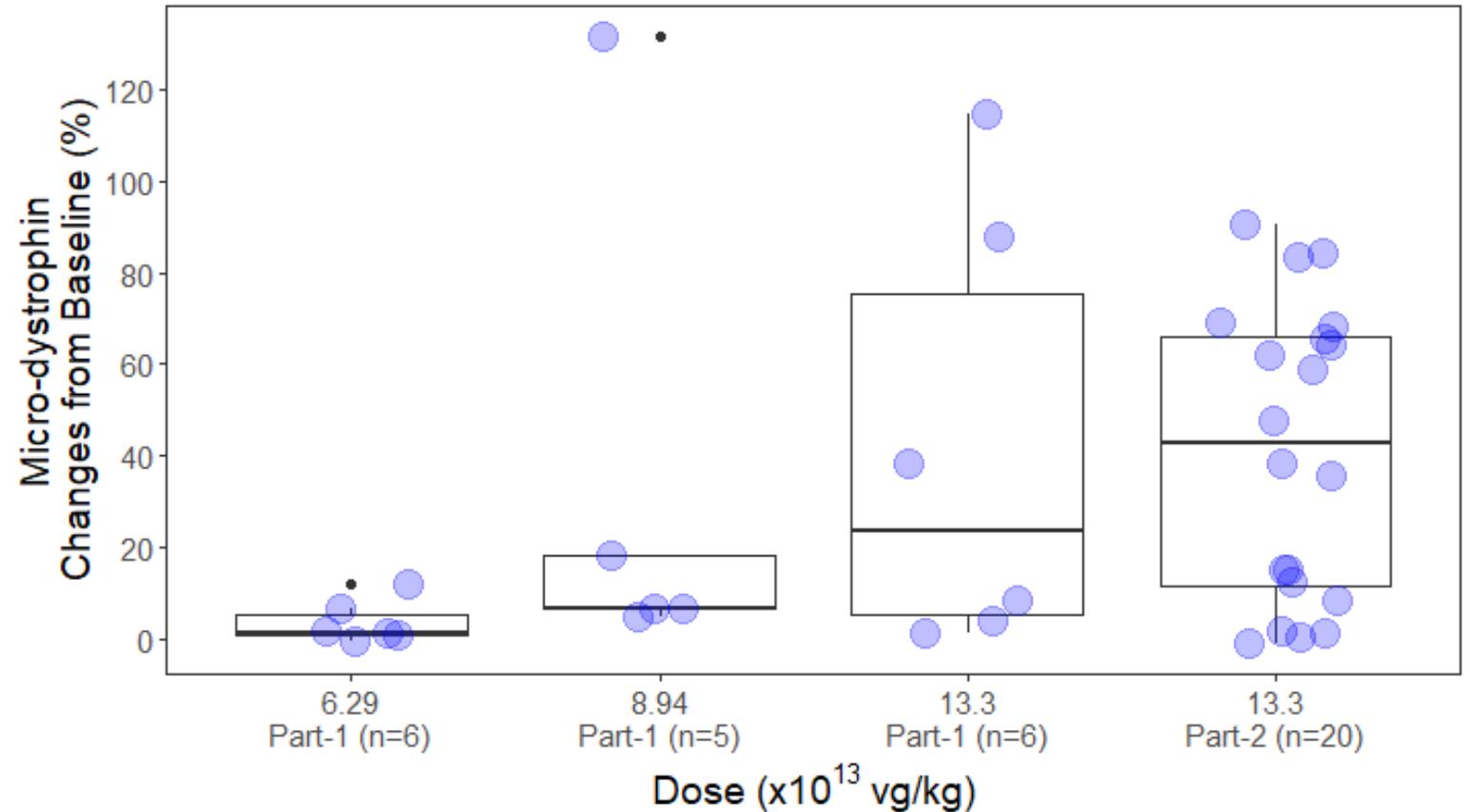
- **Immunofluorescence**

- 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 (1.33×10^{14} vg/kg)

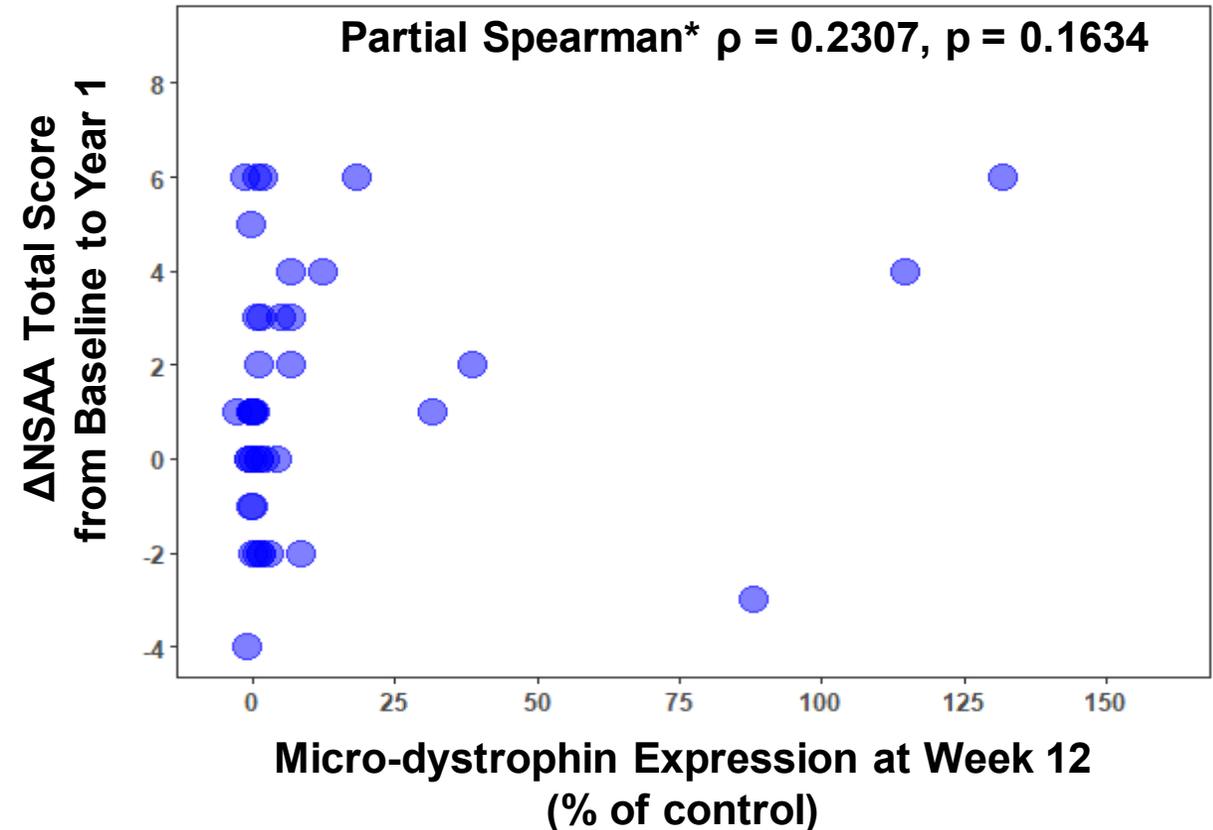


Source: FDA

No Clear Association Between Sarepta's Micro-Dystrophin Expression and Δ NSAA Total Score



- The range of Δ NSAA 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 Δ NSAA Total Score
- No clear association between expression of Sarepta's micro-dystrophin at Week 12 and Δ NSAA Total Score at Year 1



Note: *Adjusted for age and baseline NSAA Total Score Year 1: Week 48 post-administration

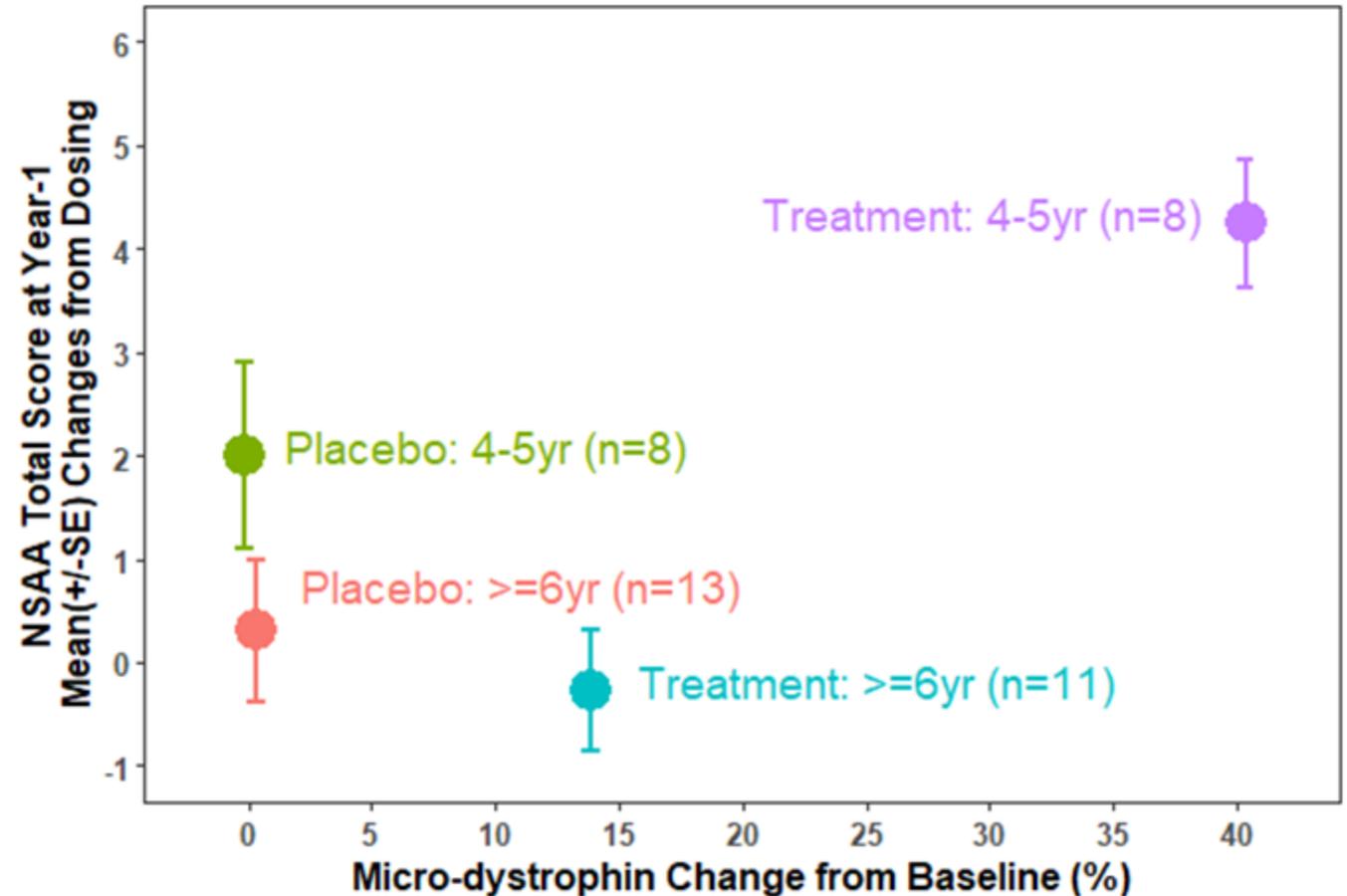
Source: FDA

Abbreviation: NSAA, North Star Ambulatory Assessment

No Clear Association Between Sarepta's Micro-Dystrophin Expression and Δ NSAA 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 Δ NSAA Total Score at Year 1.
- Limited data suggest improved Δ NSAA 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

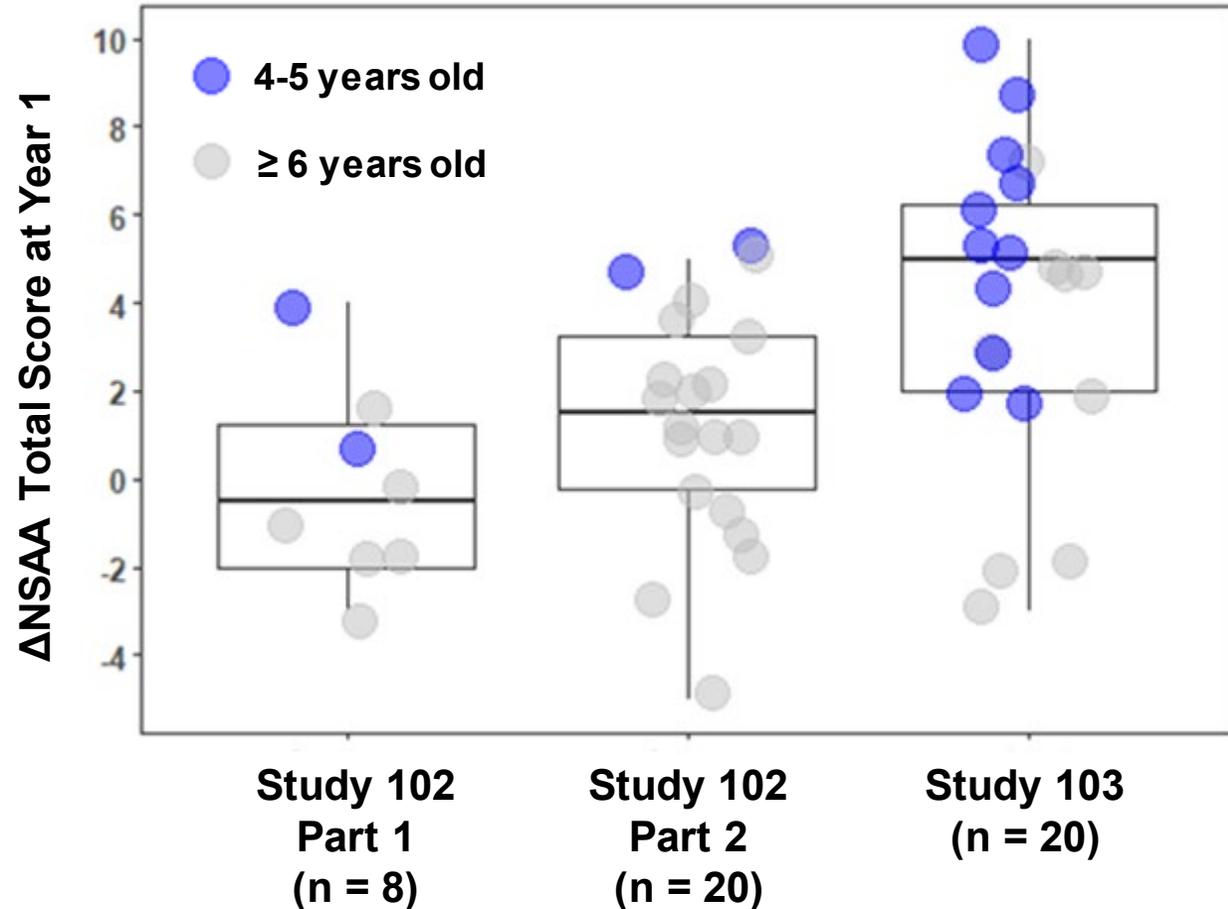
Is expression of Sarepta's micro-dystrophin associated with Δ NSAA Total Score?

Pooled data from Study 102 and Study 103

Open-label Design May Affect Δ NSAA 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 Δ NSAA Total Score may not be ruled out
 - Open-label studies show higher Δ NSAA Total Score improvement compared to double-blind Study 102 Part 1
- Open-label design may drive association between Sarepta's micro-dystrophin expression and Δ NSAA Total Score



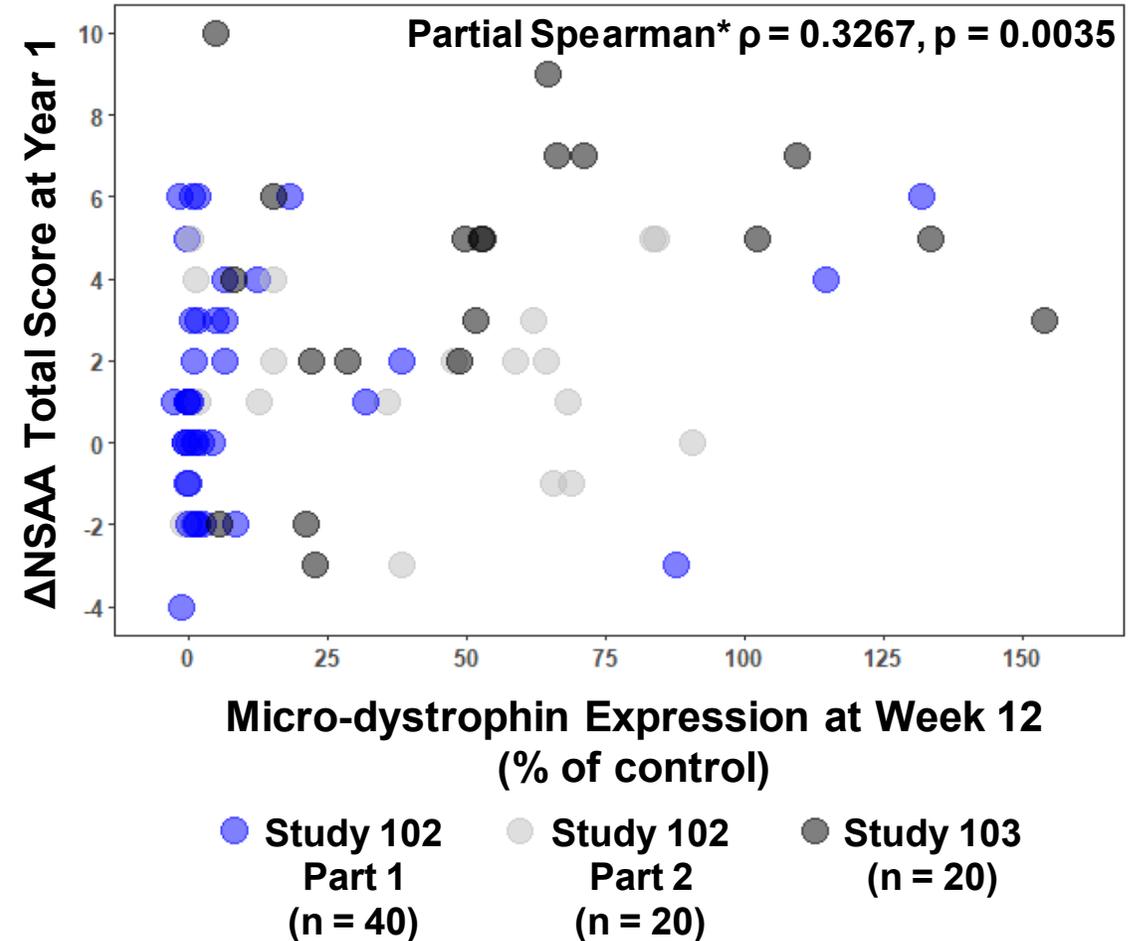
Source: FDA

Abbreviations: NSAA, North Star Ambulatory Assessment

Open-label Design Without Concurrent Control May Confound Association of Micro-dystrophin and Δ NSAA 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 Δ NSAA 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 Δ NSAA 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 Δ NSAA 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 Δ NSAA Total Score
 - Limited data suggest improved Δ NSAA 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 Δ NSAA 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*

*Fleming, T. R., & Powers, J. H. (2012). Biomarkers and surrogate endpoints in clinical trials. *Statistics in Medicine* 31(25):2973-2984

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 Δ NSAA
- 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

Safety of SRP-9001 in Clinical Studies: Exposure Analysis Set



- 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 \leq 1:400
- Four patients were excluded from clinical studies due to elevated titers ($>$ 1:400)
- Only patients with titer \leq 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



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

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 (EMBARC Study)



- Study 301 design
 - Part 1: 52-week, randomized, double-blind, placebo-controlled period, with primary endpoint Δ 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 (EMBARC 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 Δ NSAA

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 (EMBARC) to establish clinical efficacy of SRP-9001?

Summary (III)

- The uncertainties make it difficult to consider Sarepta's microdystrophin 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

Thank You!



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