A randomized, double-blind, placebo-controlled, gene-delivery clinical trial of rAAVrh74.MHCK7.micro-dystrophin for Duchenne muscular dystrophy

Jerry R. Mendell,[1,2] Perry B. Shieh,[3] Zarife Sahenk,[1] Kelly J. Lehman,[1] Linda P. Lowes,[1] Natalie F. Reash,[1] Megan Iammarino,[1] Lindsay N. Alfano,[1] Jeremy D. Woods,[3] Christy L. Skura,[3] Howard C. Mao,[3] Loretta A. Staudt,[3] Rachael A. Potter,[1,4] Danielle Griffin,[1,4] Sarah Lewis,[1,4] Larry Hu,[4] Sameer Upadhyay,[4] Teji Singh,[4] Louise R. Rodino-Klapac[4]

[1]Center for Gene Therapy, The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA; [2]Department of Pediatrics and Neurology, The Ohio State University, Columbus, OH, USA; [3]Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA; [4]Sarepta Therapeutics, Inc., Cambridge, MA, USA.

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- SRP-9001 is an investigational therapy and has not been reviewed or approved by the FDA
- Trial registration: NCT03769116
- JRM has been a consultant for AveXis, Sarepta Therapeutics, and Vertex. PBS reports being a consultant/independent contractor (AveXis, Biogen, Cytokinetics, and Sarepta Therapeutics) and receiving grants/research support (AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Sanofi Genzyme, and Sarepta Therapeutics). NFR reports receiving salary support from Sarepta Therapeutics for Clinical Evaluator training for ongoing and upcoming clinical trials. LNA reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials. RAP, DG, SL, LH, SU, TS and LRK are employees of Sarepta Therapeutics and may have stock options. LRK is a co-inventor of AAVrh74.MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics. ZS, KJL, LPL, MI, JDW, CLS, HCM and LAS report no conflicts of interest
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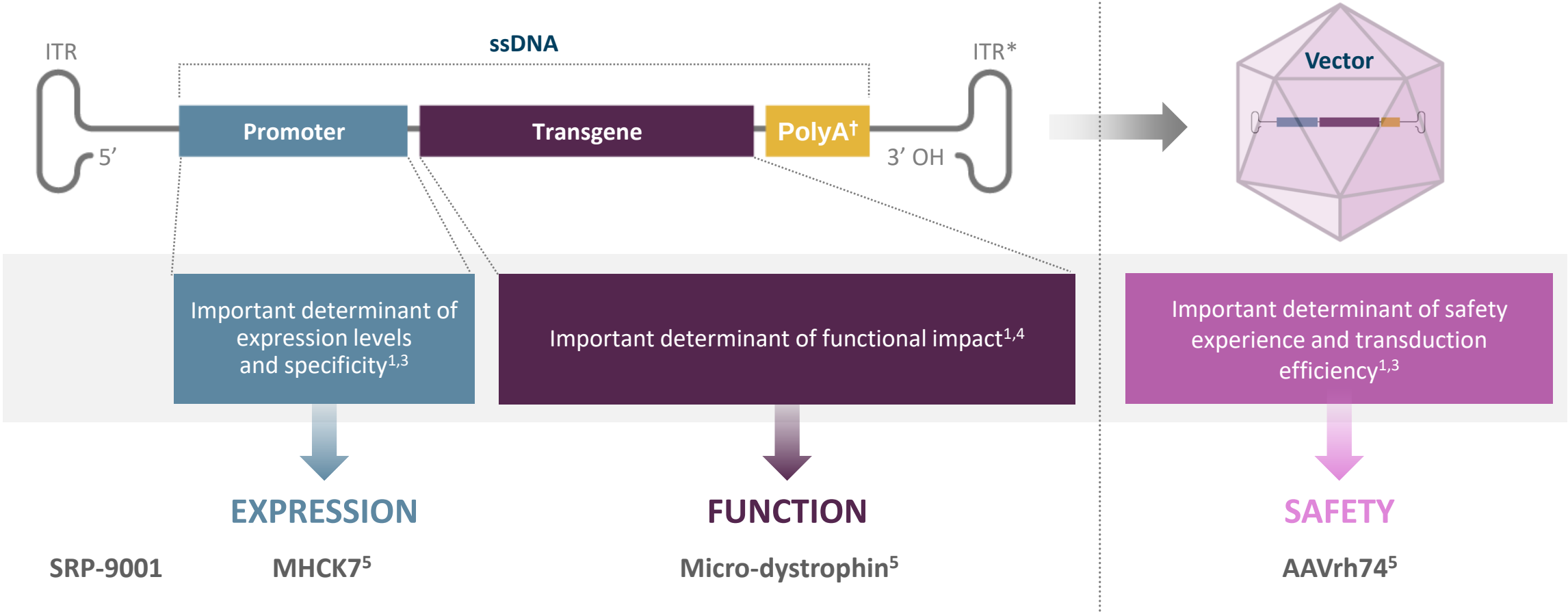
rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) is a novel AAV-based gene therapy for the treatment of DMD[1,2]



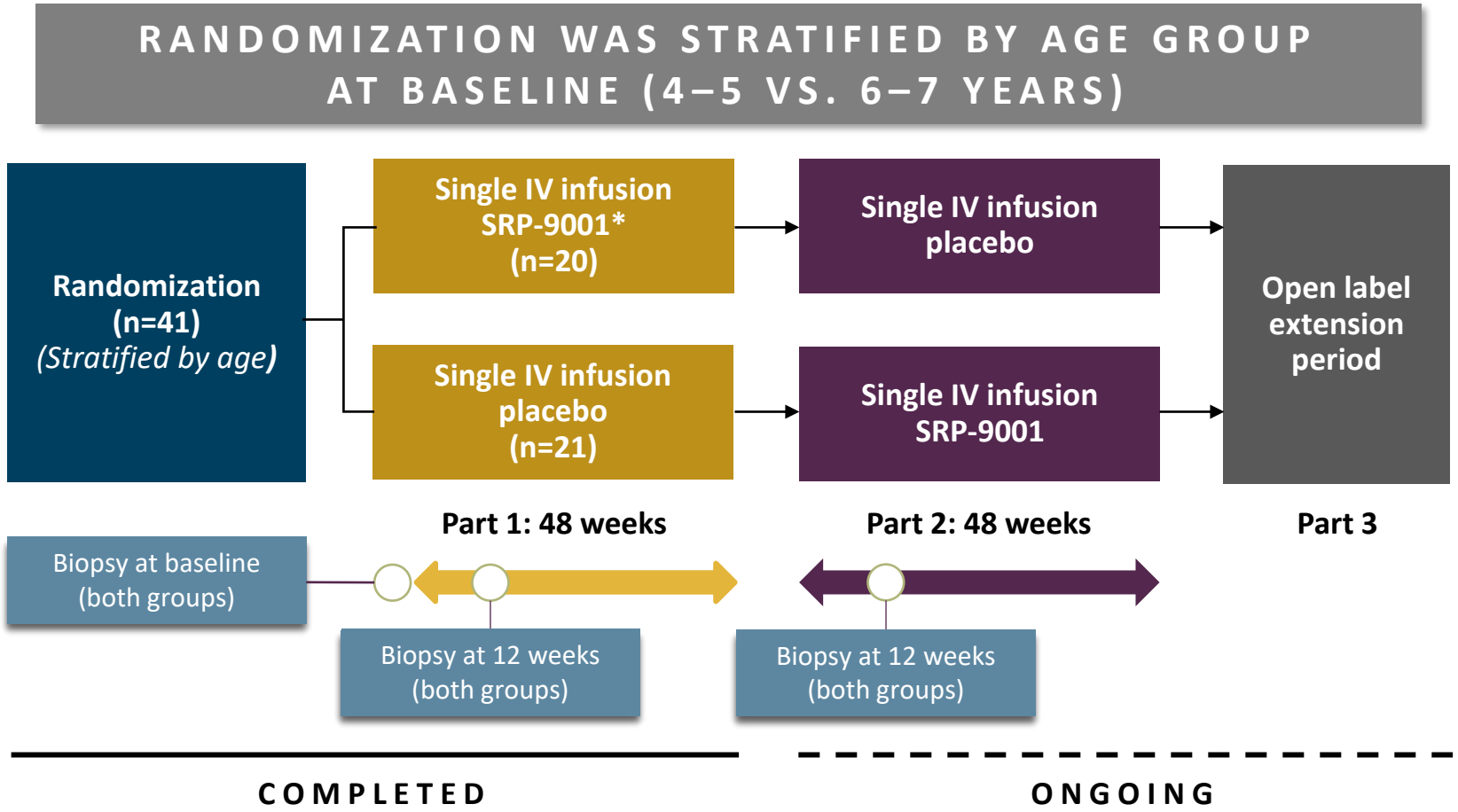
*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (i.e., copies) it. 1. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-74. 2. US National Library of Medicine. Help Me Understand Genetics: Gene Therapy; 2013. Available at: https://ghr.nlm.nih.gov/primer/therapy/genetherapy. Last accessed: April 2021. 3. Zheng C and Baum BJ. *Methods Mol Biol*. 2008;434:205-19. 4. Chandler RJ and Venditti CP. *Transl Sci Rare Dis*. 2016;1(1):73-89. 5. Mendell JR, et al. *JAMA Neurol*. 2020;77(9):1-10.

AAV, adeno-associated virus; DMD, Duchenne muscular dystrophy; ITR, inverted terminal repeat; OH, hydroxyl; polyA A, polyadenylation; rAAVrh74, recombinant AAV rhesus isolate serotype 74; ssDNA, single-stranded DNA.

SRP-9001-102 is a three-part study (NCT03769116)

A randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, efficacy, and tolerability of a single dose of SRP-9001 compared to placebo in boys with DMD aged 4–7 years

Study is ongoing and remains blinded. Functional results for all patients will be analyzed at both 48-week timepoints



*All patients received the target dose as determined by the supercoiled standard qPCR method specified in the protocol at the time. Subsequent retrospective analysis using the new linear qPCR method indicates that 60% of the patients received a dose lower than the target dose based on the new method. All patients going forward will receive target dose as determined by the new method. Target dose 2E14 vg/kg was estimated by supercoiled qPCR and is equivalent to 1.33E14 vg/kg using the linear qPCR method

DMD, Duchenne muscular dystrophy; IV, intravenous; qPCR, quantitative polymerase chain reaction. ClinicalTrials.gov Identifier: NCT03769116. Last accessed: February 2021.

Endpoints and inclusion/exclusion criteria

PRIMARY and SAFETY ENDPOINTS

- Incidence of SAEs and treatment-related AEs
- Change in micro-dystrophin protein expression, from baseline to Week 12, as measured by western blot
- Change in NSAA total score from baseline to Week 48

SECONDARY ENDPOINTS

- Change in micro-dystrophin protein expression, from baseline to Week 12, as measured by IF (fiber intensity + PDPF)
- Change in timed functional tests from baseline to Week 48

KEY INCLUSION CRITERIA

- Established clinical diagnosis of DMD and documented *DMD* gene mutation (frameshift or premature stop codon)
- Indication of symptomatic muscular dystrophy by protocol-specified criteria
- Ability to cooperate with motor assessment testing
- Stable dose equivalent of oral corticosteroids for at least 12 weeks
- Negative for AAVrh74 antibodies

KEY EXCLUSION CRITERIA

- Impaired cardiovascular function on echocardiogram
- Prior or ongoing medical condition on physical examination, ECG, or laboratory findings that could adversely affect patient safety, compromise completion of follow-up, or impair assessment of study results
- Exposure to another investigational drug or exon skipping medication within 6 months of screening
- Exposure to an investigational or commercial gene therapy product
- Abnormal liver or renal function by protocol-specified criteria
- *Other inclusion / exclusion criteria apply*

AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; IF, immunofluorescence; NSAA, North Star Ambulatory Assessment; PDPF, percentage dystrophin-positive fibers; SAEs, serious AEs; TRAEs, treatment-related AEs.
ClinicalTrials.gov Identifier: NCT03769116. Last accessed: April 2021.

Baseline demographics: intent to treat population

Characteristic	Statistics	Placebo (n=21)	SRP-9001 (n=20)
Age in years	Mean (SD) Min, Max	6.2 (1.1) 4.3, 8.0	6.3 (1.2) 4.5, 7.9
Years since corticosteroid treatment started	Mean (SD) Min, Max	1.3 (1.2) 0.2, 5.1	1.0 (1.1) 0.2, 3.8
Corticosteroid type, deflazacort	n (%)	7 (33.3)	7 (35.0)
Dosing weight in kg	Mean (SD) Min, Max	21.6 (3.5) 15.0, 30.0	23.3 (4.4) 18.0, 34.5
4-5-year-old NSAA total score at baseline	Mean P-value (vs. placebo)	20.4	20.1 0.8318
6-7-year-old NSAA total score at baseline	Mean P-value (vs. placebo)	24.0	19.6 0.0046

The majority of patients (61%) were ≥6 years of age, and age was a stratification factor for randomization

kg, kilograms; n, number; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

9001-102 Part 1: safety summary

Generally well tolerated, consistent with previous studies

85% of the SRP-9001-treated group had treatment-related TEAEs vs. 43% in the placebo group

- The most common treatment-related TEAE was vomiting
  - 60% (12/20) in the SRP-9001 group vs. 19% (4/21) in the placebo group

Among patients with treatment-related TEAEs, 82% of patients had only mild or moderate treatment related TEAEs

No clinically relevant complement activation was observed

Total of four patients with five treatment-related SAEs

- Four SAEs were reported in the group that received SRP-9001, and one in the placebo group
  - Three instances of rhabdomyolysis (two in patients who received SRP-9001 and one in the placebo group); all were resolved
  - In SRP-9001 patients: increased transaminases in one patient and liver injury in another; both had concurrent bilirubin elevation

No AE-related discontinuations and no deaths

No other important risks were identified

AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE.

SRP-9001-102 Part 1: micro-dystrophin expression was demonstrated in patients following treatment at Week 12

Micro-dystrophin expression by western blot at Week 12 (BLOQ=3.4)

	Percentage of normal (%)	Change from baseline
Mean ± SD (n=20)	28.1 ± 40.1	23.8 ± 39.8*

Micro-dystrophin expression by IF, percentage of dystrophin positive fibers at Week 12

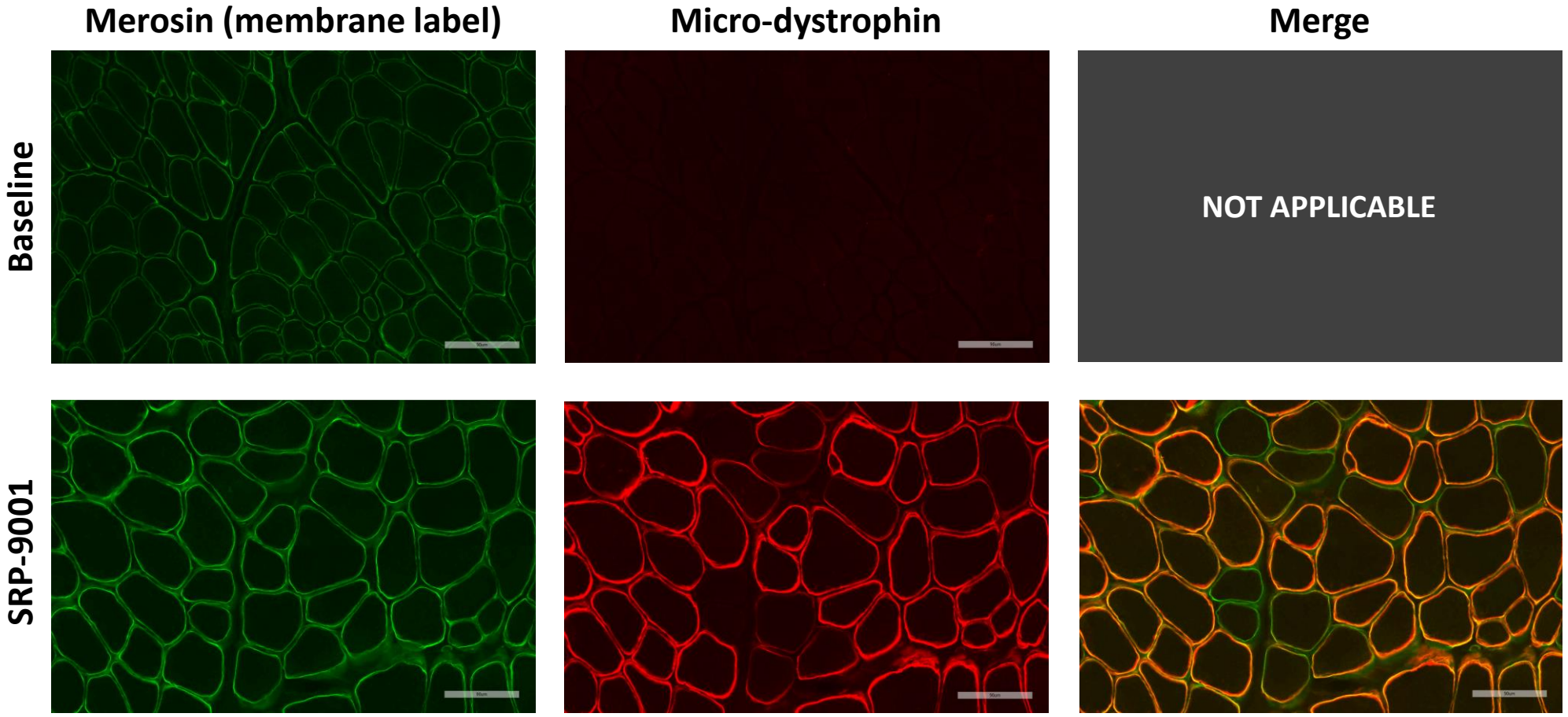
	PDPF (%)	Change from baseline
Mean ± SD (n=20)	33.0 ± 28.1	23.9 ± 25.6†

Vector genome copy number at Week 12

	Copies per nucleus at Week 12
Mean ± SD (n=20)	1.6 ± 1.5

*Western blot baseline comprised BLOQ values and non-specific protein signals. †PDPF levels at baseline include background staining and revertant fibers.
BLOQ, below limit of quantification; IF, immunofluorescence; PDPF, percentage dystrophin-positive fibers; SD, standard deviation.

Representative images of micro-dystrophin protein expression: immunofluorescence following SRP-9001 administration

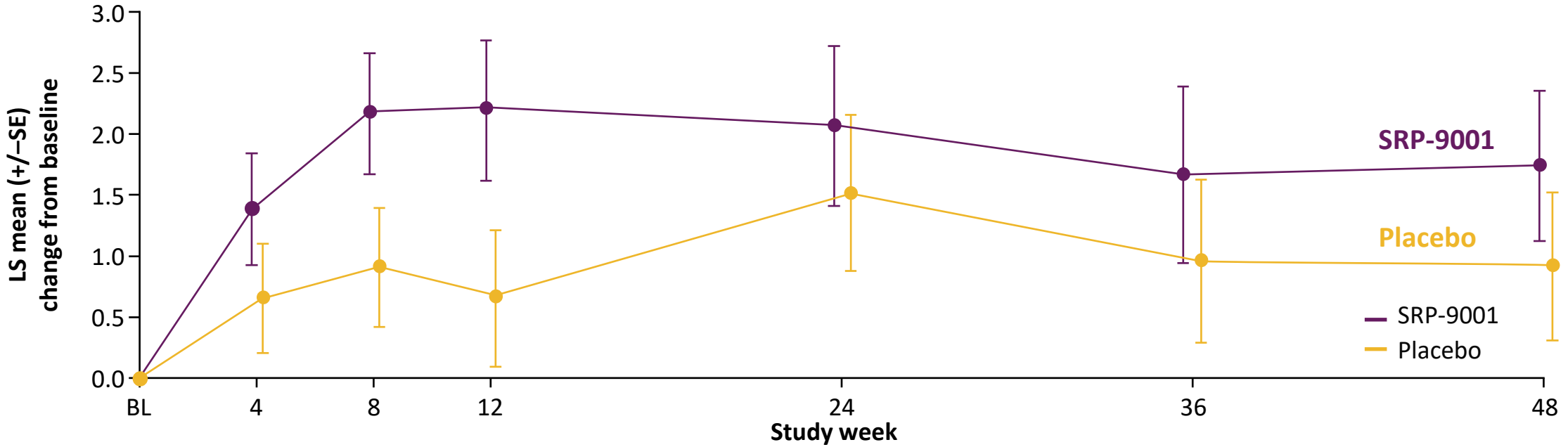


Patient had 95% PDPF on treatment

PDPF, percentage dystrophin positive fibers.

SRP-9001-102 Part 1: separation between SRP-9001 and placebo on NSAA primary functional endpoint was not statistically significant

NSAA change from baseline of +1.7 in SRP-9001 treated group vs. +0.9 in placebo group, which is not statistically different (P=0.37)

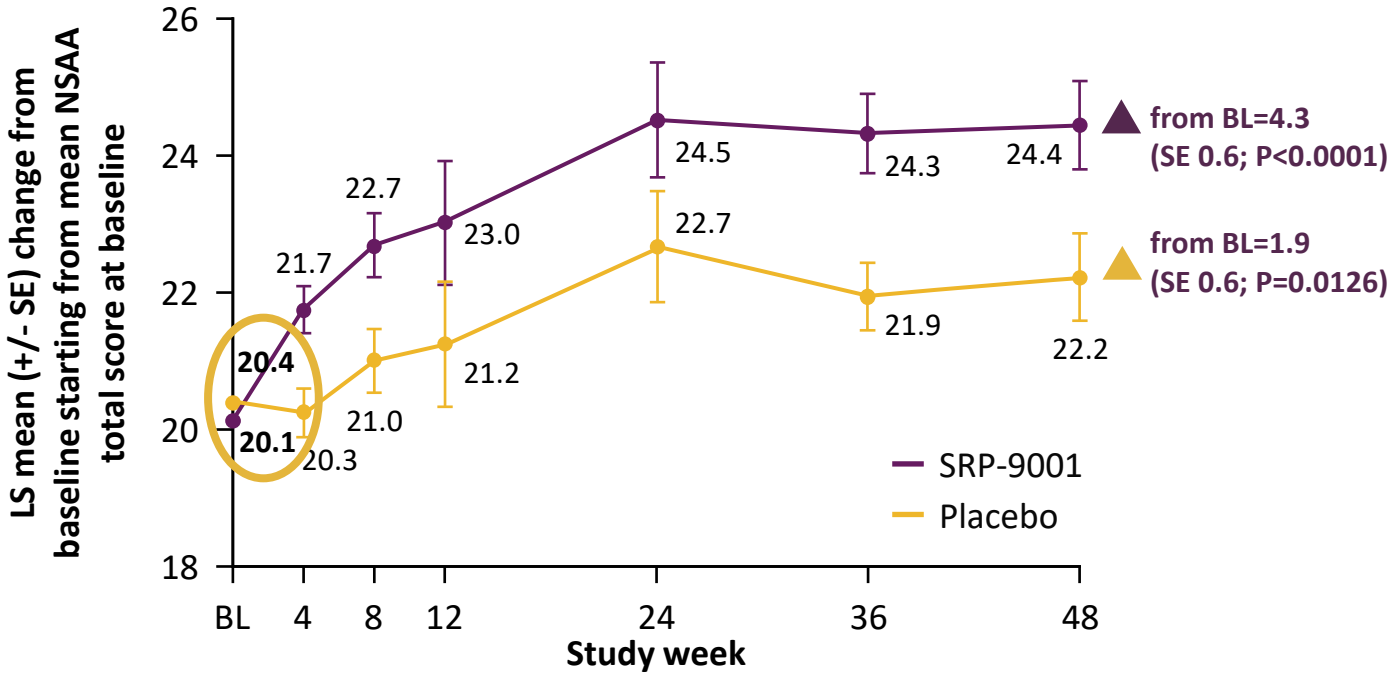


Number of patients

	BL	4	8	12	24	36	48
Placebo	21	21	19	20	16	19	21
SRP-9001	20	20	18	19	15	14	19

BL, baseline; LS, least squares; NSAA, North Star Ambulatory Assessment; SE, standard error.

NSAA 4-5-year-old subgroup analysis: SRP-9001 treated patients had a statistically significant improvement vs. placebo at Week 48



Number of patients							
Placebo	8	8	8	8	7	8	8
SRP-9001	8	8	7	8	6	5	8

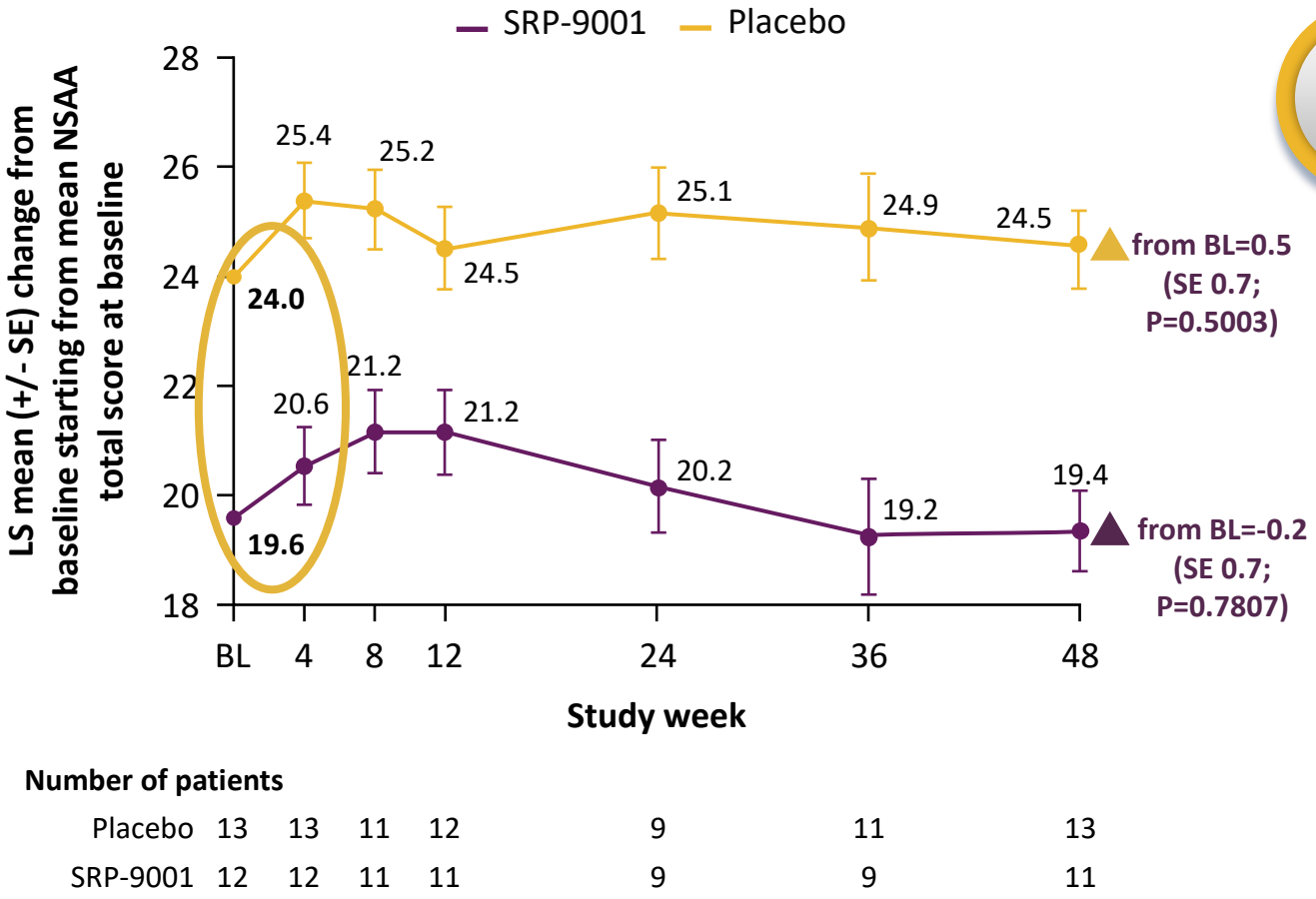
LSM change at 48 weeks SRP-9001 vs. placebo=2.5 (SE 0.9; P-value=0.0172)

In 4-5-year-olds, functional measures were well-matched between groups at baseline

Characteristic	Statistics	SRP-9001 Age 4-5 (n=8)	Placebo Age 4-5 (n=8)
NSAA	Mean ***P-value (vs. placebo)***	20.1 ***0.8318***	20.4
100 meter (s)	Mean ***P-value (vs. placebo)***	58.76 ***0.7925***	59.79
Ascend 4 Steps (s)	Mean ***P-value (vs. placebo)***	3.46 ***0.9822***	3.48
Time to Rise (s)	Mean ***P-value (vs. placebo)***	3.89 ***0.7421***	3.76
10 meter (s)	Mean ***P-value (vs. placebo)***	5.01 ***0.5832***	5.24

BL, baseline; LS, least squares; LSM, least squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error.

NSAA subgroup analysis at Week 48: functional measures were not well matched at baseline in 6-7-year-olds



Number of patients

Placebo	13	13	11	12	9	11	13
SRP-9001	12	12	11	11	9	9	11

Baseline NSAA scores for patients who received SRP-9001 vs. placebo patients 6-7 years of age: **19.6 vs. 24.0 (P-value=0.0046)**

In 6-7-year-olds, functional measures were **not well-matched** between groups at baseline; this may have contributed to the lack of statistically significant differences in NSAA change between groups

Characteristic	Statistics	SRP-9001 Age 6-7 (n=12)	Placebo Age 6-7 (n=13)
NSAA	Mean ***P-value (vs. placebo)***	19.6 ***0.0046***	24.0
100 meter (s)	Mean ***P-value (vs. placebo)***	62.56 ***0.0219***	50.21
Ascend 4 Steps (s)	Mean ***P-value (vs. placebo)***	3.83 ***0.0958***	2.86
Time to Rise (s)	Mean ***P-value (vs. placebo)***	5.91 ***0.0053***	3.44
10 meter (s)	Mean ***P-value (vs. placebo)***	5.58 ***0.0313***	4.58

BL, baseline; LS, least squares; NSAA, North Star Ambulatory Assessment; s, seconds; SE, standard error.

SRP-9001-102: Part 1 summary

QUESTION[1]

EXPERIMENT

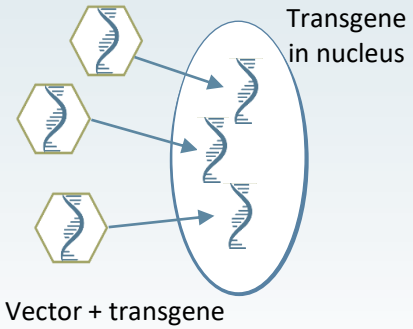
1	2	3	4	5
What was the safety and tolerability experience with SRP-9001?	Is the transgene DNA inside muscle cells?	Is the desired protein made?	Is the protein at the cell membrane?	Is muscle function improved?

SAFETY

- Findings from SRP-9001-102 Part 1 reinforce a favorable benefit–risk profile and provide important information for ongoing clinical development
- SRP-9001 is well tolerated, which is consistent with previous studies
- No unexpected immunological responses were observed

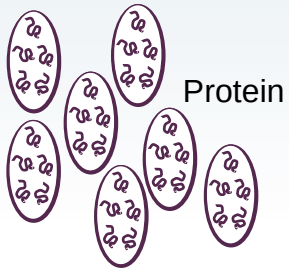
VECTOR GENOME COPIES / NUCLEUS

- **1.6** copies per nucleus at Week 12



WESTERN BLOT

- The primary biological endpoint of micro-dystrophin expression at 12 weeks post-treatment was achieved
- **Micro-dystrophin expression** (western blot): 28.1% of normal
- **Change from baseline:** 23.8%



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- **% of cells with protein:** % of dystrophin-positive fibers was 33.0% of normal at Week 12
- **Change from baseline:** 23.9% at Week 12

FUNCTIONAL OUTCOMES

North Star Ambulatory Assessment (NSAA)

- NSAA change from baseline of +1.7 in SRP-9001 vs. +0.9 in placebo was not statistically different (P=0.37). Difficult to interpret considering the significant imbalance in NSAA at baseline in the 6-7-year-old subgroup
- In 4-5-year-old group, in which baseline function was well-matched, NSAA change was statistically different in SRP-9001 (+4.3) vs. placebo (+1.9): P=0.0172

NSAA, North Star Ambulatory Assessment; PDPF.

1. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-74.