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

Louise R. Rodino-Klapac,[1] Eric R. Pozsgai,[1] Sarah Lewis,[1] Danielle A. Griffin,[1] Aaron S. Meadows,[1,2] Kelly J. Lehman,[3] Kathleen Church,[3] Natalie F. Reash,[3] Megan A. Iammarino,[3] Brenna Sabo,[3] Lindsay N. Alfano,[3] Linda P. Lowes,[3] Sarah Neuhaus,[1] Xiaoxi Li,[1] Jerry R. Mendell[3,4]

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

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Objective

Evaluate the safety and efficacy of bidridistrogene xeboparvovec (SRP-9003) gene transfer therapy in patients with limb-girdle muscular dystrophy type 2E/R4

Key Findings

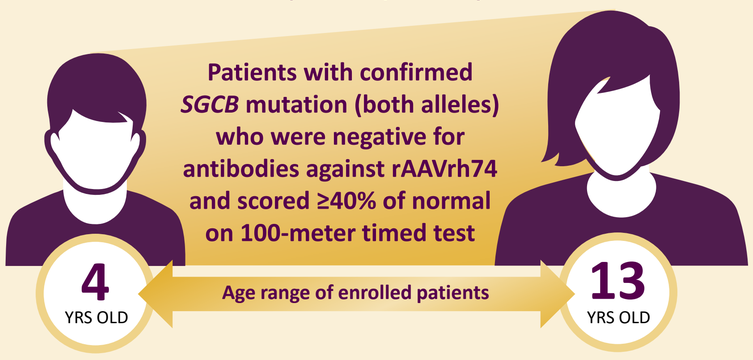
- **Bidridistrogene xeboparvovec was well tolerated with no new safety signals**
- **Persistence of bidridistrogene xeboparvovec in transduced muscle continues to drive meaningful levels of β-sarcoglycan (SGCB) expression over time, leading to sustained functional improvements in patients with LGMD2E/R4**

CONCLUSIONS

- This interim analysis reinforces the acceptable safety profile of systemically administered bidridistrogene xeboparvovec (SRP-9003)
- Bidridistrogene xeboparvovec 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
- Patients treated with bidridistrogene xeboparvovec demonstrated persistent stabilization at or over baseline in the North Star Assessment for Limb-girdle Type Muscular Dystrophies (NSAD), which were sustained up to 3 years in Cohort 1 and 2 years in Cohort 2; results were similar for timed function tests
- Exploratory post hoc analysis showed bidridistrogene xeboparvovec–treated patients had clinically important improvements in functional outcomes, as measured by NSAD, compared with a natural history (NH) cohort up to 3 years
- The observed durable treatment effect provides proof of concept and supports further clinical assessment of bidridistrogene xeboparvovec gene transfer therapy in patients with LGMD2E/R4

METHODS

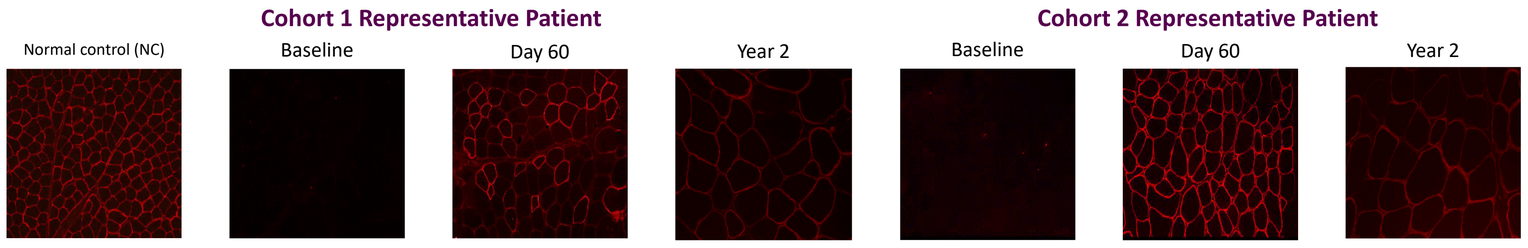
Study 9003-101 design and patients: first-in-human, open-label phase 1/2 study



Treatment: Systemic delivery of bidridistrogene xeboparvovec single dose

- **Cohort 1 dose: 1.85×10^{13} vg/kg** (linear standard qPCR)
- **Cohort 2 dose: 7.41×10^{13} vg/kg** (linear standard qPCR)

Robust SGCB Protein Expression at Skeletal Muscle Sarcolemma



Cohort, mean	Time Point	Vector Copies per Nucleus (ddPCR)[a]	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	NE	51 (10.6)	47 (9.5)	36 (2.7)
	Year 2	0.46 (0.4)	47 (21.3)	35 (22.9)	54 (16.1)
Cohort 2 (n=3)[b]	Day 60	2.26 (0.9)	72 (6.2)	73 (21.8)	62 (8.7)
	Year 2[b]	0.52 (0.3)	63 (21.6)	44 (33.2)	60 (21.4)

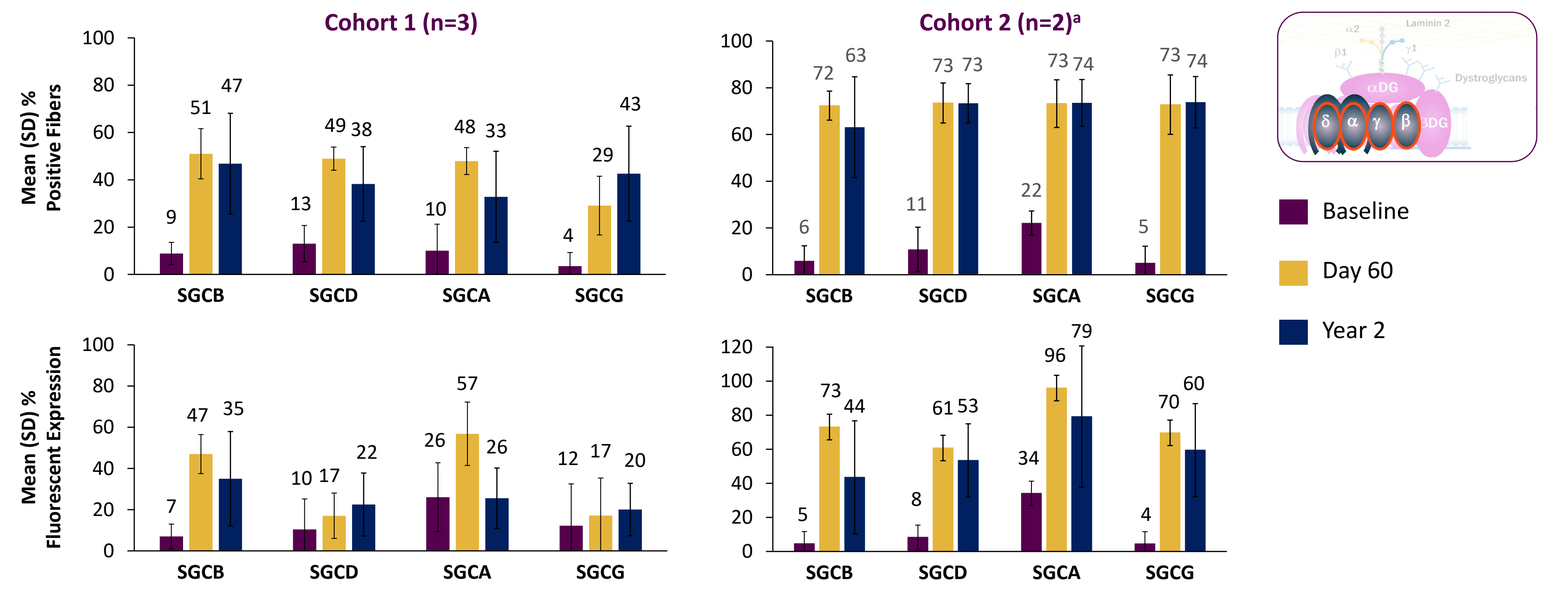
[a]Mean (SD) qPCR value of day 60 Cohort 1 was 0.59 (0.4); [b]Cohort 2 year 2, n=2.
ddPCR=droplet digital PCR; PCR=polymerase chain reaction; qPCR=quantitative PCR; SGCB=β-sarcoglycan; NC=normal control; NE=not estimated.

Bidridistrogene xeboparvovec: 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	rAAVrh74 vector	rAAVrh74 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	rAAVrh74 vector and SGCB transgene	Favorable safety profile[2,3]

CK=creatine kinase; SGCB=β-sarcoglycan.

Robust Expression of the Sarcoglycan Complex by Immunofluorescence



[a]n=2 at year 2. SGCA=α-sarcoglycan; SGCB=β-sarcoglycan; SGCD=δ-sarcoglycan; SGCG=γ-sarcoglycan.

RESULTS

Safety

Cohort 1 as of January 18, 2022 (n=3)

- 2 patients had elevated liver enzymes, 1 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 that resolved within 1 day without treatment

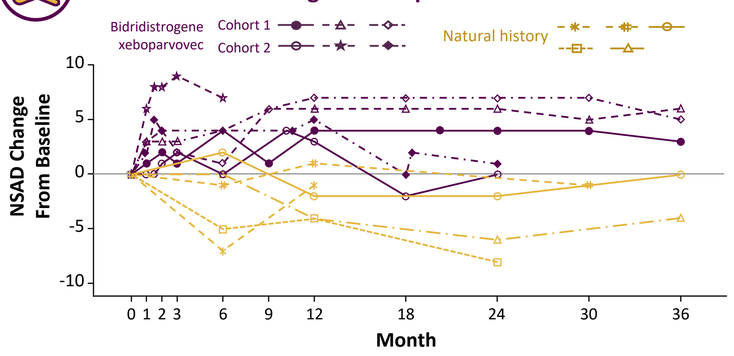
Cohort 2 as of January 18, 2022 (n=2)

- Majority of AEs were mild to moderate (eg, vomiting, pain in extremity) and resolved
- 1 treatment-related SAE was 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
- 1 patient in this trial died due to a recreational accident unrelated to the study

Both cohorts

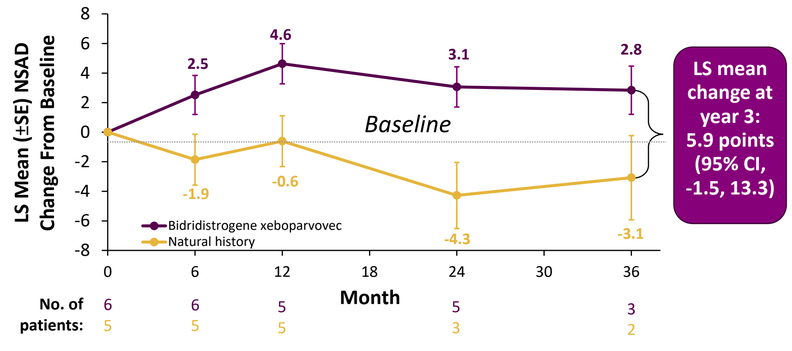
- Most common treatment-related AEs were vomiting (4 patients) and GGT elevation (3 patients)
- No stopping/discontinuation rules were triggered by AEs
- No other laboratory abnormalities were suggestive of safety concerns
  - —No decreases in platelet counts observed outside the normal range
  - —No clinical sequelae associated with complement activation

NSAD Change From Baseline for Individual Patients Treated With Bidridistrogene Xeboparvovec vs NH Cohort



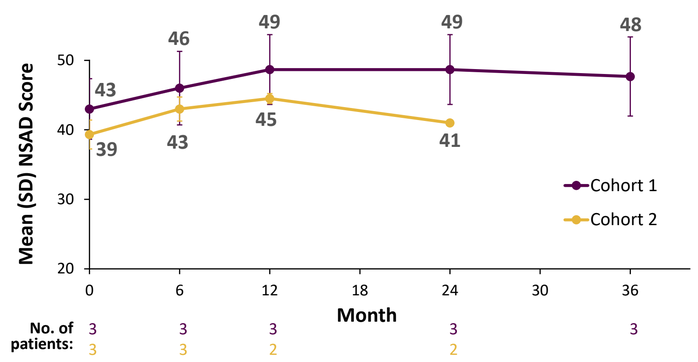
NH=natural history; NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies.

NSAD Change From Baseline In Patients Treated With Bidridistrogene Xeboparvovec vs NH Cohort



LS=least squares; NH=natural history; NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies.

Bidridistrogene Xeboparvovec Improved or Stabilized NSAD Total Scores for up to 3 Years



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

Sustained Improvements From Baseline in Functional Outcomes (Negative Numbers Correspond With Faster Test Times)

Mean (SD) Change From Baseline, s	Cohort 1 (1.85×10^{13} vg/kg)[a] 6 months (n=3)	12 months (n=3)	24 months (n=3)	36 months (n=3)	Cohort 2 (7.41×10^{13} vg/kg)[b] 6 months (n=3)	12 months (n=2)	24 months (n=2)
Time to rise	-0.2 (0.8)	-0.8 (0.4)	-0.6 (0.2)	-0.3 (0.3)	-1.3 (0.9)	-1.1 (1.1)	-0.7 (0.4)
4-stair climb	-0.5 (0.4)	-0.5 (0.3)	-0.3 (0.4)	-0.2 (0.6)	-0.4 (0.3)	-0.4 (0.0)	-0.3 (0.3)
100m	-3.8 (2.9)	-5.3 (3.2)	-2.8 (6.4)	+2.6 (13.0)	-6.3 (6.7)	-7.9 (5.4)	-2.9 (9.7)
10m	-0.6 (0.3)	-0.6 (0.2)	-0.2 (0.5)	0 (0.9)	-0.6 (0.6)	-0.6 (0.2)	-0.3 (0.9)

[a]1.85×10^{13} vg/kg measured using linear standard qPCR; [b]7.41×10^{13} vg/kg measured using linear standard qPCR.
10m=10-meter timed test; 100m=100-meter timed test; qPCR=quantitative PCR; s=second.

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