Safety, β-Sarcoglycan Expression, and Functional Outcomes From Systemic Gene Transfer of rAAVrh74.MHCK7.hSGCB in Limb-Girdle Muscular Dystrophy Type 2E/R4

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Disclosures

- LRR-K, ERP, SL, DAG, ASM, EK, SN, and XL are employees of Sarepta Therapeutics, Inc., and may have stock options
- JRM received financial support from Sarepta Therapeutics, Inc., for the travel and accommodation costs of study participants
- KL, KC, NR, and MI have no conflicts to disclose
- LL received fees from Sarepta for licensure of the natural history data set

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- rAAVrh74.MHCK7.hSGCB (SRP-9003) is an investigational therapy and has not been reviewed or approved by the FDA

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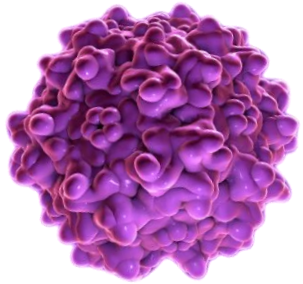
SRP-9003: Investigational gene therapy for limb-girdle muscular dystrophy type 2E/R4 (LGMD2E/R4)

- LGMD2E/R4 is caused by mutations in the *SGCB* gene[1,2]
- Adeno-associated virus (AAV)–mediated gene transfer therapy to express full-length β-sarcoglycan (SGCB) has potential to treat LGMD2E/R4

SRP-9003 construct: Self-complementary AAV vector

rAAVrh74



*Efficient **skeletal and cardiac muscle transduction**[3]*

MHCK7 PROMOTER

*Optimized for expression in **skeletal and cardiac muscle**[4-6]*

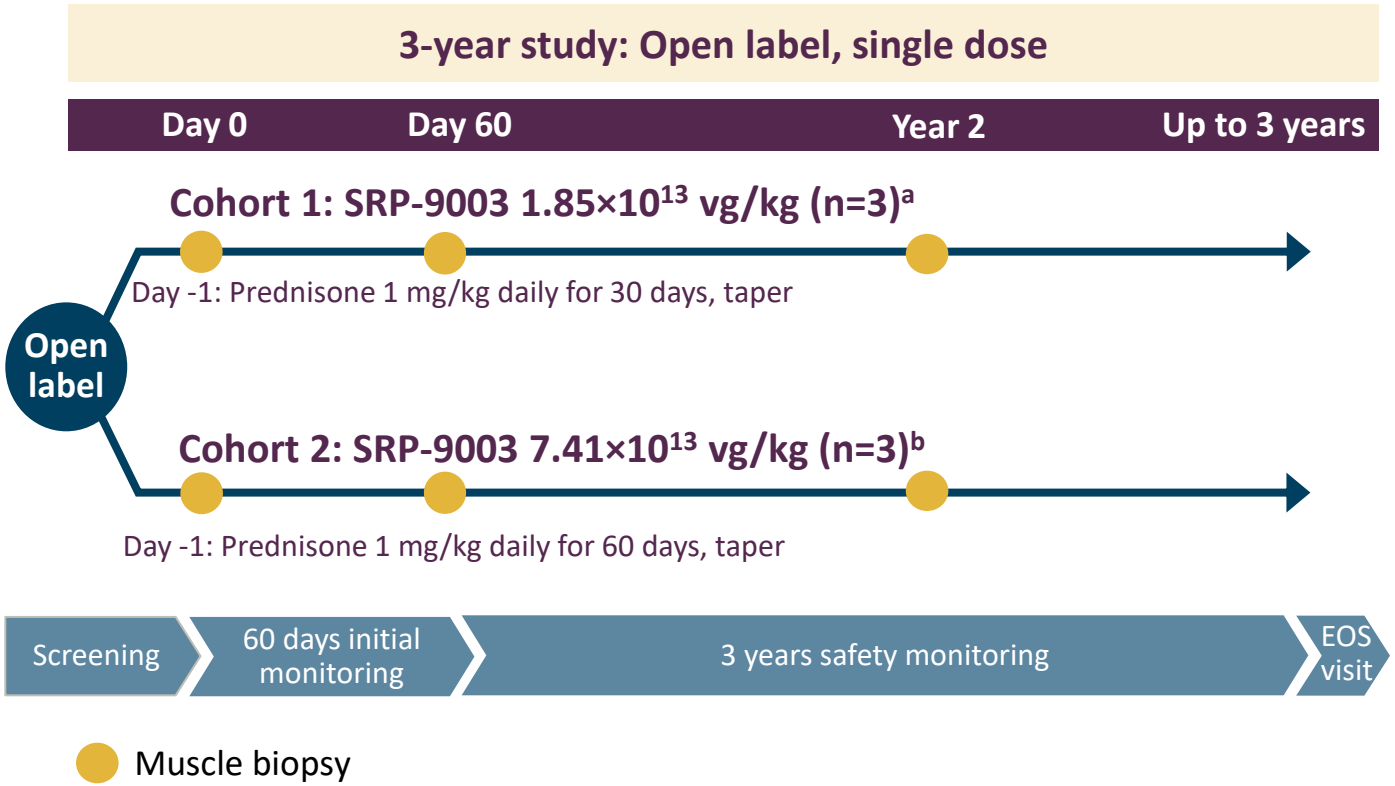
hSGCB cDNA

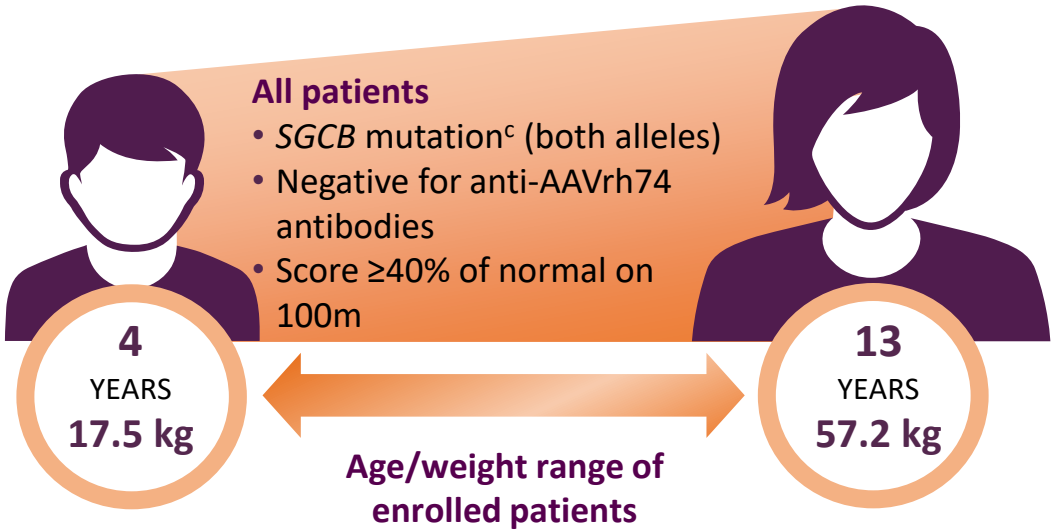
***Full-length human SGCB** gene transfer*

Objective: To report the interim findings of an ongoing Phase 1/2 clinical gene transfer trial delivering SRP-9003 to patients with LGMD2E/R4 (NCT03652259)

1. McNally EM. *The Sarcoglycans.* Austin, TX: Landes Bioscience. 2000-2013. 2. Gao Q, McNally EM. *Compr Physiol*. 2015;5(3):1223-39. 3. Chicoine LG, et al. *Mol Ther.* 2014;22:338-47. 4. Salva MZ, et al. *Mol Ther.* 2007;15:320-29. 5. Pozsgai ER, et al. *Mol Ther.* 2017;25:855-69. 6. Wang B, et al. *Gene Ther.* 2008;15:1489-99.

Study design: First-in-human, open-label, Phase 1/2 study





- **Primary endpoint:** Safety
- **Secondary endpoint:** SGCB expression at Week 8
- **Other endpoints**
  - Change in creatine kinase (CK) from baseline
  - Functional endpoints (NSAD and timed tests: 100m, 10m, 4-stair climb, and time to rise)

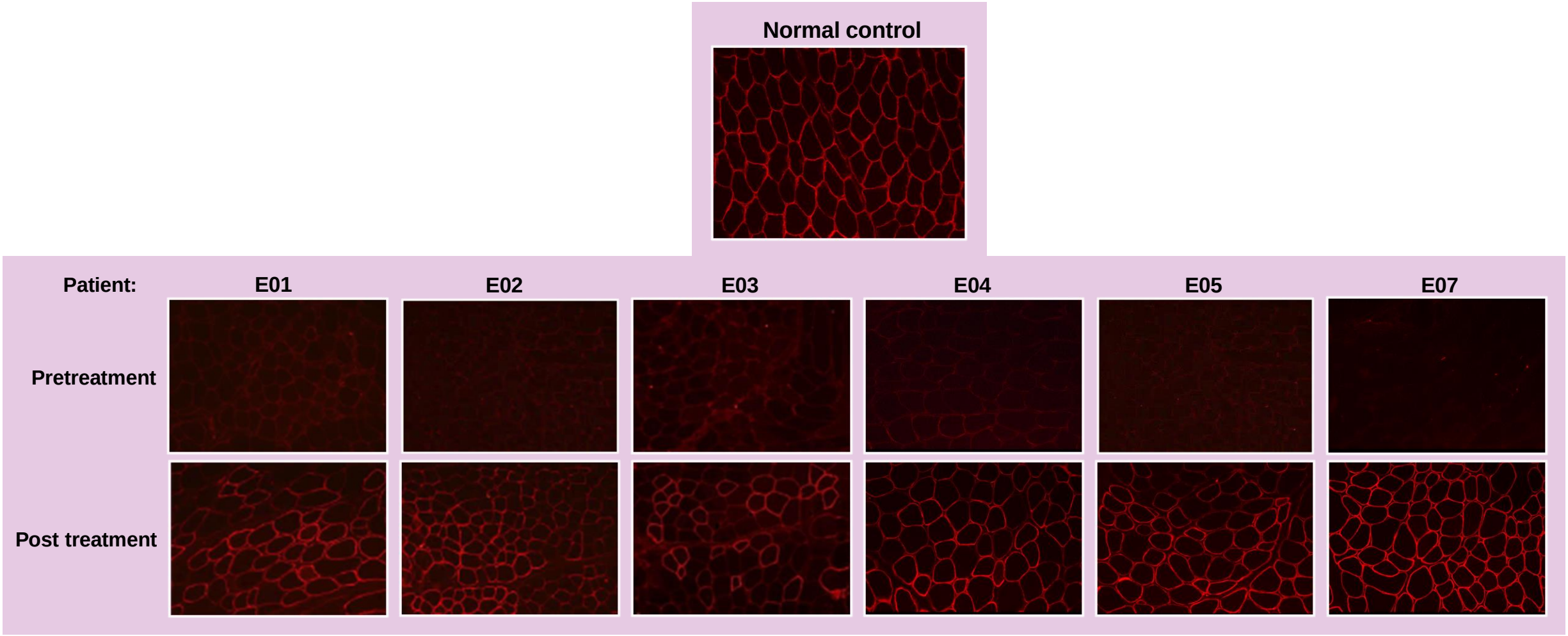
10m=10-m timed test; 100m=100-m timed test; EOS=end of study; NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies.

[a]1.85×10^{13} vg/kg measured using linear reference plasmid DNA quantitative polymerase chain reaction (qPCR); supercoiled reference DNA equivalent is 5×10^{13} vg/kg;

[b]7.41×10^{13} vg/kg measured using linear reference plasmid DNA qPCR; supercoiled reference DNA equivalent is 2×10^{14} vg/kg;

[c]Patients 1–5 had missense mutations in exons 3–6, and Patient 6 had a nonsense mutation.

Robust expression and sarcolemmal localization of SGCB at Day 60 post infusion



SGCB=β-sarcoglycan.

Expression of SGCB at 60 days post infusion was sustained for 2 years in Cohort 1

SGCB protein expression at skeletal muscle sarcolemma

Cohort 1 (1.85×10^{13} vg/kg)[a]

Time point	Western blot % NC (SD)	% SGCB+ fibers % NC (SD)	SGCB intensity % NC (SD)	Vector copies per nucleus (SD)	
				qPCR	ddPCR
Day 60	36 (2.7)	51 (10.6)	47 (9.5)	0.59 (0.4)	—
Year 2	54 (16.1)	48 (22.0)	35 (22.9)	0.13 (0.1)	0.46 (0.4)

Cohort 2 (7.41×10^{13} vg/kg)[b]

Time point	Western blot % NC (SD)	% SGCB+ fibers % NC (SD)	SGCB intensity % NC (SD)	Vector copies per nucleus (SD)	
				qPCR	ddPCR
Day 60	62 (8.7)	72 (6.2)	73 (21.8)	4.24 (2.8)	2.26 (0.9)

A dose-response in full-length SGCB protein expression was observed at Day 60 and sustained at 2 years in Cohort 1

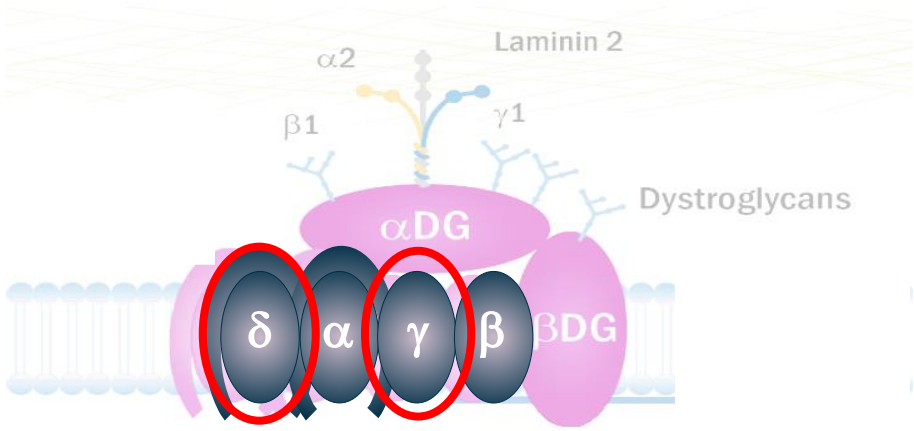
ddPCR=droplet digital PCR; NC=normal control; PCR=polymerase chain reaction; qPCR=quantitative PCR; SGCB=β-sarcoglycan. Values are mean (SD).

[a]1.85×10^{13} vg/kg measured using linear reference plasmid DNA qPCR; supercoiled reference DNA equivalent is 5×10^{13} vg/kg;

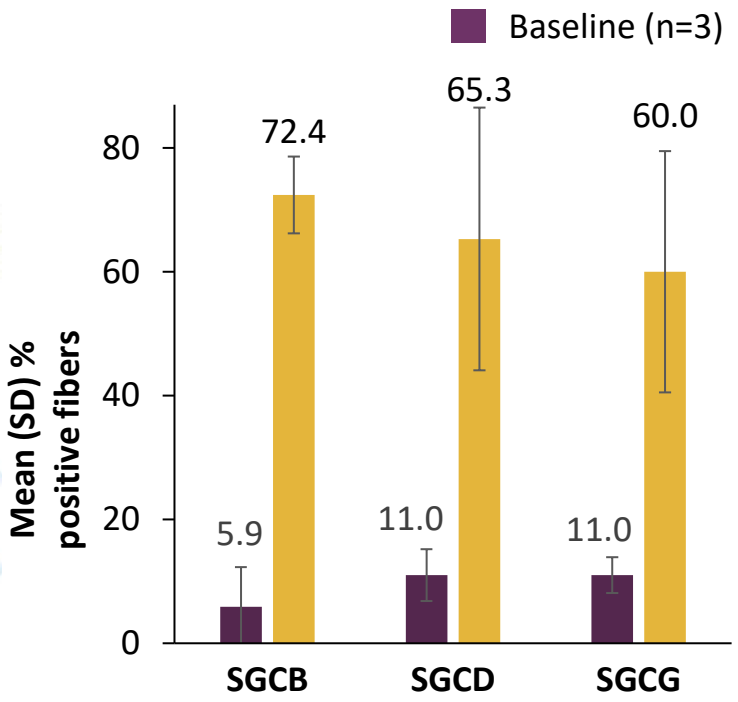
[b]7.41×10^{13} vg/kg measured using linear reference plasmid DNA qPCR; supercoiled reference DNA equivalent is 2×10^{14} vg/kg.

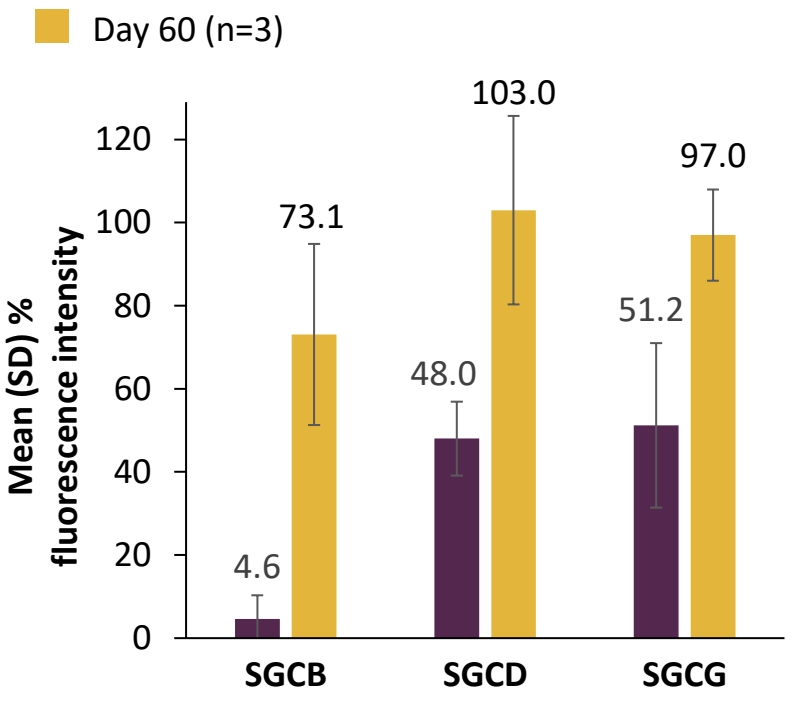
Expression of SGCB results in increased expression of SGCD and SGCG, demonstrating reconstitution of the sarcoglycan complex within the DAPC

Sarcoglycan complex



Expression of the dystrophin-associated protein complex (DAPC) (Cohort 2, Day 60)

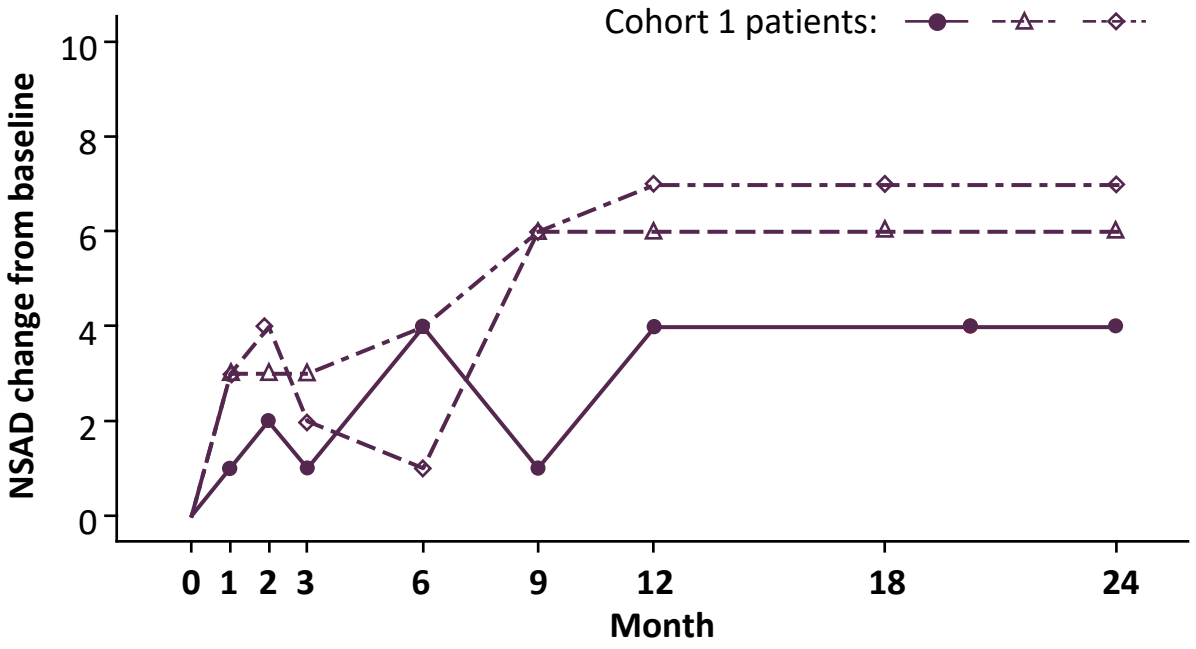




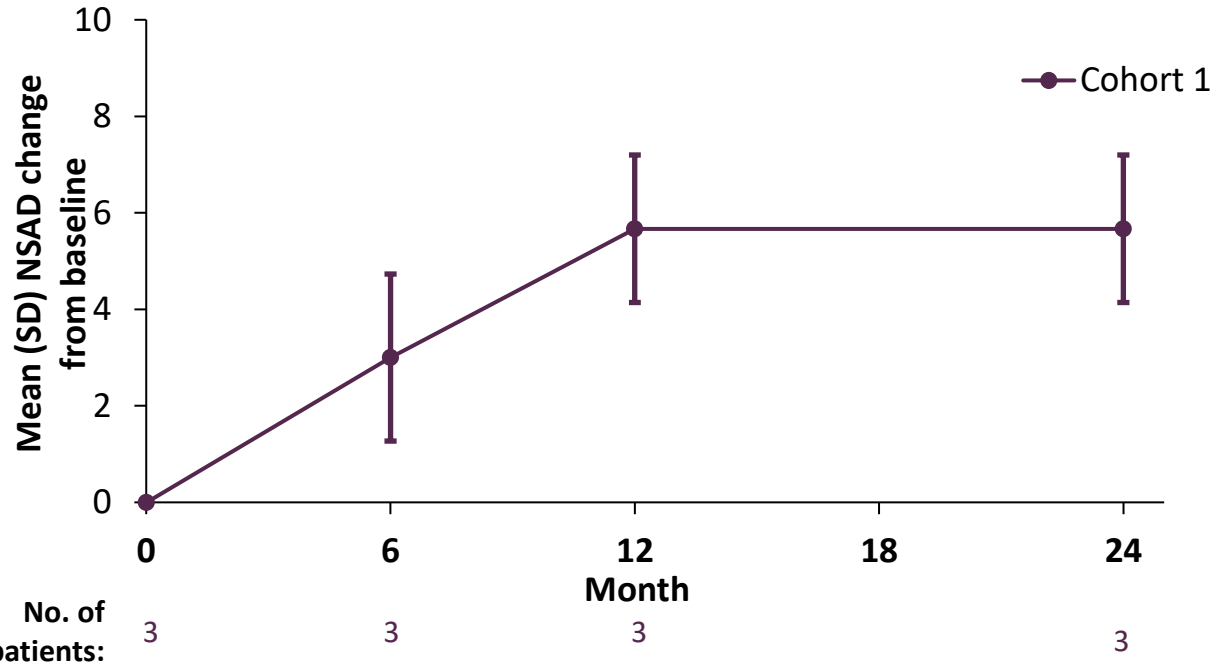
SGCB=β-sarcoglycan; SGCD=δ-sarcoglycan; SGCG=γ-sarcoglycan.

Cohort 1: SRP-9003 treatment resulted in improvement in NSAD total score sustained for 2 years

Individual patient data



Mean data

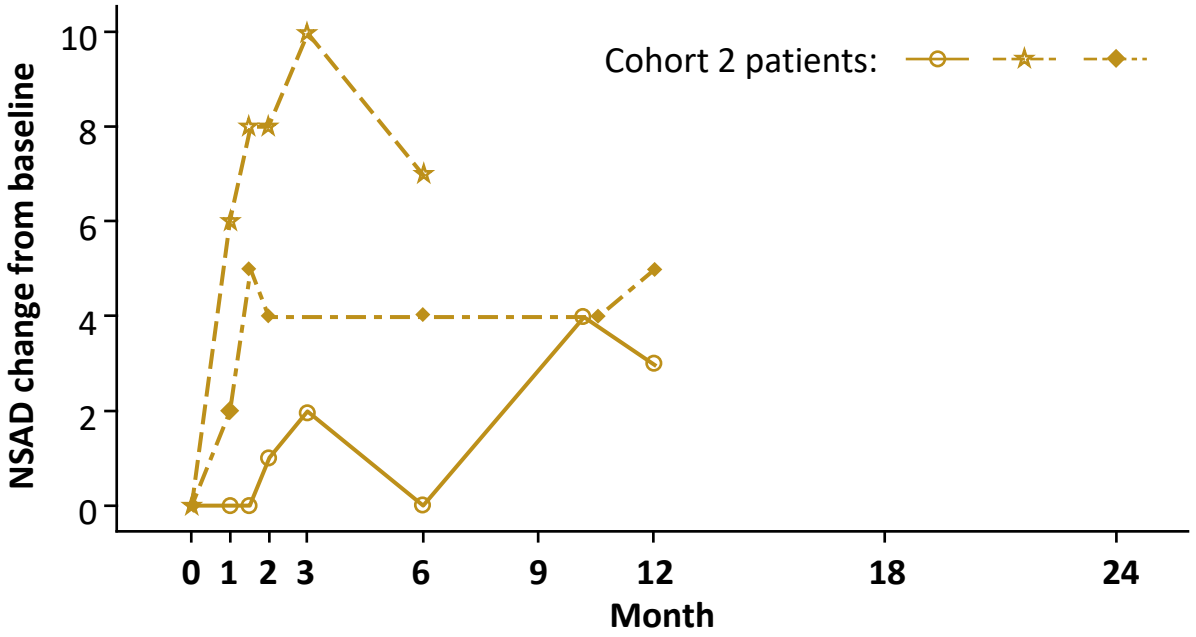


Patients treated with SRP-9003 in Cohort 1 demonstrated improvements in NSAD that were sustained for 2 years

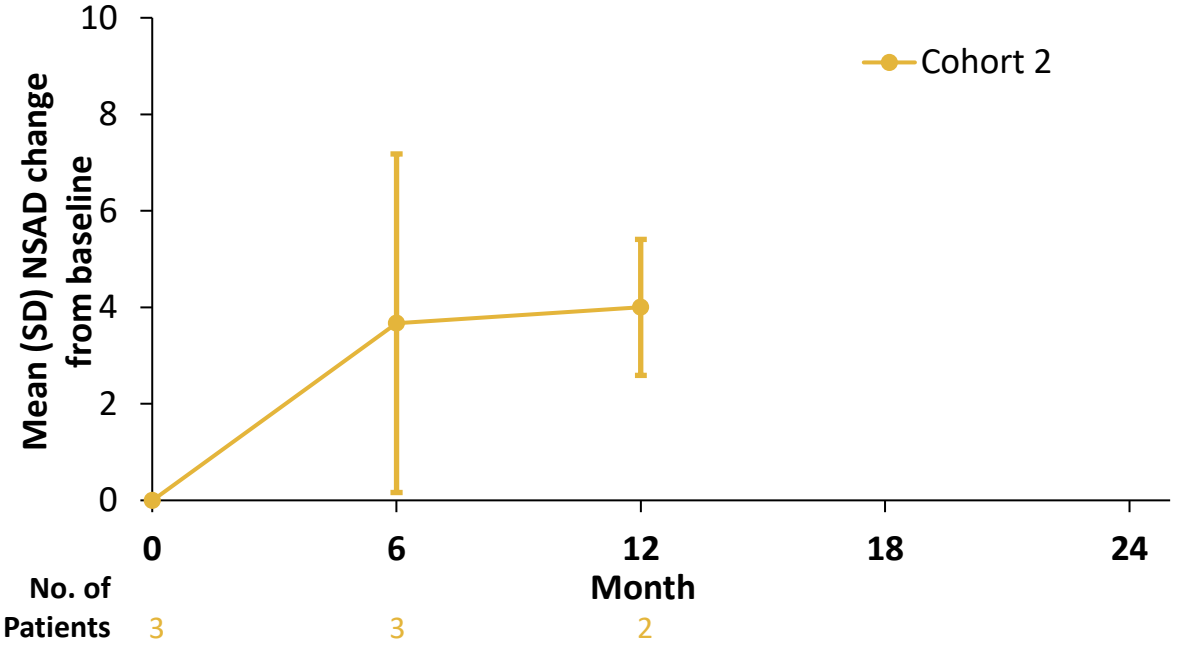
NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies.

Cohort 2: SRP-9003 treatment improved NSAD total score

Individual patient data



Mean data



Patients treated with SRP-9003 in Cohort 2 demonstrated improvements in NSAD up to 1 year

NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies.

SRP-9003 treatment resulted in sustained improvements in timed function tests

Mean (SD) change from baseline (s)	Cohort 1 (1.85×10^{13} vg/kg)[a]			Cohort 2 (7.41×10^{13} vg/kg)[b]	
	6 months	12 months	24 months	6 months	12 months
Time to rise	-0.2 (0.8)	-0.8 (0.4)	-0.6 (0.2)	-1.3 (0.9)	-1.1 (1.1)
4-stair climb	-0.5 (0.4)	-0.5 (0.3)	-0.3 (0.4)	-0.4 (0.3)	-0.4 (0.0)
100m	-3.8 (2.9)	-5.3 (3.2)	-2.8 (6.4)	-6.3 (6.7)	-7.9 (5.4)
10m	-0.6 (0.3)	-0.6 (0.2)	-0.2 (0.5)	-0.6 (0.6)	-0.6 (0.2)

Negative numbers correspond to faster test times.

Patients treated with SRP-9003 demonstrated improvements over baseline in timed function tests, which were sustained for 2 years in Cohort 1 and 1 year in Cohort 2

10m=10-m timed test; 100m=100-m timed test.

[a]1.85×10^{13} vg/kg measured using linear reference plasmid DNA quantitative polymerase chain reaction (qPCR), supercoiled reference DNA equivalent is 5×10^{13} vg/kg;

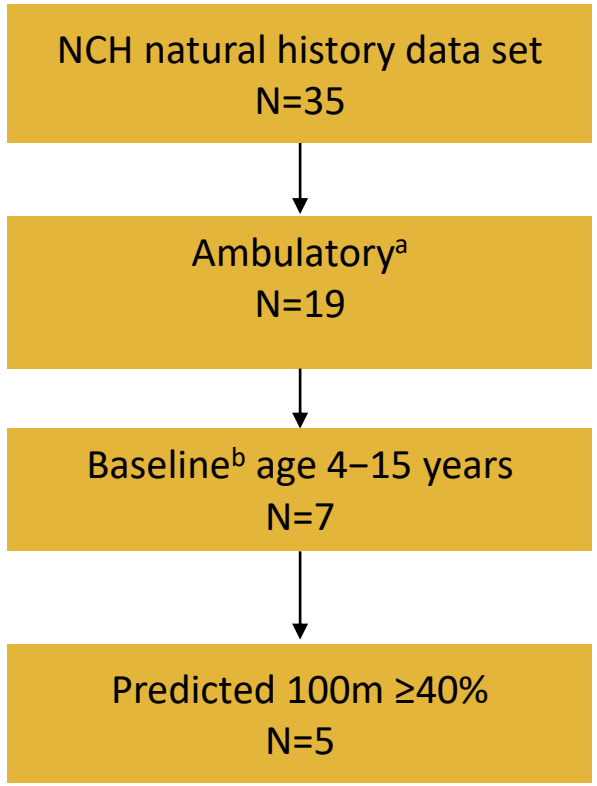
[b]7.41×10^{13} vg/kg measured using linear reference plasmid DNA qPCR, supercoiled reference DNA equivalent is 2×10^{14} vg/kg.

Selection of natural history control cohort for comparison with SRP-9003-101

Selected comparison cohort from Nationwide Children's Hospital (NCH) natural history data set, based on the same key inclusion criteria as in Study SRP-9003-101

- Ambulatory status (yes)
- Baseline age (4–15 years)
- Predicted 100m (≥40%)

NCH LGMD2E/R4 natural history cohort



10m=10-m timed test; 100m=100-m timed test; LGMD2E/R4=limb-girdle muscular dystrophy type 2E/R4; NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies.
[a]Ambulatory defined as presence of 10m timed test value; [b]Baseline was defined as the first time point where both 100m and NSAD were nonmissing.

Baseline comparison of SRP-9003–treated patients vs natural history cohort

Baseline characteristics comparison

	SRP-9003-101 (N=6)	NCH (N=5)
Age (years)	10.0 (3.5)	9.8 (3.2)
Male, n (%)	3 (50)	3 (60)
NSAD score	41.2 (3.7)	49.0 (3.9)
100m (s)	51.4 (10.5)	38.9 (3.9)
10m (s)	5.1 (0.9)	4.4 (0.3)[a]

Values are mean (SD) unless noted otherwise.

Age and sex are well balanced between 9003-101 patients and the NCH control cohort

Baseline functional endpoints scores are ***higher*** in the NCH control cohort

Explored alternative matching criteria; however, still unable to achieve balanced baseline functions

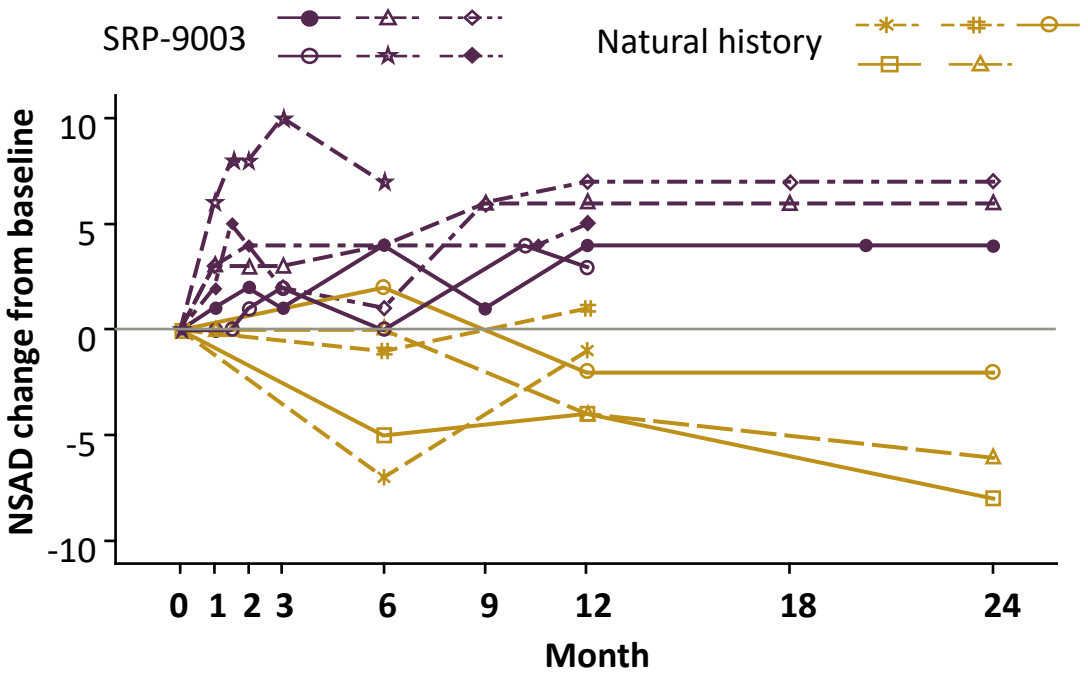
Therefore, used mixed-model repeated measures (MMRM) analysis to adjust for baseline function

10m=10-m timed test; 100m=100-m timed test; NCH=Nationwide Children's Hospital; NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies.

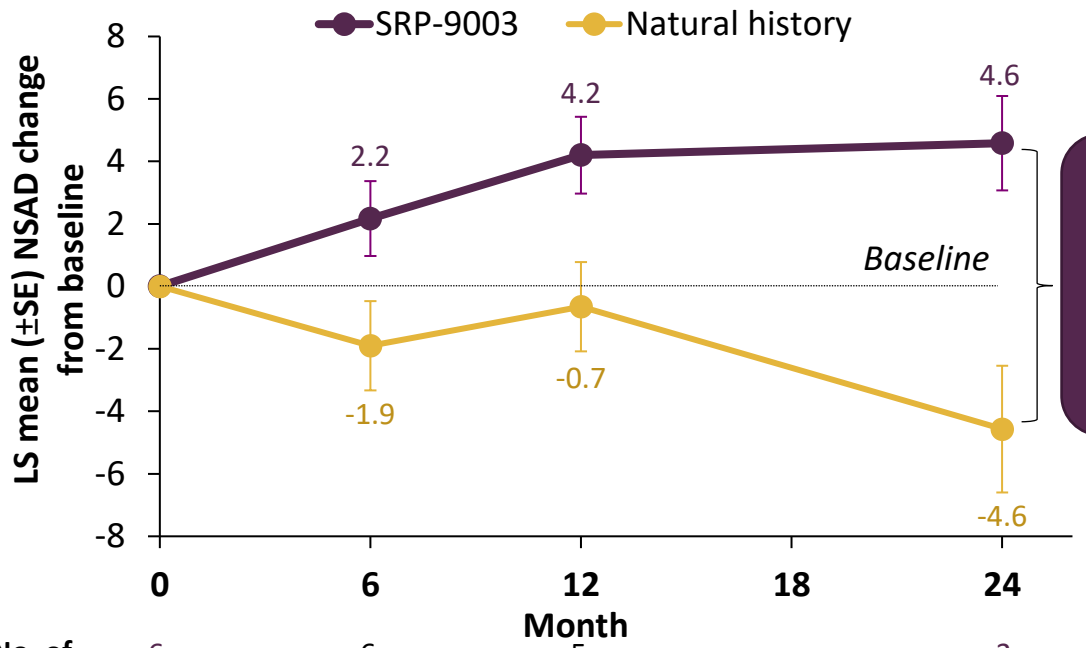
[a]N=4.

SRP-9003–treated patients display an improvement in total NSAD score vs natural history

NSAD change from baseline: Individual patient data



NSAD change from baseline: LS means by cohort



No. of patients:				
SRP-9003	6	6	5	3
Natural history	5	5	5	3

LS mean change at Year 2: 9.2 points (95% CI, 3.2–15.1)

Patients treated with SRP-9003 demonstrated clinically meaningful improvements in functional outcomes in an exploratory comparison vs an LGMD2E/R4 natural history cohort, as measured by NSAD

LGMD2E/R4=limb-girdle muscular dystrophy type 2E/R4; LS=least-squares; MMRM=mixed-model repeated measures; NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies.
MMRM analysis included fixed effects for treatment arm, visit, and treatment arm by visit interaction, and baseline NSAD, baseline 100m, and baseline 10m as continuous covariates; the first-order autoregressive structure was used for variance-covariance matrix of within-patient errors.

Safety results reinforce favorable safety profile, with no new safety signals

Cohort 1 as of January 14, 2021 (n=3)

- 2 patients had elevated liver enzymes, 1 of which was designated a serious adverse event (SAE) and associated with transient increase in bilirubin
  - Occurred during or after steroid tapering; resolved within days following supplemental steroid treatment
- 1 patient experienced mild vomiting which resolved within 1 day without treatment

Cohort 2 as of January 14, 2021 (n=3)

- Majority of AEs were mild to moderate (e.g., vomiting, pain in extremity) and resolved
- 1 treatment-related SAE observed
  - Dehydration resulting from vomiting 3 days after infusion; resolved within 2 days with treatment
- 1 patient had mildly elevated gamma glutamyl transferase (GGT)
  - Returned to within normal limits while on tapering dose of steroids; GGT levels did not increase after steroid treatment
- No stopping/discontinuation rules were triggered by AEs
- One of the participants in this trial died unexpectedly due to a recreational accident unrelated to the study

Both cohorts

- No other laboratory abnormalities were suggestive of safety concerns
  - No decreases in platelet counts observed outside the normal range
  - No clinical sequelae associated with complement activation

Results show no new safety signals, and treatment-related AEs occurred early and were transient and manageable

Conclusions

- This interim analysis reinforces the favorable safety profile of systemically administered SRP-9003
- SRP-9003 showed efficient transduction and drove robust, dose-dependent SGCB protein expression in all patients at Day 60, resulting in reconstitution of the sarcoglycan complex; SGCB expression was sustained up to 2 years
- Creatine kinase decreased by 77% at Year 2 in Cohort 1 and 74% at Year 1 in Cohort 2 (data not presented)
- Patients treated with SRP-9003 demonstrated improvements over baseline in NSAD and timed function tests that were sustained up to 2 years in Cohort 1 and 1 year in Cohort 2
- Exploratory post hoc analysis showed SRP-9003–treated patients had clinically meaningful improvements in functional outcomes, as measured by NSAD, compared with a natural history cohort
- The observed durable treatment effect provides proof of concept and supports further clinical assessment of SRP-9003 gene transfer therapy in patients with LGMD2E/R4

Key Takeaway:
Persistence of SRP-9003 in transduced muscle continues to drive meaningful levels of SGCB expression over time, leading to sustained functional improvements

LGMD2E/R4=limb-girdle muscular dystrophy type 2E/R4; NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies; SGCB=β-sarcoglycan.

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  - Megan Iammarino
  - Brenna Powers
  - Natalie Reash
  - Kiana Shannon