Clinical Updates: Gene Therapy Programs

SRP-9001 (Duchenne muscular dystrophy):
Two-year Functional Data, Study 101

SRP-9003 (Limb-girdle muscular dystrophy type 2E):
18-month Functional Data, Cohort 1

DOUG INGRAM
President and CEO

LOUISE RODINO-KLAPAC, PH.D.
Sr. Vice President, Gene Therapy

September 28, 2020
8:30 a.m. ET

SAREPTA THERAPEUTICS

Welcome and Introduction

Doug Ingram
President and CEO

SAREPTA THERAPEUTICS

Forward-Looking Statements

This presentation contains "forward-looking statements." Any statements contained in this presentation that are not statements of historical fact may be deemed to be forward-looking statements. Words such as "believes," "anticipates," "plans," "expects," "will," "intends," "potential," "possible" and similar expressions are intended to identify forward-looking statements. These forward-looking statements include statements regarding the potential benefits of SRP-9001 and SRP-9003, potential market opportunities and expected timelines and milestones.

These forward-looking statements involve risks and uncertainties, many of which are beyond our control. Known risk factors include, among others: success in preclinical trials and clinical trials, especially if based on a small patient sample, does not ensure that later clinical trials will be successful; the data presented in this release may not be consistent with the final data set and analysis thereof or result in a safe or effective treatment benefit; different methodologies, assumptions and applications we utilize to assess particular safety or efficacy parameters may yield different statistical results, and even if we believe the data collected from clinical trials of our product candidates are positive, these data may not be sufficient to support approval by the FDA or foreign regulatory authorities; if the actual number of patients suffering from DMD and LGMD is smaller than estimated, our revenue and ability to achieve profitability may be adversely affected; we may not be able to execute on our business plans and goals, including meeting our expected or planned regulatory milestones and timelines, clinical development plans, and bringing our product candidates to market, due to a variety of reasons, some of which may be outside of our control, including possible limitations of company financial and other resources, manufacturing limitations that may not be anticipated or resolved for in a timely manner, regulatory, court or agency decisions, such as decisions by the United States Patent and Trademark Office with respect to patents that cover our product candidates and the COVID-19 pandemic; and even if Sarepta's programs result in new commercialized products, Sarepta may not achieve the expected revenues from the sale of such products; and those risks identified under the heading "Risk Factors" in Sarepta's most recent Annual Report on Form 10-K for the year ended December 31, 2019, and most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) as well as other SEC filings made by the Company which you are encouraged to review.

Any of the foregoing risks could materially and adversely affect the Company's business, results of operations and the trading price of Sarepta's common stock. For a detailed description of risks and uncertainties Sarepta faces, you are encouraged to review the SEC filings made by Sarepta. We caution investors not to place considerable reliance on the forward-looking statements contained in this presentation. Sarepta does not undertake any obligation to publicly update its forward-looking statements based on events or circumstances after the date hereof.

Clinical Update: Gene Therapy Programs
SRP-9001 (Duchenne muscular dystrophy)

Louise Rodino-Klapac, Ph.D.
Sr. Vice President, Gene Therapy

SAREPTA THERAPEUTICS

Durability is a Key Consideration in the Era of Gene Transfer Therapy Development

Durability of Transgenes Delivered via AAV Vectors (To Date)

DISEASE	TRANSGENE PERSISTENCE
Hemophilia B	**Canine (AAV2/8)**: 8 years[1,*]
	Nonhuman primate (AAV2): ~5 years[2,†] **Human (AAV2):** 10 years[3,*]
	Human (AAV8): 3 years[4,†]
SMA	**Mouse (AAV9)**: >250 days[5,†] **Human (AAV9)**: 5 years[6,†]
LGMD	**Mouse (AAVrh74)**: >24 months[7,†] **Human (AAVrh74)**: 18 months[8,†]
DMD	**Canine (AAV9)**: 8 years[9,*,†]
	Human (AAVrh74): >2 years[10,11,†]

*Transgene persistence determined by presence in tissues. †Persistence of treatment effect.

1. Niemeyer GP, et al. *Blood.* 2009;113(4):797-806. 2. Nathwani AC, et al. *Mol Ther.* 2011;19(5):876-885. 3. Buchlis G, et al. *Blood.* 2012;119(13):3038-3041. 4. Nathwani AC, et al. *N Engl J Med.* 2014;371(21):1994-2004. 5. Foust KD, et al. *Nat Biotechnol.* 2010;28(3):271-274. 6. Novartis Press Release. Zolgensma® data shows rapid, significant, clinically meaningful benefit in SMA including prolonged event-free survival, motor milestone achievement and durability now up to 5 years post-dosing. https://www.novartis.com/news/media-releases/zolgensma-data-shows-rapid-significant-clinically-meaningful-benefit-sma-including-prolonged-event-free-survival-motor-milestone-achievement-and-durability-now; Published March 24, 2020. Accessed September 2, 2020. 7. Pozgai E, et al. Poster presented at: ASGCT 23rd Annual Meeting; May 12-15, 2020; Virtual Format. #1137. 8. Rodino-Klapac L, et al. Poster presented at: 25th International Annual Congress of the World Muscle Society; September 30-October 2, 2020; Virtual format. P.140. 9. Li J, et al. *Mol Ther.* 2016;24(Supp):S284. 10. Mendell JR, et al. *JAMA Neurol.* 2020. Online ahead of print. doi: 10.1001/jamaneurol.2020.1484. 11. Mendell J, et al. Poster presented at: 25th International Annual Congress of the World Muscle Society; September 30-October 2, 2020; Virtual format. P.280.

Muscle & Neuronal Cellular Biology: A Case For Therapeutic Durability

DMD gene transfer therapy (including SRP-9001) aims to target skeletal and cardiac muscle cells

- **Skeletal muscle**
  - Multinucleated contractile cells (myofibers), post-mitotic[1,2]
  - **Neonatal juvenile stages:** number of myofibers remain constant, but each myofiber grows by fusion of satellite cells (postnatal muscle stem cells) and their nuclei[2]
  - **Adult mammalian skeletal muscle:** stable under normal conditions, with only sporadic fusion of satellite cells to compensate for muscle turnover caused by daily wear and tear[2]
    - Intercostal skeletal muscle cells estimated to have an average age of 15.1 years in adults[3]
- **Cardiomyocytes**
  - **Low turnover:** Less than 50% of cardiomyocytes are exchanged during a normal lifespan[4]
  - Turnover decreases exponentially with age and is <1% per year in adults[4]

SRP-9001 (rAAVrh.74.MHCK7.micro-dystrophin) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.

1. Partridge TA. *Gene Ther*. 2002;9(11):752-753. 2. Yin H, et al. *Physiol Rev*. 2013;93(1):23-67. 3. Spalding KL, et al. *Cell*. 2005;122(1):133-143. 4. Bergmann O, et al. *Science.* 2009;324(5923):98-102.

Durability: Muscle as a Substrate for Gene Transfer Therapy

Factors influencing durability of AAV gene therapy in muscle[1]

- Viral vector transduction and biodistribution
- Choice of promoter
- Corticosteroid use
- Target tissue

Long-term durability of AAV gene therapy has been demonstrated in canine nonclinical models for up to 8 years after treatment[2]

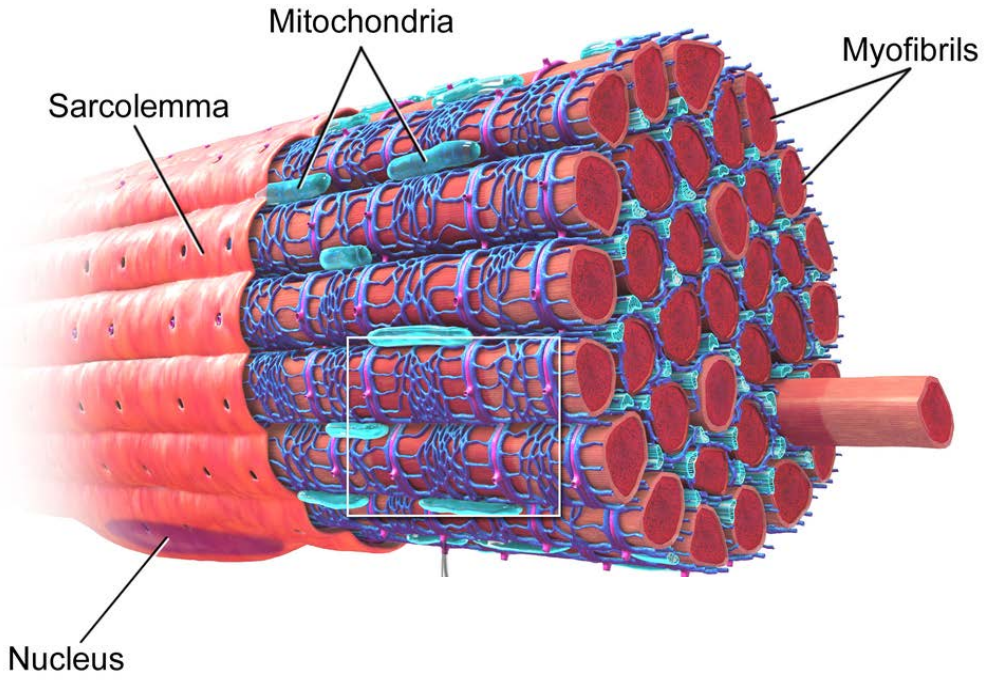


Image from Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436. - Own work.

AAV, adeno-associated virus.

1. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-274.
2. Li J, et al. *Mol Ther.* 2016;24(Supp):S284.

Duchenne Muscular Dystrophy

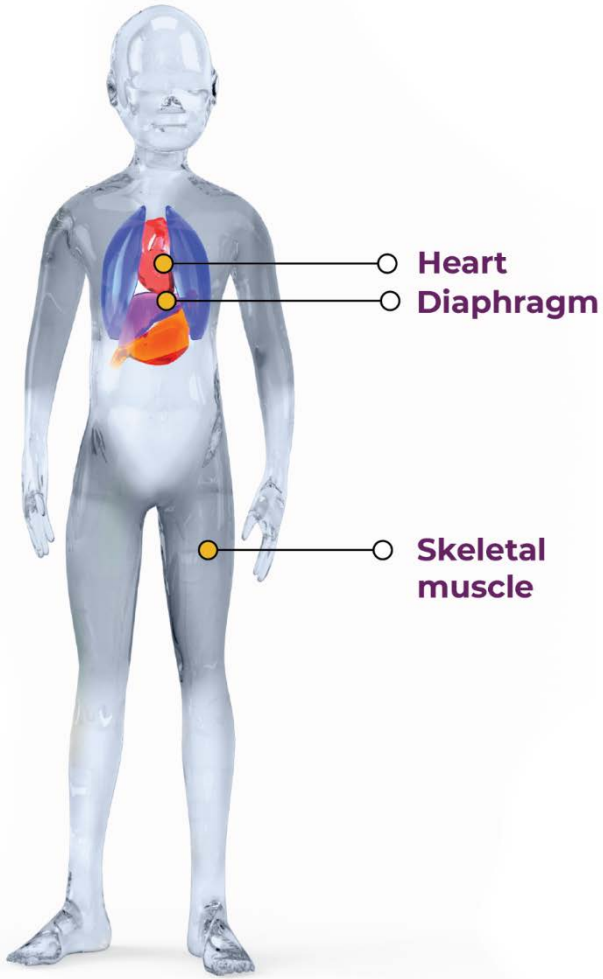
Micro-dystrophin SRP-9001 Clinical Update

Study 101 (N=4)

Duchenne Muscular Dystrophy (DMD)

DMD affects approximately 1 in 3,500-5,000 males worldwide[1]

- DMD is a rare, fatal neuromuscular genetic disease inherited in an X-linked recessive pattern[2]
- Muscle weakness becomes increasingly noticeable by age 3 to 5, and most patients use a wheelchair by the time they are 11[2]
- During adolescence, cardiac and respiratory muscle deterioration lead to serious, life-threatening complications[3]



1. National Institutes of Health. Genetics Home Reference. Duchenne and Becker muscular dystrophy. https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy. Accessed Jan 2020.
2. Hoffman EP, Brown RH, et al. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell. 1987;51:919-928.
3. Passamano L, Taglia A, et al. Improvement of survival in Duchenne Muscular Dystrophy: retrospective analysis of 835 patients. Acta Myologica. 2012;31(1): 121-125.

SRP-9001-101: Open-Label Trial Design

- **Cohort B**
  - 4 Patients
  - 4-7 years of age

- **Inclusion criteria**
  - Confirmed *DMD* mutation
  - Negative for AAVrh74 antibodies

ClinicalTrials.gov Identifier: NCT03375164.
SRP-9001 (rAAVrh.74.MHCK7.micro-dystrophin) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.

Cohort B (4-7 Years of Age) Endpoints

- **Primary endpoint**
  - Safety
- **Secondary endpoints**
  - Change in micro-dystrophin expression pre- vs post-treatment
  - Decrease in CK
  - 100-meter timed test (100 m)
  - North Star Ambulatory Assessment (NSAA; 10-meter timed test included)
  - Timed up and go (TUG)
  - Ascend and descend 4 steps
  - Hand-held dynamometry (HHD)
  - Cardiac magnetic resonance imaging (at 1 year)

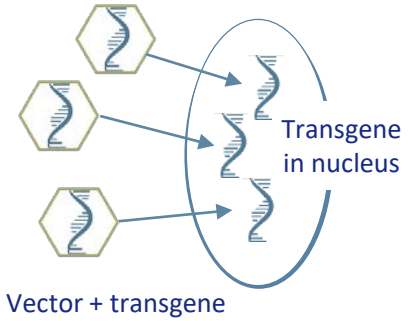
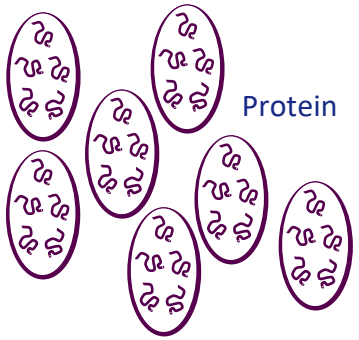
ClinicalTrials.gov Identifier: NCT03375164.
SRP-9001 (rAAVrh.74.MHCK7.micro-dystrophin) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.

Subject Demographics at Baseline

Subject	Age (years)	CK Levels at Baseline (U/L)
1	5	20,691
2	4	23,414
3	6	34,942
4	4	29,210

ClinicalTrials.gov Identifier: NCT03375164.
SRP-9001 (rAAVrh.74.MHCK7.micro-dystrophin) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.

Questions to Consider When Evaluating Gene Transfer Therapies

QUESTION[1]	1	2	3	4	5
	What was the safety and tolerability experience?	Is the transgene DNA inside muscle cells?	Is the desired protein made?	Is the protein at the cell membrane? How much is there?	Is muscle function improved?
EXPERIMENT	Safety	Vector Genome Copies/Nucleus	Western Blot	IF	Varied Functional Outcomes
				**% Positive Fibers:** % cells with protein **Intensity of Fluorescent Signal:** How strong is expression in cells with protein? **Is DAPC Reconstituted?** Are associated proteins also present?	**Assessments could include:** • **NSAA** • **Timed Function Tests**

IF, immunofluorescence; NSAA, North Star Ambulatory Assessment.

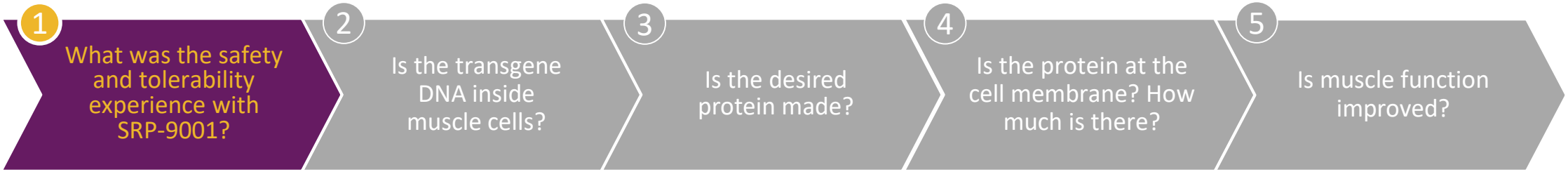
1. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-274.

Safety Experience (N=4)

Safety Data (AEs) Through Patients' 2-year Visit Post-SRP-9001 Infusion Have Been Monitored

TRIAL 101
Phase I
4 patients

QUESTION[2]



- No patients experienced a serious adverse event (SAE) or an AE that led to discontinuation
- There were no serious abnormalities observed in hematologic and chemistry panels, which included liver function tests
- 3 patients had elevated γ-glutamyl transpeptidase in the first 3 months post-treatment, which resolved with steroid treatment
- No other clinically significant laboratory findings were reported
- Platelets remained within normal range (mean range, 232.2–398.5)
- The most common treatment-related adverse event (TRAE) was vomiting (9 of 18 TRAEs)
- Patients had transient vomiting generally within the first week post-infusion
  - It did not correlate with liver enzyme elevations or any other abnormality
- All TRAEs occurred within 90 days post-infusion
- None of the adverse events were associated with complement activation

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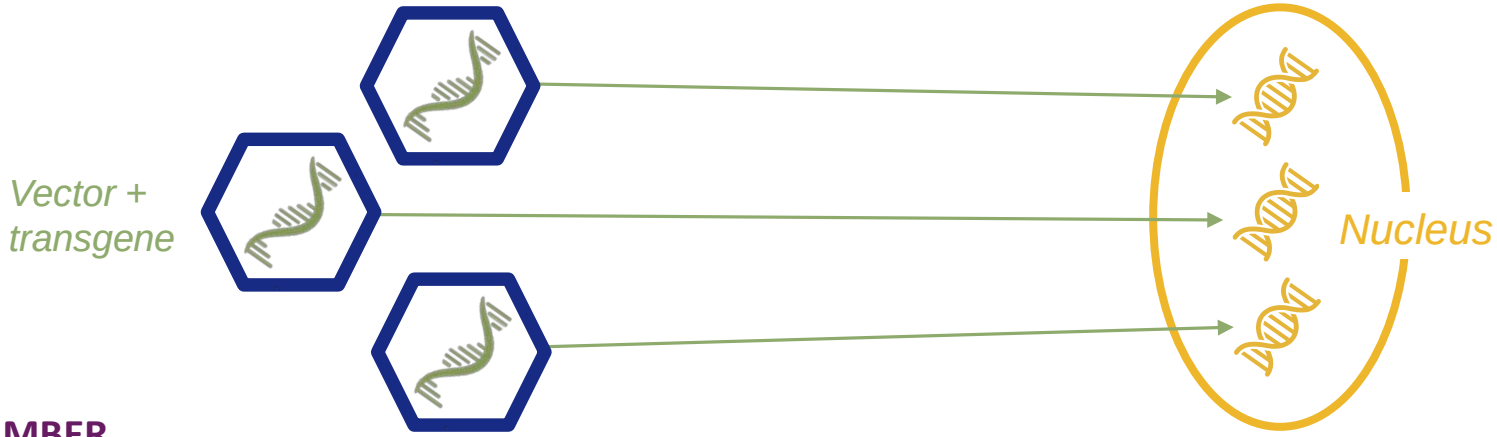
2. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-274.

Micro-dystrophin Transduction by Vector Genome Count in 4 Subjects[1]

TRIAL 101
Phase I
4 patients

QUESTION[2]

1. What was the safety and tolerability experience with SRP-9001?
2. Is the transgene DNA inside muscle cells?
3. Is the desired protein made?
4. Is the protein at the cell membrane? How much is there?
5. Is muscle function improved?



VECTOR GENOME NUMBER

	VECTOR COPIES/µg DNA	COPIES PER NUCLEUS
Mean (n=4)	>10^5	3.3

SRP-9001 (AAVrh74.MHCK7.Microdystrophin) gene transfer therapy is investigational and has not been reviewed or approved by any regulatory authority.
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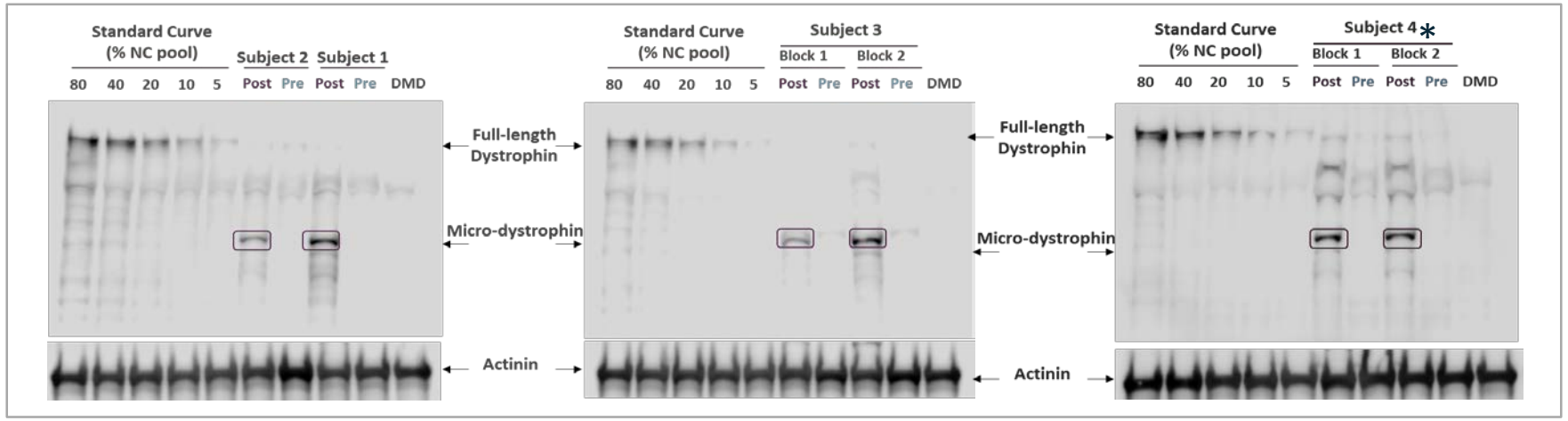
1. Mendell JR, et al. *JAMA Neurol.* 2020. Online ahead of print. doi: 10.1001/jamaneurol.2020.1484. 2. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-274.

Micro-dystrophin Expression by Western Blot at Day 90 Post-treatment in 4 Subjects[1]

TRIAL 101
Phase I
4 patients

QUESTION[2]

1. What was the safety and tolerability experience with SRP-9001?
2. Is the transgene DNA inside muscle cells?
3. **Is the desired protein made?**
4. Is the protein at the cell membrane? How much is there?
5. Is muscle function improved?



WESTERN BLOT QUANTITATION METHOD	MEAN MICRO-DYSTROPHIN EXPRESSION (N=4) VS NORMAL	
Sarepta	74.3%	(Not adjusted for fat and fibrotic tissue)
Nationwide	95.8%	(Adjusted for fat and fibrotic tissue)

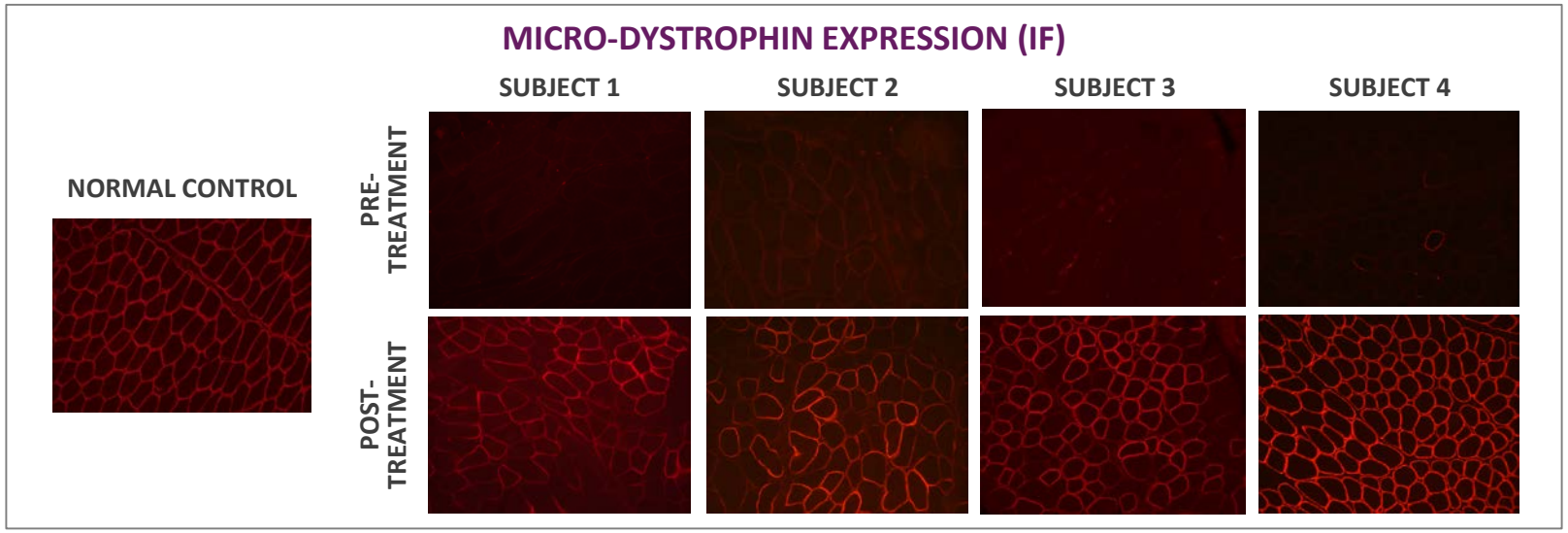
SRP-9001 (AAVrh74.MHCK7.Microdystrophin) gene transfer therapy is investigational and has not been reviewed or approved by any regulatory authority.
NC, normal control; ULOQ, upper limit of quantitation.
*Samples diluted 1:4 because ULOQ (>80%) was exceeded in initial analysis. Mean values were multiplied by correction factor for final value compared with NC.
ClinicalTrials.gov Identifier: NCT03375164.
1. Mendell JR, et al. *JAMA Neurol.* 2020. Online ahead of print. doi: 10.1001/jamaneurol.2020.1484. 2. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-274.

Micro-dystrophin Expression in Muscle Fibers From the Gastrocnemius Post-treatment in 4 Subjects[1]

TRIAL 101
Phase I
4 patients

QUESTION[2]

1. What was the safety and tolerability experience with SRP-9001?
2. Is the transgene DNA inside muscle cells?
3. Is the desired protein made?
4. **Is the protein at the cell membrane? How much is there?**
5. Is muscle function improved?



	PERCENTAGE OF DYSTROPHIN-POSITIVE FIBERS	INTENSITY
Mean (n=4)	81.2%	96.0%

Micro-dystrophin gene transfer therapy is investigational and has not been reviewed or approved by any regulatory authority.
ClinicalTrials.gov Identifier: NCT03375164.

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Expression of the DAPC Protein, β-Sarcoglycan, in Gastrocnemius Muscle Fibers in All 4 Patients at Day 90

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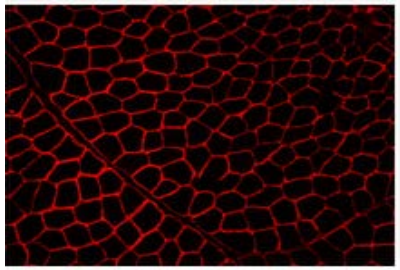
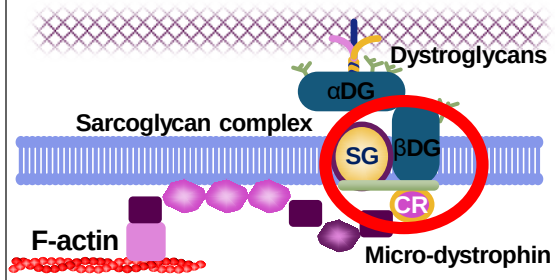
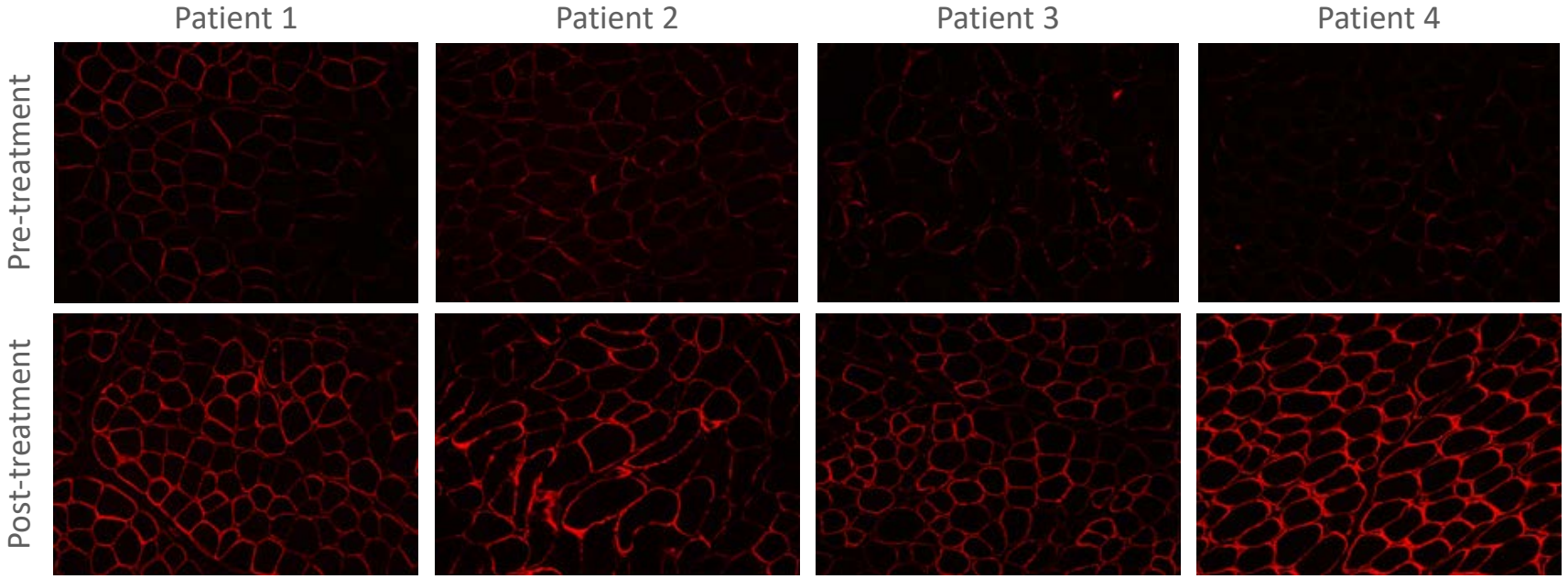
Phase I
4 patients

Normal control





β-Sarcoglycan expression (IF)



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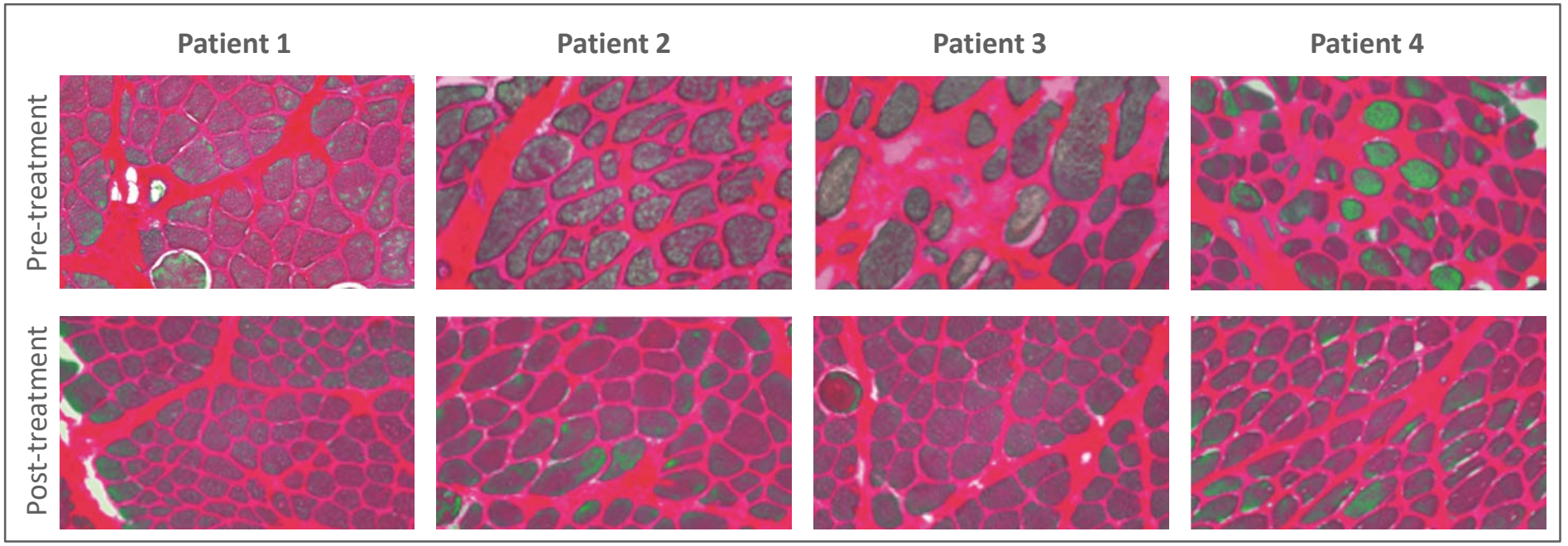
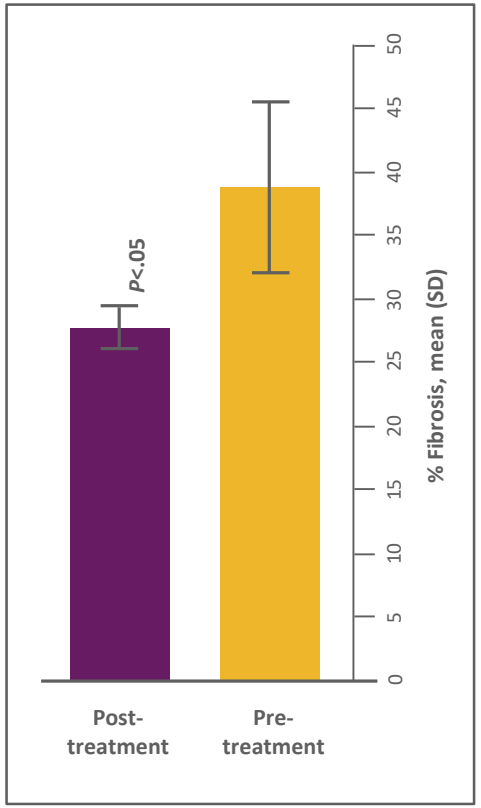
ClinicalTrials.gov Identifier: NCT03375164.
Mendell JR, et al. *JAMA Neurol.* 2020. Online ahead of print. doi: 10.1001/jamaneurol.2020.1484.

Fibrosis Assessed by Reduction in Percent Collagen Content in Muscle Tissue Post-treatment Relative to Baseline at Day 90

TRIAL 101
Phase I
4 patients

REPRESENTATIVE IMAGES OF PICROSIRIUS RED–STAINED MUSCLE TISSUE





- Vector treatment was not associated with ringed fibrosis or other morphology alterations

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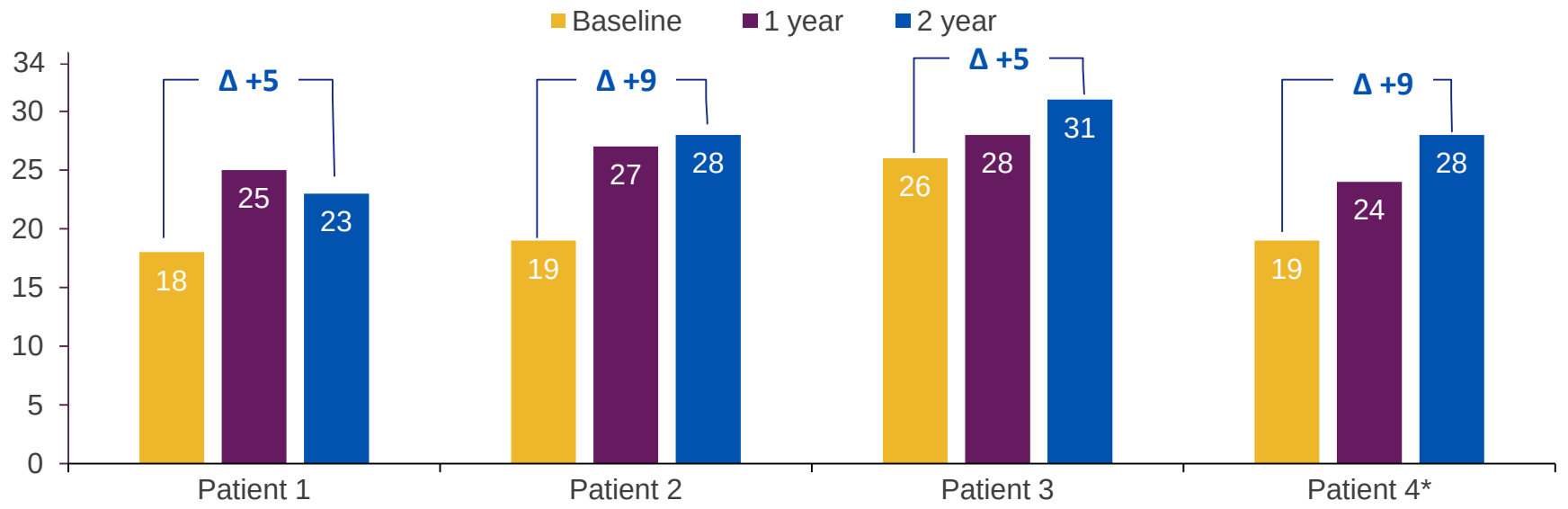
ClinicalTrials.gov Identifier: NCT03375164.
Mendell JR, et al. *JAMA Neurol.* 2020. Online ahead of print. doi: 10.1001/jamaneurol.2020.1484.

Two-year Functional Data, Study 101 (N=4)

NSAA Total Score By Age at Time of Assessment Over 2 Years

TRIAL 101
Phase I
4 patients

MEAN NSAA CHANGE FROM BASELINE TO YEAR 1[1]: +5.5
MEAN NSAA CHANGE FROM BASELINE TO YEAR 2[2]: +7.0



	Patient 1	Patient 2	Patient 3	Patient 4*
Age at Baseline (years)	5.71	4.79	6.02	4.03
Age at Year 1 (years)	6.77	5.79	7.07	5.08
Age at Year 2 (years)	7.73	6.83	8.03	6.31

*The 2-year NSAA value for Patient 4 was from a remote assessment due to COVID-19 related restrictions at the site.

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2. Mendell J, et al. Poster presented at: 25th International Annual Congress of the World Muscle Society; September 30-October 1, 2020; Virtual format. P.280.

Summary of 2-Year Timed Function Tests

TRIAL 101
Phase I
4 patients

	PATIENT 1			PATIENT 2			PATIENT 3			PATIENT 4*		
	BL	1 YEAR	2 YEAR	BL	1 YEAR	2 YEAR	BL	1 YEAR	2 YEAR	BL	1 YEAR	18 MONTH
Time to rise (sec)	3.7	3.4	**4.1**	3.0	3.4	**3.2**	3.9	3.9	**2.8**	4.1	2.6	**2.4**
4-stair climb (sec)	3.4	2.4	**2.4**	3.8	2.6	**2.2**	1.9	1.8	**2.2**	4.8	2.0	**2.0**
100 m (sec)	49.3	42.9	**41.8**	49.8	47.4	**40.9**	59.3	55.5	**50.7**	67.2	43.6	**47.5**
100 m (%p)	64.8	71.2	**70.1**	67.9	68.8	**76**	54.1	55.3	**61.1**	46.7	75.7	**76.6**

*Patient 4 did not have 2-year timed function tests assessed due to COVID-19 related restrictions at the site. The 18-month data are presented.

SRP-9001 (AAVrh74.MHCK7.Microdystrophin) gene transfer therapy is investigational and has not been reviewed or approved by any regulatory authority.
BL, baseline.
ClinicalTrials.gov Identifier: NCT03375164.
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SRP-9001-101 Summary (N=4)[1,2]

TRIAL 101
Phase I
4 patients

Micro-dystrophin gene transfer therapy is investigational and has not been reviewed or approved by any regulatory authority.
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Limb-girdle Muscular Dystrophy Type 2E

SRP-9003 β-Sarcoglycan Clinical Results

Phase I/II Study (N=6)

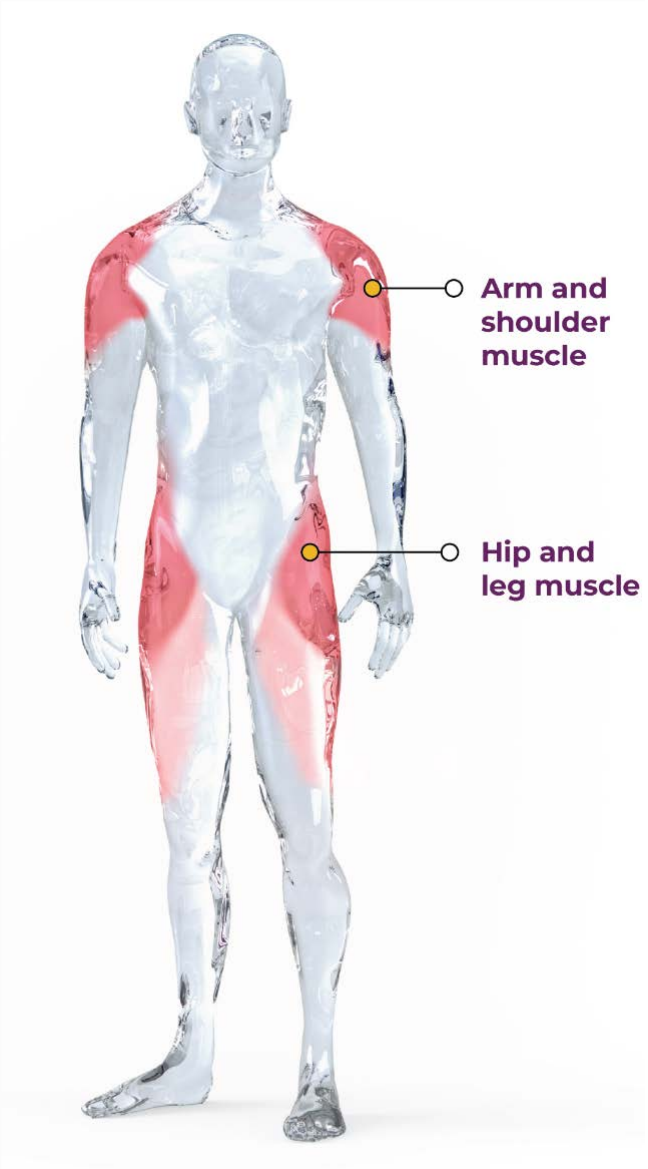
Limb-girdle Muscular Dystrophies (LGMDs)

Approximate global prevalence of LGMDs as a group is 1.63 per 100,000[1]

Over 30 subtypes exist[2]

Both genders are affected equally[3]

- The LGMDs are a group of genetically heterogeneous, autosomal inherited (recessive more common than dominant) muscular dystrophies with a childhood to adult onset[4]



*Prevalence estimates range from 0.56 to 5.75 per 100,000[1]

1. Liewluck T, Milone M, et al. Untangling the complexity of limb-girdle muscular dystrophies. Muscle Nerve. 2018;58(2):167-177.
2. Murphy AP, Straub V. The Classification, Natural History and Treatment of the Limb Girdle Muscular Dystrophies. *J Neuromuscular Diseases*. 2015;2(s2):S7-S19.
3. Muscular Dystrophy Association. Limb-girdle muscular dystrophy (LGMD). Accessed Jan 2020 4. Liewluck T, Milone M, et al. Untangling the complexity of limb-girdle muscular dystrophies. Muscle Nerve. 2018;58(2):167-177.

SRP-9003 Pre-clinical Summary

FINDINGS TO DATE

	1	2	3	4	5
QUESTION	What safety-related events are associated with vector delivery to target cells?	Did the vector deliver transgene DNA to muscle cells?	Do the promoter and enhancer drive sufficient transgene expression in muscle? Is the desired protein made?	Is the protein at the cell membrane? How much is there? Is dystrophic pathology of muscle improved?	Has the protein expression resulted in functional benefit?[2]
RESULTS IN *SGCB*-/- MICE	LOW PREVALENCE OF PRE-EXISTING ANTIBODIES[1]	>10^5 COPIES/µg DNA IN TA, QUAD, GLUT, DIAPHRAGM AND HEART[2]	>90% EXPRESSION IN BOTH SKELETAL MUSCLE & HEART[2]	SGCB PROTEIN EXPRESSED AT SARCOLEMMA (OBSERVED BY IF)[2]	STATISTICALLY SIGNIFICANT DIFFERENCES IN SPECIFIC FORCE, FATIGUE, KYPHOSCOLIOSIS, ACTIVITY, AND MOVEMENT[2]

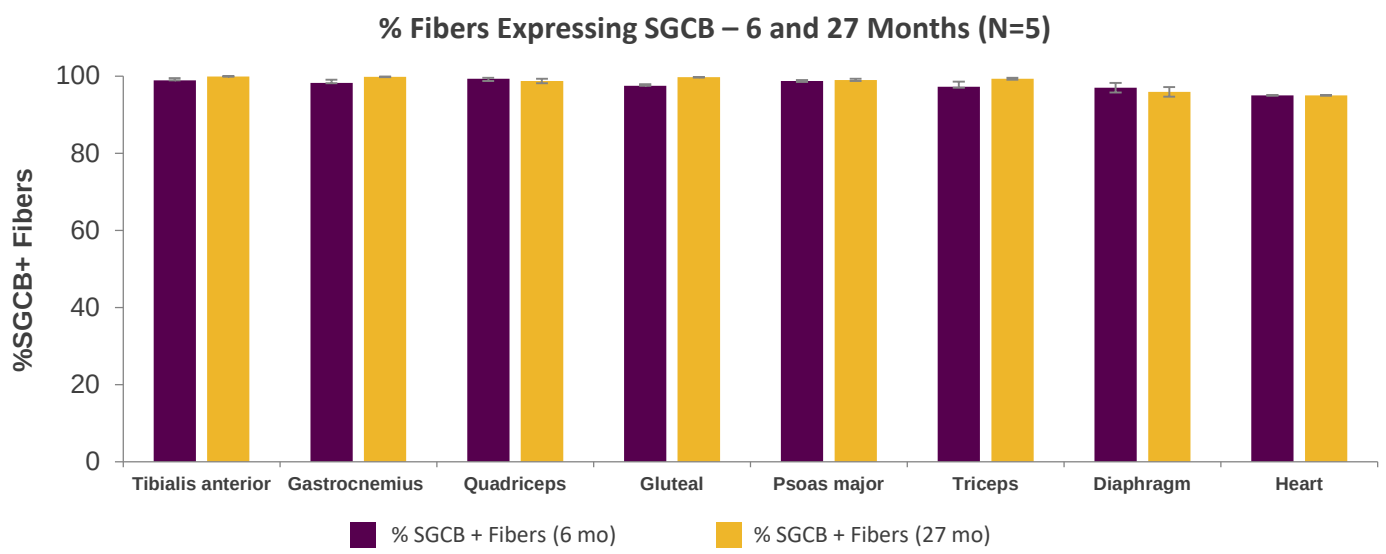
Glut, gluteus; IF, immunofluorescence; ITR, inverted terminal repeat; pA, polyadenylation signal; Quad, quadriceps; TA, tibialis anterior.

1. Zygmunt DA, et al. *Hum Gene Ther*. 2017;28(9):737-746. 2. Pozsgai ER, et al. *Mol Ther*. 2017;25(4):855-869.

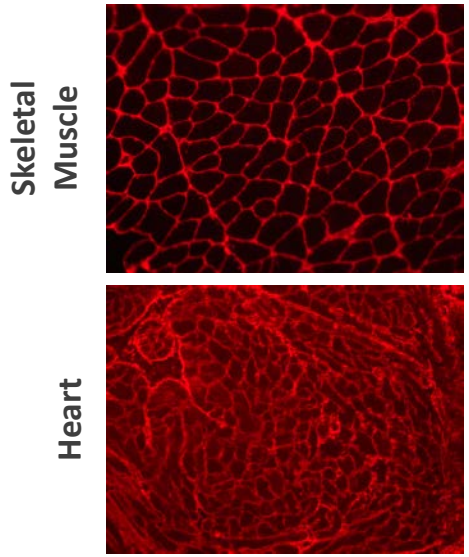
Duration of Expression Over Life Span of Mouse (27 Months Post-treatment)

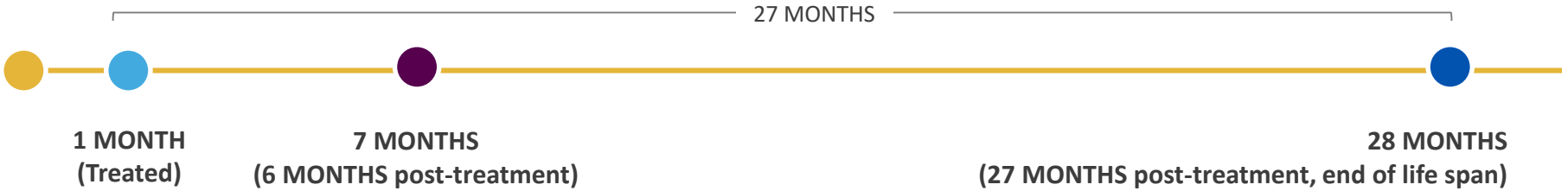
EVIDENCE OF DURABILITY

SGCB EXPRESSION IN TARGET MUSCLES FOLLOWING IV DOSE (1 x 10^{12} vg TOTAL)



hSGCB EXPRESSION 27 MONTHS POST-INJECTION (IF)





Sarepta Therapeutics, Inc. 2020. Data on file.

SRP-9003-101 Open-label Trial Design: Study Overview

COHORT 1,2
Phase I/IIa
6 patients

- **Key Inclusion criteria**
  - A confirmed *SGCB* mutation in both alleles
  - Negative for AAVrh74 antibodies
  - >40% of normal 100-meter walk test
- **Prednisone 1 mg/kg daily starting 1 day before study treatment for 30 days for Cohort 1 and 60 days for Cohort 2, with taper**
- **Baseline and 60-day muscle biopsy**

- **Primary endpoint**
  - Safety
- **Secondary endpoint**
  - β-Sarcoglycan expression at Week 8*
- **Other endpoints**
  - Change in CK
  - Functional endpoints
    - North Star Ambulatory Assessment for Dysferlinopathy (NSAD)
    - 100MWR
    - 10MWR
    - 4-stair climb
    - Time to rise

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.

*Based on pre-clinical studies, the goal was to achieve expression levels of ≥20%.

10MWR, 10-meter walk/run; 100MWR, 100-meter walk/run; CK, creatine kinase.
ClinicalTrials.gov Identifier: NCT03652259.

SRP-9003-101 Subject Demographics at Baseline[1]

COHORT 1,2
Phase I/IIa
6 patients

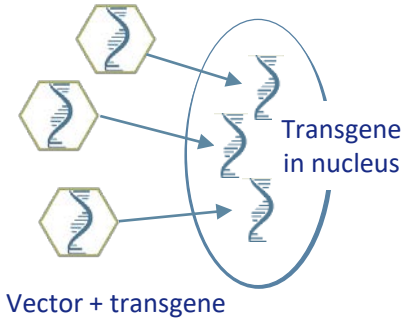
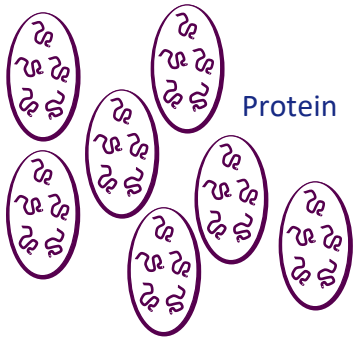
COHORT/DOSE	SUBJECT	GENDER	AGE (YEARS)	MUTATION	WEIGHT (KG)	CK LEVELS (U/L)
COHORT 1 0.5×10^{14} vg/kg	1	F	13	Exon 3	57.2	10,727
	2	M	4	Exon 4	17.5	12,286
	3	F	13	Exon 3	50.4	10,985
COHORT 2 2.0×10^{14} vg/kg	4	M	11	Exon 4	29.1	6320
	5	M	11	Exon 3	39.5	8938
	6	F	8	Exon 1	26.6	5743

- Exons 3-6 encode for the extracellular domain of SGCB
  - Mutations in these exons lead to complete absence of or severely reduced expression of β-sarcoglycan and a severe phenotype that includes cardiomyopathy[2]

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
ClinicalTrials.gov Identifier: NCT03652259.

1. Rodino-Klapac L, et al. Poster presented at: 25th International Annual Congress of the World Muscle Society; September 30-October 2, 2020; Virtual format. P.140.
2. Semplicini C, et al. *Neurology* 2015;84(17):1772-1781.

Questions to Consider When Evaluating Gene Transfer Therapies

	1	2	3	4	5
QUESTION	What was the safety and tolerability experience?	Is the transgene DNA inside muscle cells?	Is the desired protein made?	Is the protein at the cell membrane? How much is there?	Is muscle function improved?
EXPERIMENT	Safety	Vector Genome Copies/Nucleus	Western Blot	IF	Varied Functional Outcomes
				**% Positive Fibers:** % cells with protein **Intensity of Fluorescent Signal:** How strong is expression in cells with protein? **Is DAPC Reconstituted?** Are associated proteins also present?	**Assessments could include:** • **NSAD** • **Timed Function Tests**

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.

NSAD, North Star Ambulatory Assessment for Dysferlinopathy.

ClinicalTrials.gov Identifier: NCT03652259.

Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-274.

Cohort 1 (0.5 × 10^{14} vg/kg) Safety Experience

(AS OF JULY 8, 2020 [N=3])

COHORT 1
Phase I/IIa
3 patients

QUESTION

1. What was the safety and tolerability experience with SRP-9003?
2. Is the β-sarcoglycan transgene DNA inside muscle cells?
3. Is the desired β-sarcoglycan protein made?
4. Is the β-sarcoglycan protein at the cell membrane? How much is there?
5. Is muscle function improved?

- 2 subjects had elevated liver enzymes, 1 of which was designated an SAE, as the subject had an associated transient increase in bilirubin
  - 1 event occurred when the subject was tapered off oral steroids, the other occurred while the patient was being tapered
  - Returned to baseline and symptoms resolved within days following supplemental steroid treatment
- 1 patient experienced mild vomiting, which resolved within 1 day without treatment
- No other clinically significant laboratory findings
  - No decreases in platelet counts observed outside of the normal range
  - No clinical sequelae associated with complement activation

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
SAE, serious adverse event.
ClinicalTrials.gov Identifier: NCT03652259.
Rodino-Klapac L, et al. Poster presented at: 25th International Annual Congress of the World Muscle Society; September 30-October 2, 2020; Virtual format. P.216.

Cohort 2 (2.0 × 10^{14} vg/kg) Safety Experience

(AS OF JULY 8, 2020 [N=3])

COHORT 2
Phase I/IIa
3 patients

QUESTION

1. What was the safety and tolerability experience with SRP-9003?
2. Is the β-sarcoglycan transgene DNA inside muscle cells?
3. Is the desired β-sarcoglycan protein made?
4. Is the β-sarcoglycan protein at the cell membrane? How much is there?
5. Is muscle function improved?

- Majority of AEs were mild to moderate (eg, vomiting, pain in extremity), which resolved
- 1 treatment-related SAE observed
  - Dehydration resulting from vomiting 3 days after infusion, which resolved within 2 days with ondansetron, promethazine, and IV fluids
- 1 patient had mildly elevated GGT
  - Returned to within normal limits while on tapering dose of steroids; the patient did not experience an increase after tapering was concluded
- No stopping/discontinuation rules were triggered by AEs
- No other clinically significant laboratory findings
  - No decreases in platelet counts observed outside of the normal range
  - No clinical sequelae associated with complement activation

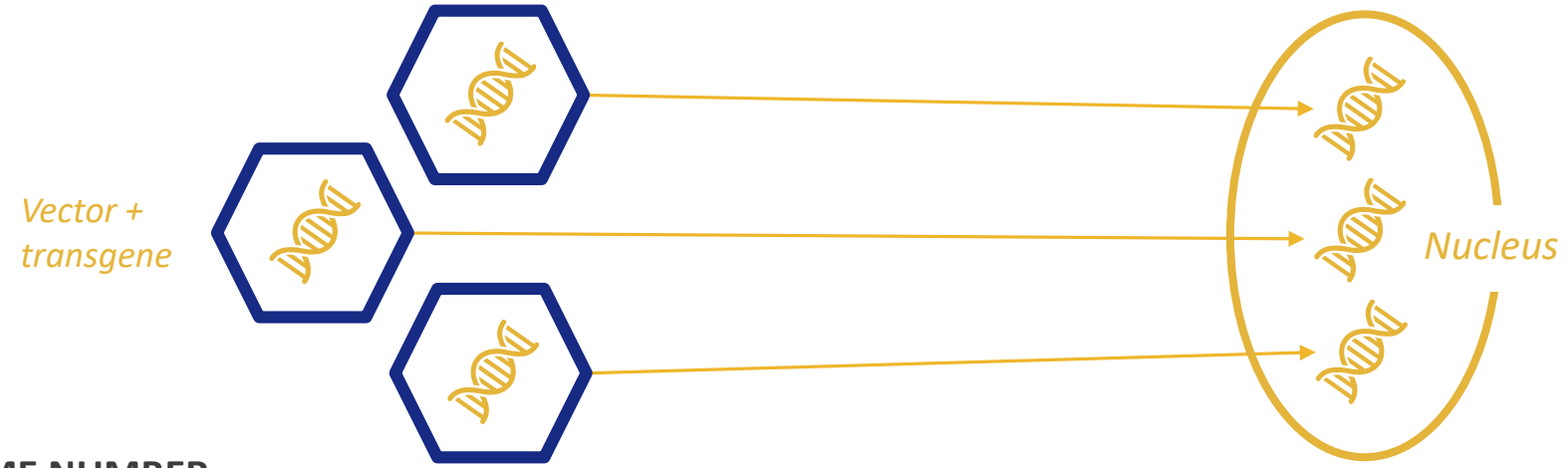
SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
IV, intravenous; GGT, gamma-glutamyl transferase.
ClinicalTrials.gov Identifier: NCT03652259.
Rodino-Klapac L, et al. Poster presented at: 25th International Annual Congress of the World Muscle Society; September 30-October 2, 2020; Virtual format. P.216.

Transduction by Vector Genome Count in All 6 Subjects

COHORT 1,2
Phase I/IIa
6 patients

QUESTION

1. What was the safety and tolerability experience with SRP-9003?
2. **Is the β-sarcoglycan transgene DNA inside muscle cells?**
3. Is the desired β-sarcoglycan protein made?
4. Is the β-sarcoglycan protein at the cell membrane? How much is there?
5. Is muscle function improved?



VECTOR GENOME NUMBER

	VECTOR COPIES/µg DNA	COPIES PER NUCLEUS
Mean Cohort 1 (n=3), Dose 0.5 × 10^{14} vg/kg	>10^4	0.60
Mean Cohort 2 (n=3), Dose 2.0 × 10^{14} vg/kg	>10^5	4.2

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
ClinicalTrials.gov Identifier: NCT03652259.
Rodino-Klapac L, et al. Poster presented at: 25th International Annual Congress of the World Muscle Society; September 30-October 2, 2020; Virtual format. P.216.

Western Blot Expression Post-treatment (2 Months)

FULL-LENGTH β-SARCOGLYCAN EXPRESSION

COHORT 1,2
Phase I/IIa
6 patients

QUESTION

1. What was the safety and tolerability experience with SRP-9003?
2. Is the β-sarcoglycan transgene DNA inside muscle cells?
3. **Is the desired β-sarcoglycan protein made?**
4. Is the β-sarcoglycan protein at the cell membrane? How much is there?
5. Is muscle function improved?

COHORT/DOSE	SUBJECT	MEAN β-SARCOGLYCAN EXPRESSION VS NORMAL
COHORT 1 0.5×10^{14} vg/kg	1	34.7%
	2	39.2%
	3	34.5%
	Mean Cohort 1	**36.1%**
COHORT 2 2.0×10^{14} vg/kg	4	53.0%
	5	63.1%
	6	70.3%
	Mean Cohort 2	**62.1%**

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
ClinicalTrials.gov Identifier: NCT03652259.

Percentage of Positive Fibers and Intensity[1] (2 Months)

β-SARCOGLYCAN PROTEIN EXPRESSION IN MUSCLE BIOPSIES

COHORT 1,2
Phase I/IIa
6 patients

≥20% β-SARCOGLYCAN EXPRESSION LEADS TO INCREASED FUNCTION IN LGMD2E MICE

COHORT/DOSE	SUBJECT	% OF SGCB+ FIBERS	MEAN INTENSITY
COHORT 1 0.5×10^{14} vg/kg	1	63%	47%
	2	49%	57%
	3	42%	38%
	Mean Cohort 1	**51%**	**47%**
COHORT 2 2.0×10^{14} vg/kg	4	65%	55%
	5	77%	67%
	6	75%	97%
	Mean Cohort 2	**72%**	**73%**

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
ClinicalTrials.gov Identifier: NCT03652259.

1. Rodino-Klapac L. Presented at the 24th International Annual Congress of the World Muscle Society; October 1-5, 2019; Copenhagen, Denmark.

SGC Complex Expression in a Cohort 1 (0.5×10^{14} vg/kg) Patient at 2 Months

COHORT 1
Phase I/IIa
3 patients

QUESTION

1. What was the safety and tolerability experience with SRP-9003?
2. Is the β-sarcoglycan transgene DNA inside muscle cells?
3. Is the desired β-sarcoglycan protein made?
4. **Is the β-sarcoglycan protein at the cell membrane? How much is there?**
5. Is muscle function improved?

IMMUNOFLUORESCENT (IF) STAINING OF MUSCLE BIOPSY FROM 1 PATIENT FROM COHORT 1

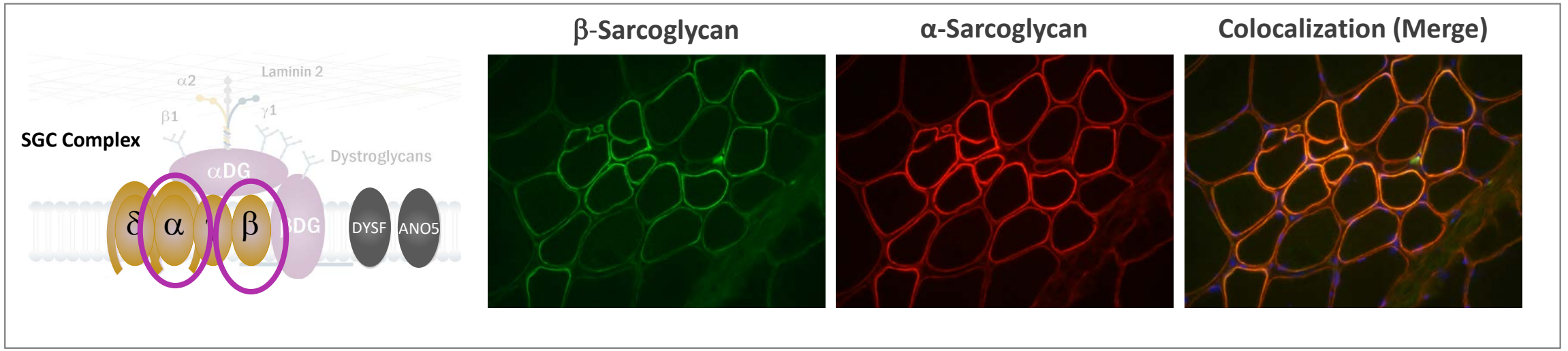


Image adapted from Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
ClinicalTrials.gov Identifier: NCT03652259.

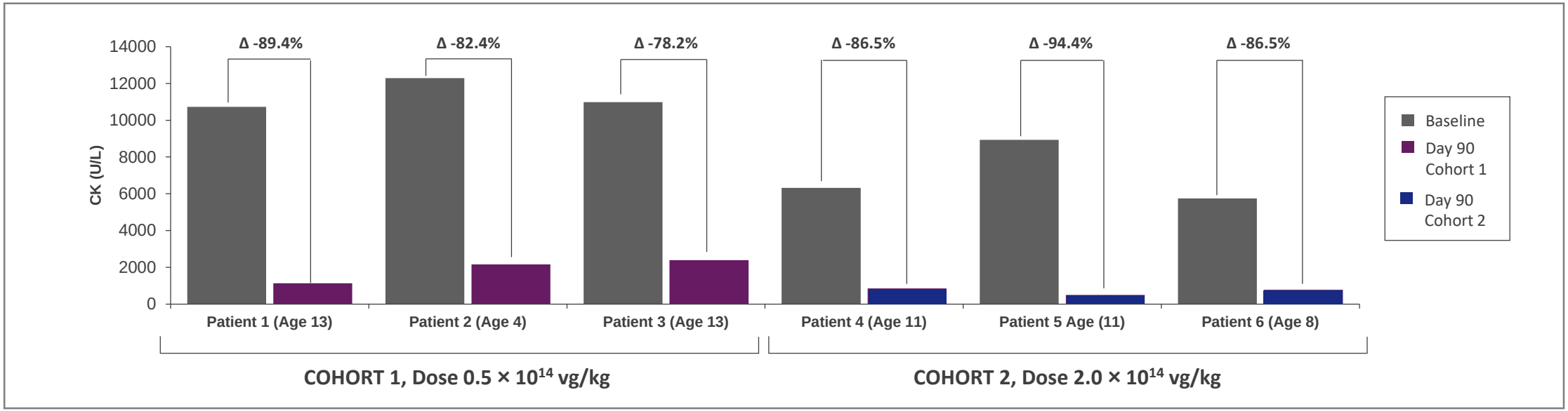
Cohort 1 (0.5×10^{14} vg/kg) and Cohort 2 (2.0×10^{14} vg/kg): CK Levels (3 Months)

COHORT 1,2
Phase I/IIa
6 patients

QUESTION

1. What was the safety and tolerability experience with SRP-9003?
2. Is the transgene DNA inside muscle cells?
3. Is the desired β-sarcoglycan protein made?
4. Is the β-sarcoglycan protein at the cell membrane? How much is there?
5. Is muscle **function** improved?

CK LEVELS FOLLOWING SGCB DELIVERY



Mean change in CK from baseline to Day 90: Cohort 1, -83.4%; Cohort 2, -89.1%

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
ClinicalTrials.gov Identifier: NCT03652259.

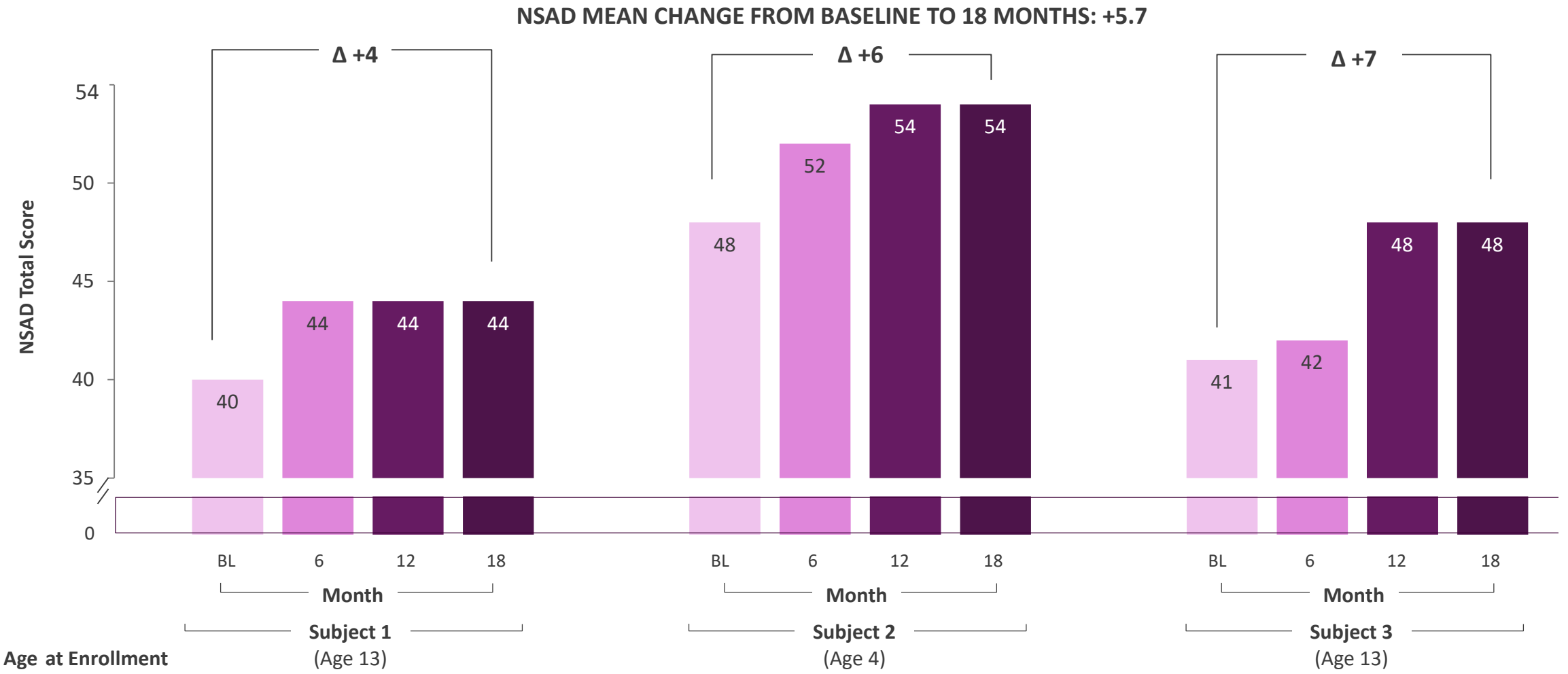
Functional Data (N=6)

Cohort 1 - 18 Months

Cohort 2 - 6 Months

Summary of NSAD Data for Cohort 1 (0.5×10^{14} vg/kg) Subjects Over 18 Months

COHORT 1
Phase I/IIa
3 patients



SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
BL, baseline.
ClinicalTrials.gov Identifier: NCT03652259.
Rodino-Klapac L, et al. Poster presented at: 25th International Annual Congress of the World Muscle Society; September 30-October 2, 2020; Virtual format. P.216.

Cohort 1: Functional Outcomes

SUMMARY OF CLINICAL DATA AT 18 MONTHS AT A DOSE OF 0.5 × 10^{14} VG/KG

COHORT 1
Phase I/IIa
3 patients

QUESTION

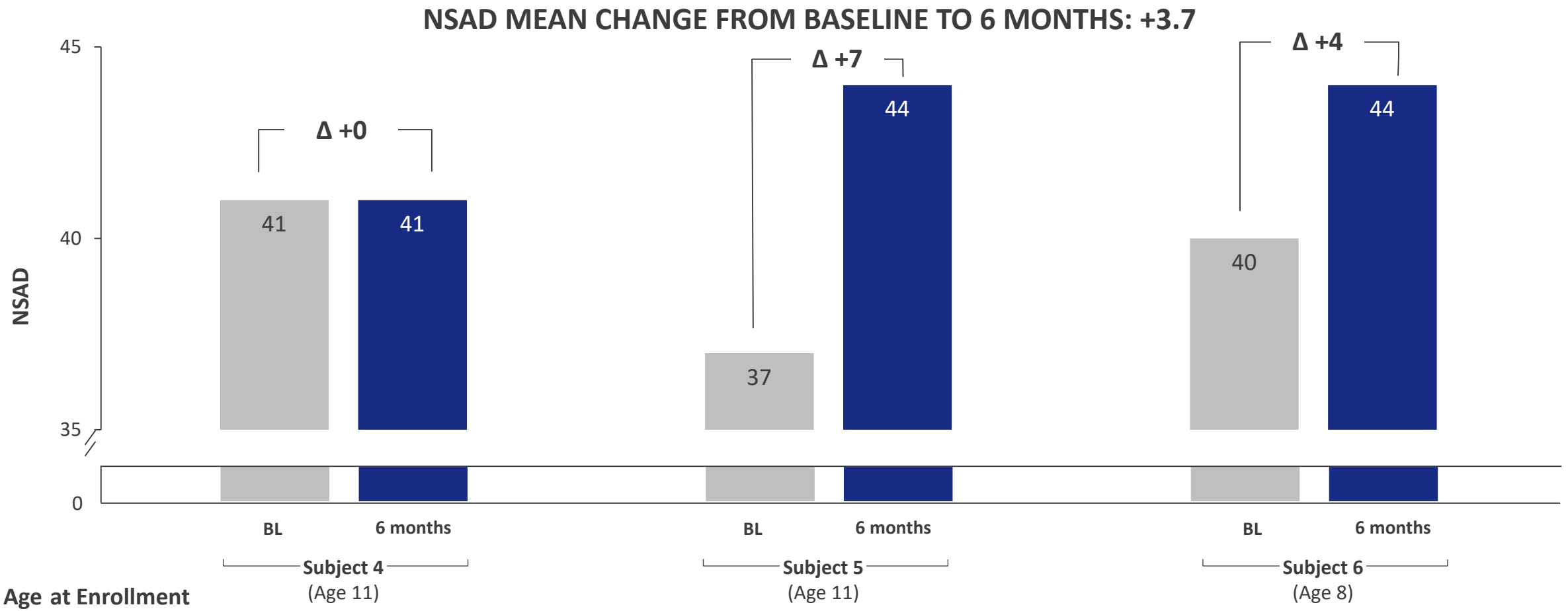
1. What was the safety and tolerability experience with SRP-9003?
2. Is the β-sarcoglycan transgene DNA inside muscle cells?
3. Is the desired β-sarcoglycan protein made?
4. Is the β-sarcoglycan protein at the cell membrane? How much is there?
5. Is muscle function improved?

SUBJECT	ASSESSMENT	NSAD	TIME TO RISE (SEC)	4 STAIRS UP (SEC)	100 MWR (SEC)	10 MWR (SEC)
1 (age 13)	Baseline	40	5.0	2.4	52.0	5.0
	Month 18*	44	4.8	2.5	50.4	4.8
	Change from Baseline	**+4**	**-0.2**	**+0.1**	**-1.6**	**-0.2**
2 (age 4)	Baseline	48	1.5	1.6	35.1	3.4
	Month 18	54	0.9	1.5	29.4	2.9
	Change from Baseline	**+6**	**-0.6**	**-0.1**	**-5.7**	**-0.5**
3 (age 13)	Baseline	41	3.5	2.8	48.8	5.2
	Month 18	48	3.7	1.7	42.9	4.3
	Change from Baseline	**+7**	**+0.2**	**-1.1**	**-5.9**	**-0.9**
Mean Change Improvement from Baseline to 18 Months		**5.7**	**0.2 sec**	**0.35 sec**	**4.4 sec**	**0.5 sec**

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
*Subjects 1's 18-month assessment was delayed due to COVID-19 and occurred within 6 weeks following the designated 18-month assessment window.
ClinicalTrials.gov Identifier: NCT03652259.
Rodino-Klapac L, et al. Poster presented at: 25th International Annual Congress of the World Muscle Society; September 30-October 2, 2020; Virtual format. P.216.

Summary of NSAD Data for Cohort 2 (2.0×10^{14} vg/kg) Subjects at 6 Months

COHORT 2
Phase I/IIa
3 patients



SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
ClinicalTrials.gov Identifier: NCT03652259.
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Cohort 2: Functional Outcomes

COHORT 2
Phase I/IIa
3 patients

SUMMARY OF CLINICAL DATA AT 6 MONTHS AT A DOSE OF 2.0 × 10^{14} VG/KG

QUESTION

1. What was the safety and tolerability experience with SRP-9003?
2. Is the β-sarcoglycan transgene DNA inside muscle cells?
3. Is the desired β-sarcoglycan protein made?
4. Is the β-sarcoglycan protein at the cell membrane? How much is there?
5. Is muscle function improved?

SUBJECT	ASSESSMENT	NSAD	TIME TO RISE (SEC)	4 STAIRS UP (SEC)	100 MWR (SEC)	10 MWR (SEC)
4 (age 11)	Baseline	41	3.3	3.0	47.2	4.9
	Month 6	41	2.5	2.3	45.1	4.6
	Change from Baseline	**0**	**-0.8**	**-0.7**	**-2.1**	**-0.3**
5 (age 11)	Baseline	37	3.5	3.1	59.7	5.8
	Month 6	44	2.8	3.0	56.9	5.6
	Change from Baseline	**+7**	**-0.7**	**-0.1**	**-2.8**	**-0.2**
6 (age 8)	Baseline	40	5.7	3.1	65.3	6.1
	Month 6	44	3.4	2.7	51.3	4.8
	Change from Baseline	**+4**	**-2.3**	**-0.4**	**-14.0**	**-1.3**
Mean Change Improvement from Baseline to 6 Months		**3.7**	**1.3 sec**	**0.4 sec**	**6.3 sec**	**0.6 sec**

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ClinicalTrials.gov Identifier: NCT03652259.
Sarepta Therapeutics, Inc. 2020. Data on file.

Summary of Functional Clinical Data at 6 Months

COHORT 1,2
Phase I/IIa
6 patients

MEAN CHANGE IMPROVEMENT FROM BASELINE TO 6 MONTHS

Measure	COHORT 1 (0.5×10^{14} vg/kg) n=3 Mean	COHORT 2 (2.0×10^{14} vg/kg) n=3 Mean
NSAD (total score)	**+3.0**	**+3.7**
Time to Rise (sec)	**+0.1**	**+1.3**
4 Stairs Up (sec)	**+0.5**	**+0.4**
100 MWR (sec)	**+3.8**	**+6.3**
10 MWR (sec)	**+0.6**	**+0.6**

SRP-9003 (AAVrh74.MHCK7.hSGCB) gene therapy is investigational and has not been reviewed or approved by any regulatory authority.
ClinicalTrials.gov Identifier: NCT03652259.
Sarepta Therapeutics, Inc. 2020. Data on file.

Conclusions

- Durability is an important consideration for a one-time treatment, such as gene therapies
- Durability of transgenes delivered via AAV constructs has been observed
- Muscle is an ideal target for a durable gene therapy response due to the low cell turnover in muscle
- Higher expression levels protecting more muscle fibers should lead to a more durable functional response
- Preclinical data from the micro-dystrophin and LGMD 2E programs supports durable functional responses post gene therapy transfer
- Clinical data from the micro-dystrophin SRP-9001-101 study and LGMD2E SRP-9003-101 study support durable functional outcomes at the two-year and 18-month time points, respectively

Question and Answer