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

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- Trial registration: NCT03769116
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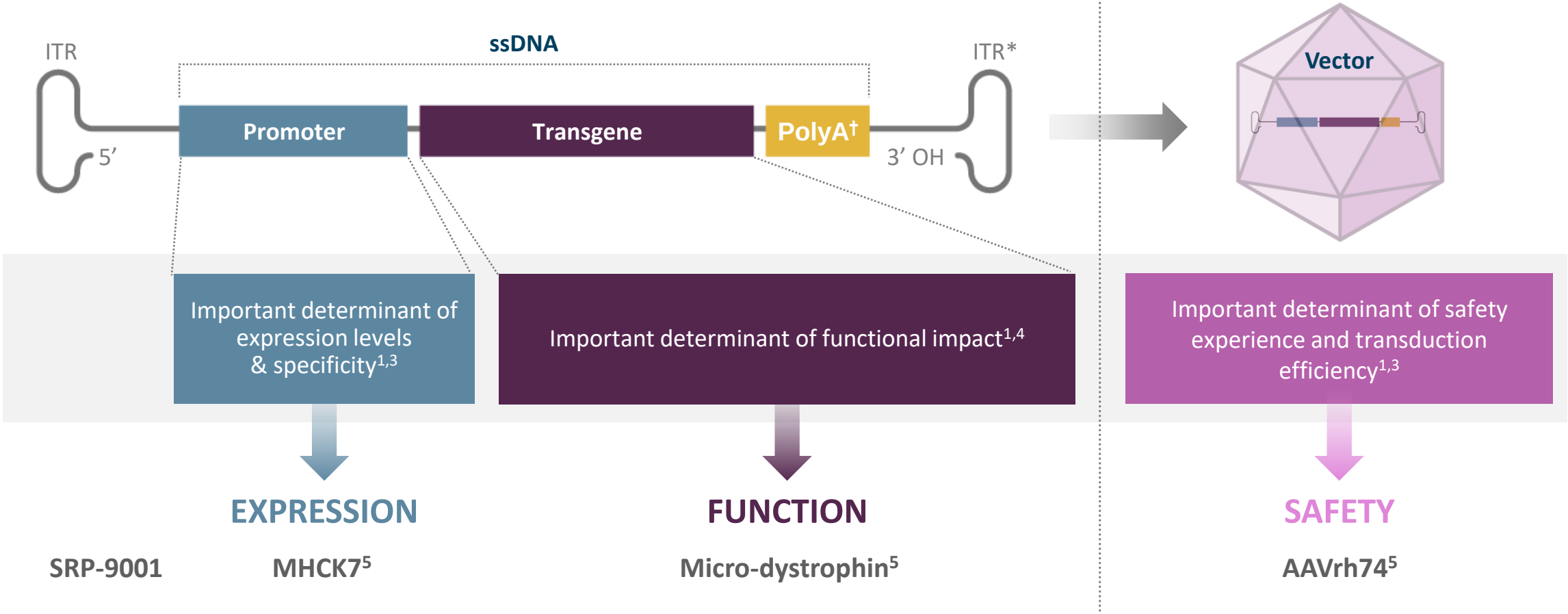
rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) is a novel AAV-based gene therapy for the treatment of DMD[1,2]



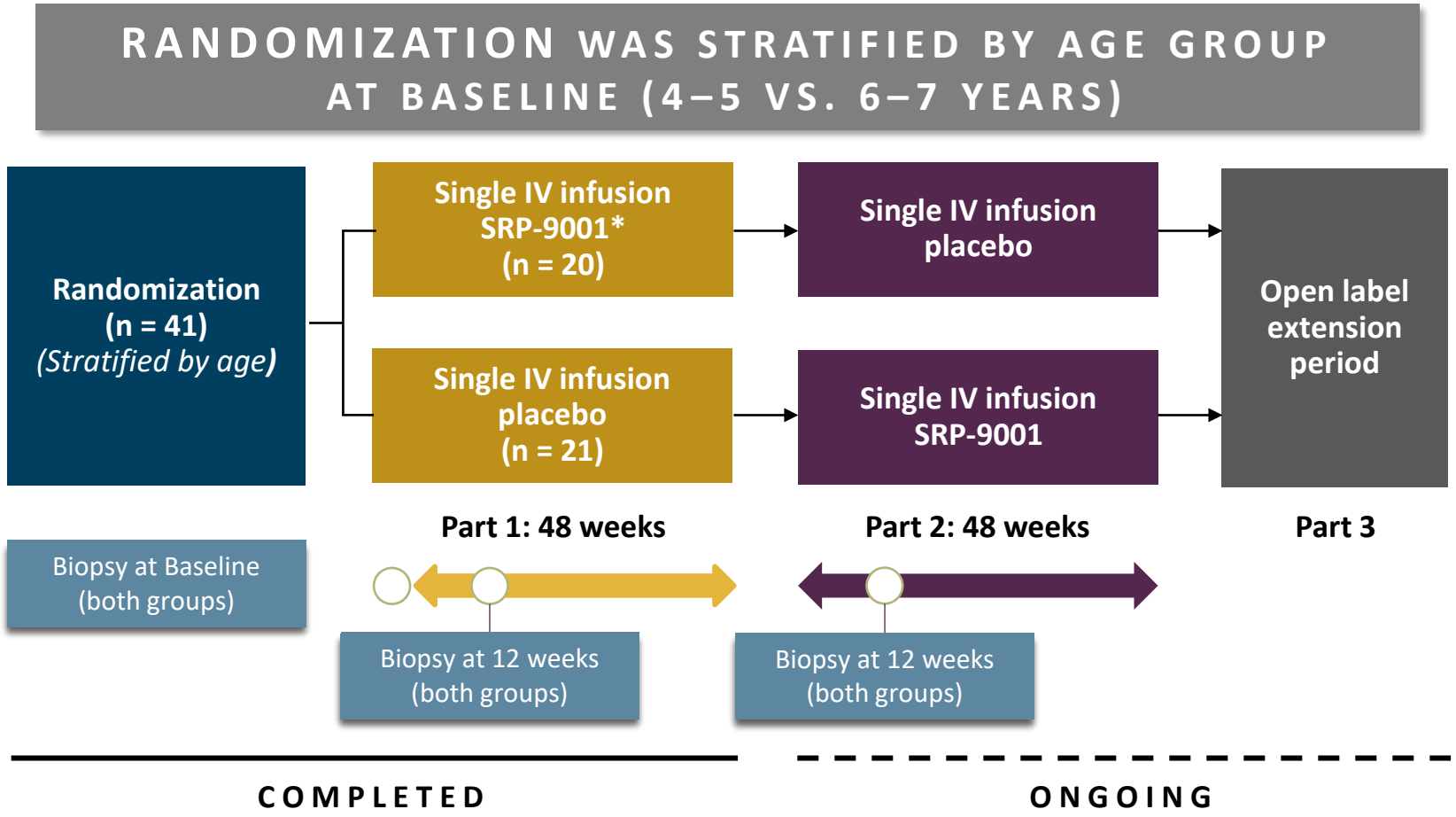
AAV, adeno-associated virus; DMD, Duchenne muscular dystrophy; ITR, inverted terminal repeat; OH, hydroxyl; polyA A, polyadenylation; rAAVrh74, recombinant AAV rhesus isolate serotype 74; ssDNA, single-stranded DNA.

*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: February 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.

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 in Part 1 received the intended target dose of $2x10^{14}$ vg/kg by supercoiled standard qPCR. Following transition to the validated linear standard qPCR method, lots used in Part 1 were retrospectively titered and demonstrated variability, with only one lot at the target dose of 1.33e14 vg/kg. ~60% of patients received less than the target dose by linear standard qPCR.
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 as measured by IF (fiber intensity + PDPF)
- Change from Baseline in timed functional tests

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; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; IF, immunofluorescence; NSAA, North Star Ambulatory Assessment; PDPF, percentage dystrophin-positive fibers; SAEs, serious adverse events; TRAEs, treatment-related adverse events.
ClinicalTrials.gov Identifier: NCT03769116. Last accessed: February 2021.

Baseline demographics: intent to treat population

Characteristic	Statistics	Placebo (n = 21)	SRP-9001 (n = 20)
Age (years)	Mean (SD) Min, Max	6.24 (1.13) 4.34, 7.98	6.29 (1.19) 4.47, 7.85
Years since corticosteroid treatment started	Mean (SD) Min, Max	1.26 (1.22) 0.23, 5.07	0.99 (1.07) 0.22, 3.80
Corticosteroid type, deflazacort	n (%)	7 (33.3)	7 (35.0)
Dosing weight (kg)	Mean (SD) Min, Max	21.60 (3.49) 15.0, 30.0	23.28 (4.37) 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

SD, standard deviation.

SRP-9001-102 Part 1: overview of AEs

	SRP-9001 (n = 20) n (%)	Placebo (n = 21) n (%)	Total (n = 41) n (%)
Number of AEs	306	229	535
Number of TEAEs	283	208	491
Number of SAEs	4	2	6
Number of treatment-related TEAEs	62	11	73
Number of treatment-related SAEs	4	1	5
Patients with any AE	20 (100.0)	21 (100.0)	41 (100.0)
Patients with any TEAE	20 (100.0)	21 (100.0)	41 (100.0)
Patients with any SAEs	3 (15.0)	2 (9.5)	5 (12.2)
Patients with any treatment-related TEAE	17 (85.0)	9 (42.9)	26 (63.4)
Patients with any treatment-related SAEs	3 (15.0)	1 (4.8)	4 (9.8)
Patients with any AEs leading to study discontinuation	0	0	0
Deaths	0	0	0

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

Overview of AEs: treatment-related SAEs

System organ class Preferred term	SRP-9001 (n = 20) n (%)	Placebo (n = 21) n (%)	Total (n = 41) n (%)
Patients with any treatment-related SAE	3 (15.0)	1 (4.8)	4 (9.8)
Liver injury	1 (5.0)	0	1 (2.4)
Transaminases increased	1 (5.0)	0	1 (2.4)
Rhabdomyolysis	2 (10.0)	1 (4.8)	3 (7.3)

Liver enzyme elevation in some patients, with onset 6–8 weeks after infusion

- Serious in two patients receiving SRP-9001, who had concurrent bilirubin elevation

Rhabdomyolysis in two patients receiving SRP-9001 and one receiving placebo may be due to disease activity, not treatment[1]

No patients with hepatic events had signs of hepatic failure; all hepatic events were transient and responsive to corticosteroids

SAE, serious adverse event.

1. Torres PA, et al. *Ochsner J*. 2015;15(1):58-69.

9001-102 Part 1: safety summary

Generally well tolerated, consistent with previous studies

85% of the group who received treatment had treatment-related TEAEs vs. 43% in the placebo group

- The most common treatment-related TEAE was vomiting
  - 60% (12/20) in treatment group vs. 19% (4/21) in 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) that resolved
  - Increased transaminases in one patient and liver injury in another (both in patients who received SRP-9001)

No AE related discontinuations and no deaths

No other important risks were identified

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

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

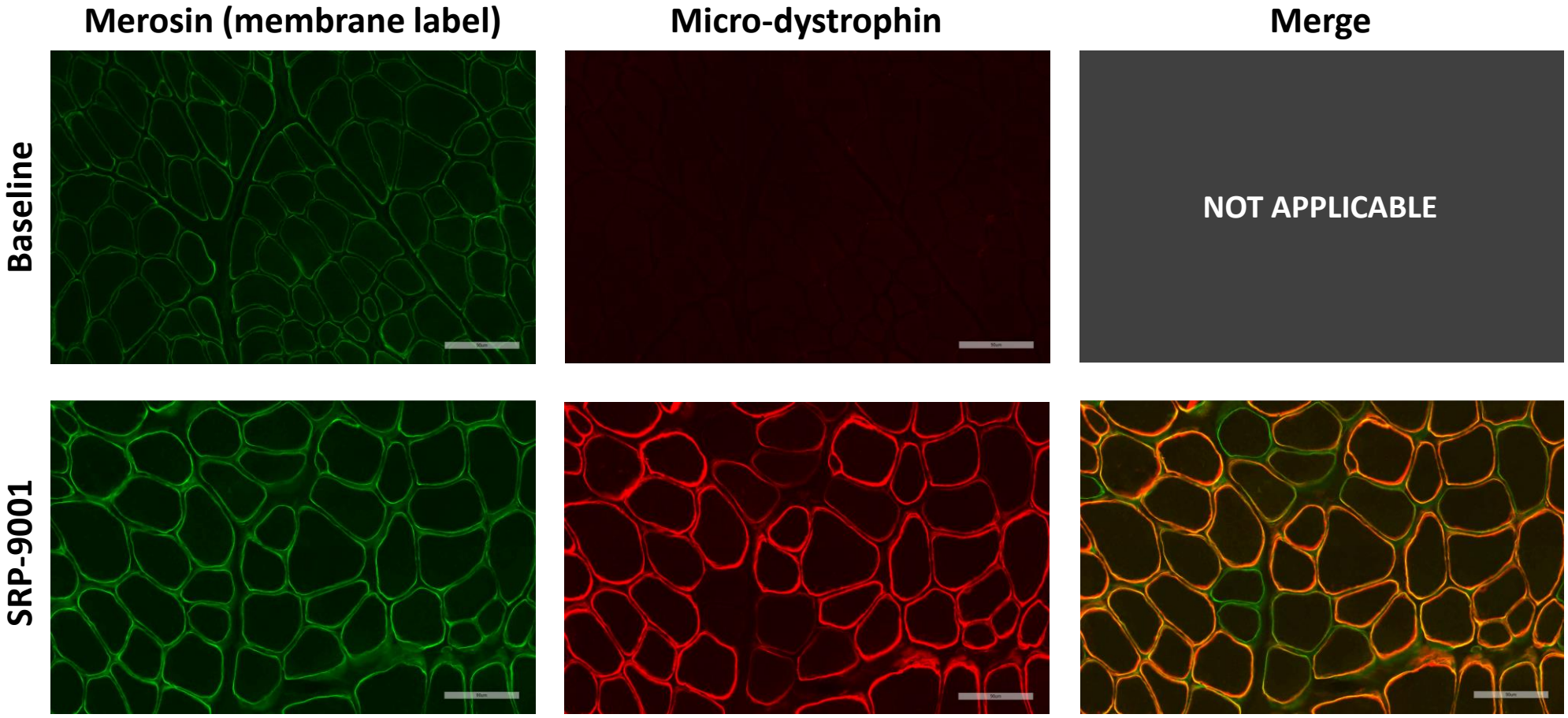
Micro-dystrophin expression Western blot* (BLOQ = 3.42)	Percentage of normal (%)
Mean, SD (n = 20)	28.1 ± 40.1

Micro-dystrophin expression (IF)	PDPF (% normal)†	Intensity (% normal)‡
Mean, SD (n = 20)	33.0 ± 28.1	63.7 ± 46.4

Vector genome copy number	Copies per nucleus
Mean (n = 20), SD	1.6 ± 1.5

*Western baseline sample background levels BLOQ, †PDPF levels at baseline was 8.8%, which includes background staining and revertant fibers, ‡Calculating a baseline % intensity of normal control can not be reliably measured due to <10% dystrophin positive fibers at baseline. Fluorescent mean stain density at baseline is 0.065 on scale of 0 to 1. 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

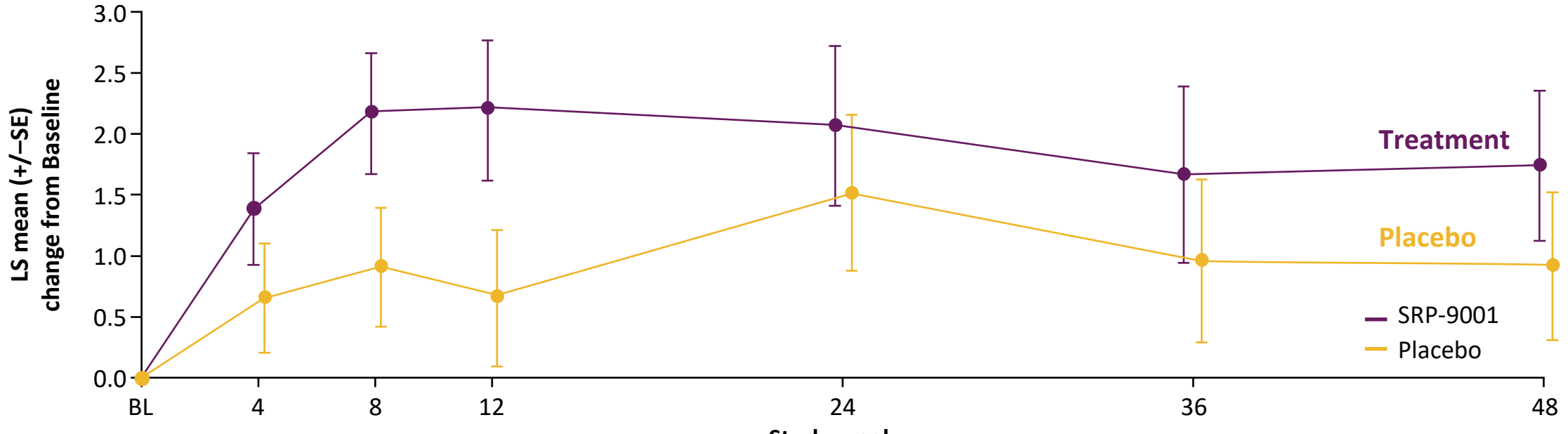


Patient had 95% PDPF on treatment

PDPF, percentage dystrophin positive fibers.

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

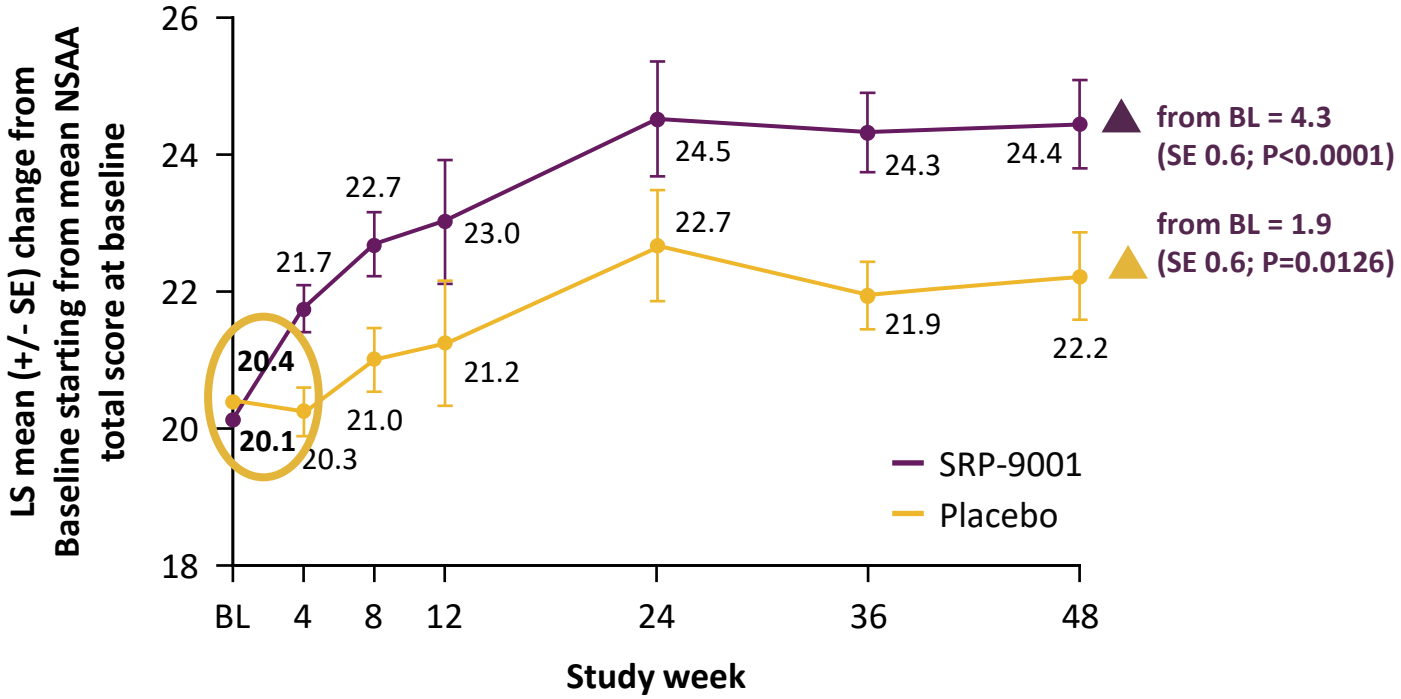
NSAA change from baseline of +1.7 in SRP-9001 treated group vs. +0.9 in placebo group, which is not statistically different (P=0.37)



Number of patients							
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- to 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

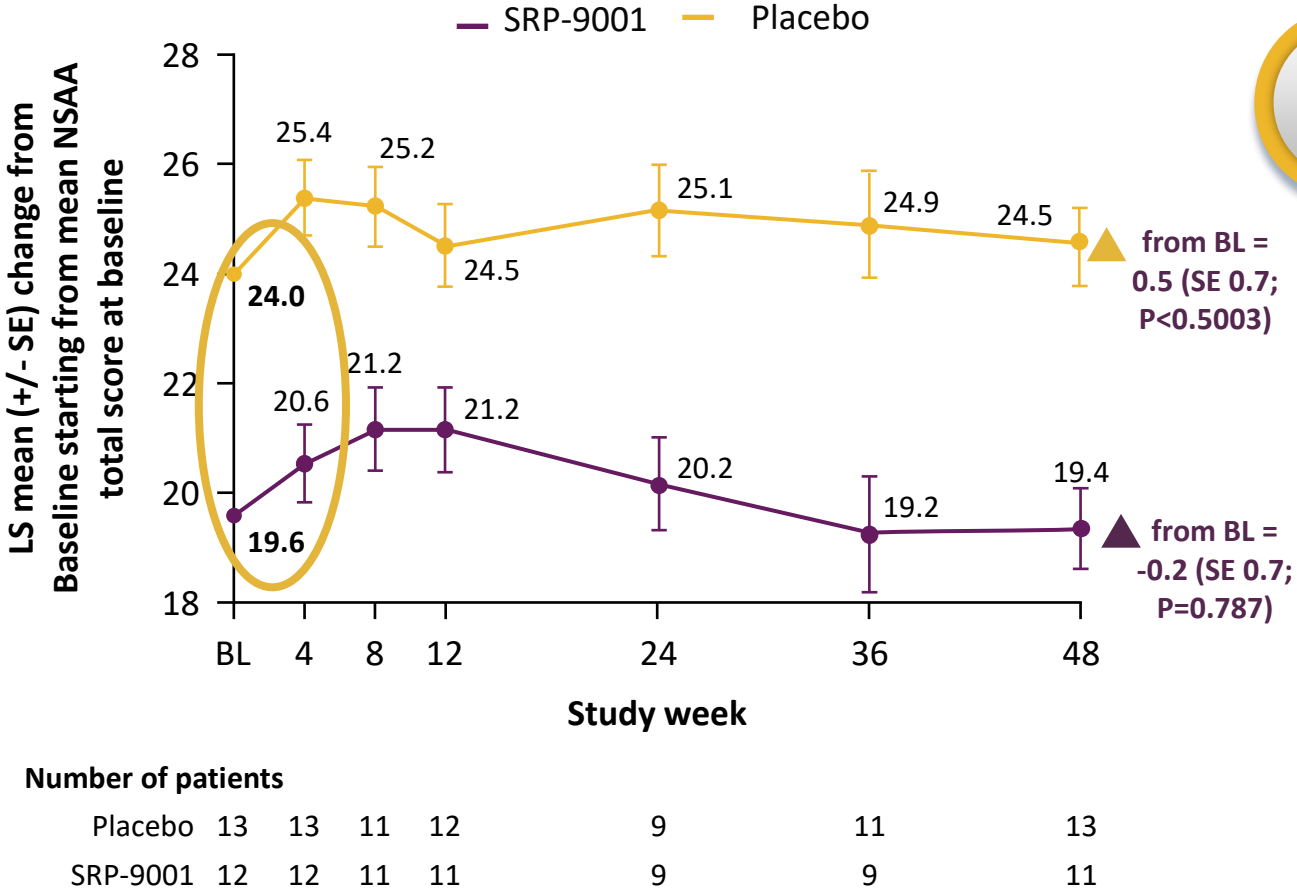
LSM change at 48 weeks SRP-9001 vs. Placebo = 2.5 (SE 0.9; P=0.0172)

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; NSAA, North Star Ambulatory Assessment; SE, standard error.

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



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

Functional measures were **not well matched** between groups at Baseline. The group treated with SRP-9001 (with lower baseline) would be expected to decline faster; 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; SE, standard error.

SRP-9001-102: Part 1 summary

QUESTION[1]

EXPERIMENT

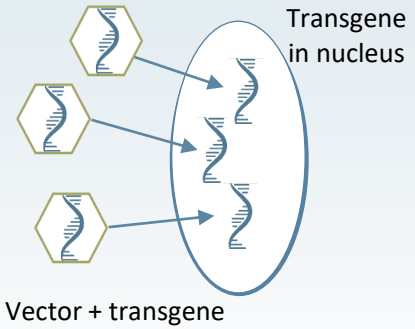
1. What was the safety and tolerability experience with SRP-9001?
2. Is the transgene DNA inside muscle cells?
3. Is the desired protein made?
4. Is the protein at the cell membrane?
5. Is muscle function improved?

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 in these patients

VECTOR GENOME COPIES / NUCLEUS

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



WESTERN BLOT

- Primary biological endpoint of micro-dystrophin expression at 12 weeks post-treatment was achieved
- Micro-dystrophin expression (western blot): **28.1% of normal**

IMMUNOFLUORESCENCE

At Week 12

- **% cells with protein:** % of dystrophin-positive fibers 33.0% of normal at Week 12
- **Intensity of fluorescent signal:** 63.7% of normal

FUNCTIONAL OUTCOMES

North Star Ambulatory Assessment (NSAA)

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

NSAA, North Star Ambulatory Assessment.

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