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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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Objective

To report the interim findings of an ongoing Phase 1/2 clinical gene transfer trial delivering rAAVrh74.MHCK7.hSGCB (SRP-9003) to patients with LGMD2E/R4 (NCT03652259)

Key Takeaways

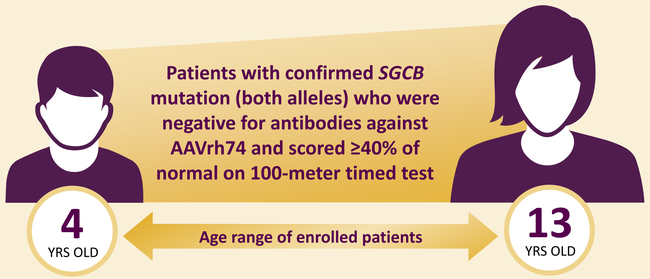
- **SRP-9003 was well tolerated with no new safety signals**
- **Persistence of SRP-9003 in transduced muscle continues to drive meaningful levels of SGCB expression over time, leading to sustained functional improvements**

CONCLUSIONS

- Results of this interim analysis reinforce the favorable safety profile of systemically administered SRP-9003
- SRP-9003 showed efficient transduction and drove robust, dose-dependent β-sarcoglycan (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 (CK) decreased by 77% at Year 2 in Cohort 1 and 74% at Year 1 in Cohort 2
- Patients treated with SRP-9003 demonstrated improvements over baseline in North Star Assessment for Limb-girdle Type Muscular Dystrophies (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 that 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 limb-girdle muscular dystrophy type 2E/R4 (LGMD2E/R4)

METHODS

Study 9003-101 design and patients: First-in-human, open-label Phase 1/2 study



Treatment: Systemic delivery of SRP-9003 single dose

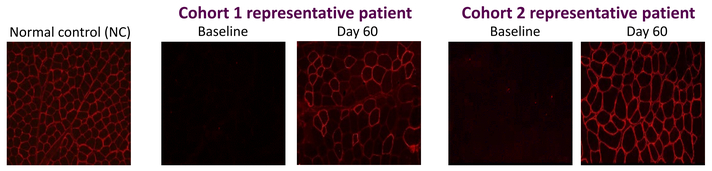
- **Cohort 1 dose: 1.85×10[13] vg/kg** (linear qPCR; 5×10[13] vg/kg supercoiled qPCR equivalent)
- **Cohort 2 dose: 7.41×10[13] vg/kg** (linear qPCR; 2×10[14] vg/kg supercoiled qPCR equivalent)

SRP-9003: Self-complementary adeno-associated virus (AAV) vector containing a codon-optimized, full-length human SGCB transgene driven by a muscle-specific promoter

Characteristic	Driven by	Expectations based on preclinical and clinical studies
Transduction	AAVrh74 vector	AAVrh74 efficient transduction to muscles[1-3]
Expression	MHCK7 promoter	MHCK7 selective for cardiac and skeletal transgene muscle expression[2-4] Widespread SGCB expression in all muscles[2,3]
Efficacy	SGCB transgene	Reduction in CK[2,3] Improved functional outcomes[2,3]
Safety	AAVrh74 vector and SGCB transgene	Favorable safety profile[2,3]

RESULTS

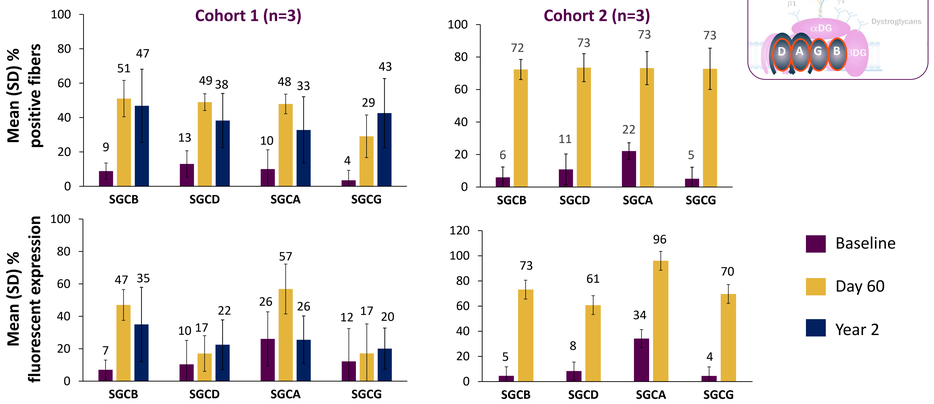
Robust SGCB protein expression at skeletal muscle sarcolemma



Cohort mean	Time point	Transduced vector copies: qPCR, copies/nucleus (SD)	Transduced vector copies: ddPCR, copies/nucleus (SD)	SGCB protein expression: SGCB+ fibers % NC (SD)	SGCB protein expression: SGCB intensity, % NC (SD)	SGCB protein expression: Western blot, % NC (SD)
Cohort 1 (n=3)	Day 60	0.59 (0.4)	NE	51 (10.6)	47 (9.5)	36 (2.7)
	Year 2	0.14 (0.1)	0.46 (0.4)	47 (21.3)	35 (22.9)	54 (16.1)
Cohort 2 (n=3)	Day 60	4.24 (2.8)	2.26 (0.9)	72 (6.2)	73 (21.8)	62 (8.7)

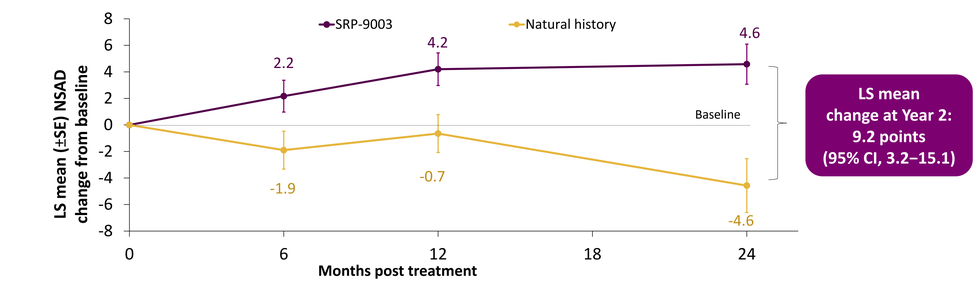
ddPCR=droplet digital PCR; PCR=polymerase chain reaction; qPCR=quantitative PCR; NE=not estimated

Robust expression of the sarcoglycan complex by immunofluorescence



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

NSAD change from baseline comparison of SRP-9003 and external natural history cohort



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

Sustained improvements from baseline in functional outcomes

Mean (SD) change from baseline	Cohort 1 (1.85×10[13] vg/kg): 6 months	Cohort 1 (1.85×10[13] vg/kg): 12 months	Cohort 1 (1.85×10[13] vg/kg): 24 months	Cohort 2 (7.41×10[13] vg/kg): 6 months	Cohort 2 (7.41×10[13] vg/kg): 12 months
NSAD score	+3 (1.7)	+5.7 (1.5)	+5.7 (1.5)	+3.7 (3.5)	+4 (1.4)
Time to rise, s	-0.2 (0.8)	-0.8 (0.4)	-0.6 (0.2)	-1.3 (0.9)	-1.1 (1.1)
4-stair climb, s	-0.5 (0.4)	-0.5 (0.3)	-0.3 (0.4)	-0.4 (0.3)	-0.4 (0.0)
100m, s	-3.8 (2.9)	-5.3 (3.2)	-2.8 (6.4)	-6.3 (6.7)	-7.9 (5.4)
10m, s	-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

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

Safety

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, which resolved in 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
- 1 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

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1. Chicoine LG, et al. *Mol Ther.* 2014;22:713-24. **2.** Mendell JR, et al. *JAMA Neurol.* 2020;e201484. **3.** Pozsgai ER, et al. *Mol Ther.* 2017;25:855-69. **4.** Salva MZ, et al. *Mol Ther.* 2007;15:320-9. **5.** Liewluck T, Milone M. *Muscle Nerve.* 2019;58:167-77. **6.** McNally EM. *The Sarcoglycans.* Dallas, TX: Landes Bioscience; 2000-2013. **7.** Taghizadeh E, et al. *J Cell Physiol.* 2018;234:7874-84. **8.** Li J, et al. *Mol Ther.* 2016;24:S284.

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BACKGROUND

- Limb-girdle muscular dystrophy (LGMD) refers to a group of autosomally inherited neuromuscular dystrophies that are genetically diverse;[5] each subtype carries mutations in a unique gene and represents a unique compilation of symptoms
- LGMD type 2E/R4 (LGMD2E/R4) is caused by mutations in the β-sarcoglycan gene (*SGCB*) that result in loss of functional protein affecting other structural components of the dystrophin-associated protein complex[6]
- LGMD2E/R4 usually manifests with progressive hip/shoulder muscle weakness and often includes cardiac involvement and elevated creatine kinase (CK)[7]
- There are currently no approved disease-modifying therapies for LGMD2E/R4
- Adeno-associated virus (AAV)–mediated gene transfer therapy has shown early signs of potential to treat sarcoglycanopathies
- A self-complementary rAAVrh74.MHCK7.hSGCB construct (SRP-9003) was designed to restore functional SGCB to muscles
  - Long-term durability has been demonstrated in preclinical models for up to 8 years after treatment[8]

METHODS DETAILS

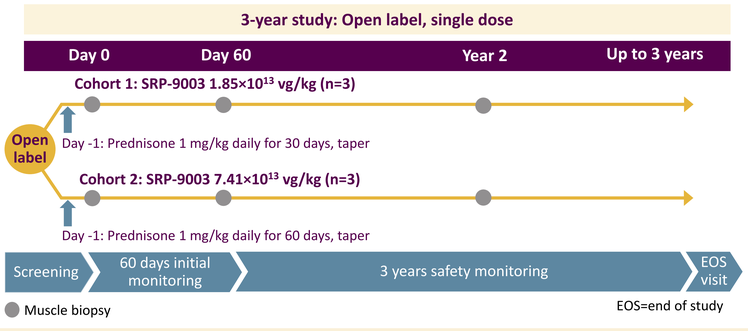
Study design and treatment

- Systemic delivery of SRP-9003 in a peripheral vein at a dose of
  - Cohort 1: 1.85×10^{13} vg/kg[a]
  - Cohort 2: 7.41×10^{13} vg/kg[b]
- SRP-9003 was infused over approximately 1–2 hours
- Prednisone 1 mg/kg/day was initiated to dampen the immune response to AAV therapy 1 day before treatment, tapering after 60 days
- Muscle biopsies were performed at baseline, 60 days, and 2 years

Endpoints

- Primary: Safety
- Secondary: SGCB expression at Week 8
- Other: Change in CK from baseline, functional endpoints (North Star Assessment for Limb-girdle Type Muscular Dystrophies [NSAD], 100-meter timed test [100m], 10-meter timed test [10m], 4-stair climb, and time to rise)

Study 9003-101 design

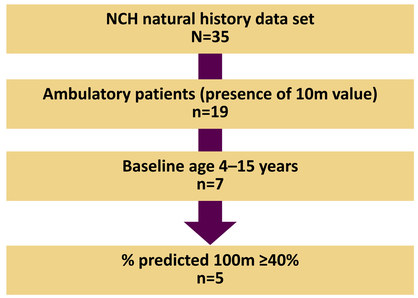


[a]1.85×10^{13} vg/kg measured by qPCR using linear reference plasmid DNA qPCR; supercoiled reference DNA equivalent is 5×10^{13} vg/kg;
[b]7.41×10^{13} vg/kg measured by qPCR using linear reference plasmid DNA qPCR; supercoiled reference DNA equivalent is 2×10^{14} vg/kg

Post hoc analysis

- A natural history cohort of 35 patients with LGMD2E/R4 was obtained from Nationwide Children's Hospital (NCH)
- Age and sex were well balanced between 9003-101 patients and the NCH cohort, but baseline functional endpoint scores were higher in the NCH cohort
  - Explored alternative matching criteria; however, still unable to achieve balanced baseline functions
- Therefore, used mixed-model repeated measures (MMRM) analysis to adjust for the baseline functions
  - MMRM analysis, including fixed effects for treatment arm, visit, treatment arm by visit interaction, baseline NSAD, baseline 100m, and baseline 10m as continuous covariates

Natural history cohort patient selection



SUPPLEMENTARY RESULTS

Baseline characteristics

Cohort, dose	Patient	Age, years	Mutation	Weight, kg	CK, U/L
Cohort 1, 1.85×10^{13} vg/kg[a]	1	13	Exon 3[c]	57.2	10,727
	2	4	Exon 4[c]	17.5	12,286
	3	13	Exon 3[c]	50.4	10,985
Cohort 2, 7.41×10^{13} vg/kg[b]	4	11	Exon 4[c]	29.1	6320
	5	11	Exon 3[c]	39.5	8938
	6	8	Exon 1[d]	26.6	5743

[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]Missense mutation; [d]Nonsense mutation

CK decreased after SRP-9003 treatment

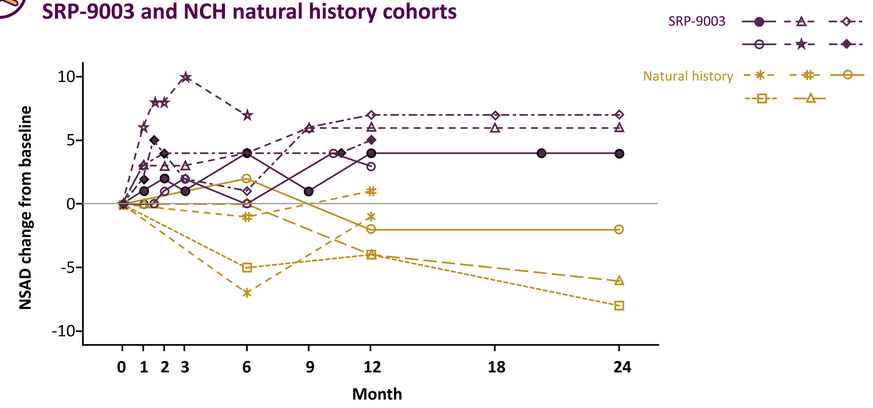
Cohort	Time point	Mean (SD) change in CK levels from baseline
Cohort 1	Year 2	-77.4% (9.2)
Cohort 2	Year 1	-73.7% (9.9)

Baseline comparison of SRP-9003 and NCH natural history cohorts

Characteristic	SRP-9003 (N=6)	NCH natural history (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]

[a]n=4; Values are mean (SD) unless noted otherwise

NSAD change from baseline for individual patients in SRP-9003 and NCH natural history cohorts



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