RGX-202, an Investigational Gene Therapy for the Treatment of Duchenne Muscular Dystrophy: Interim Clinical Data

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LBP19

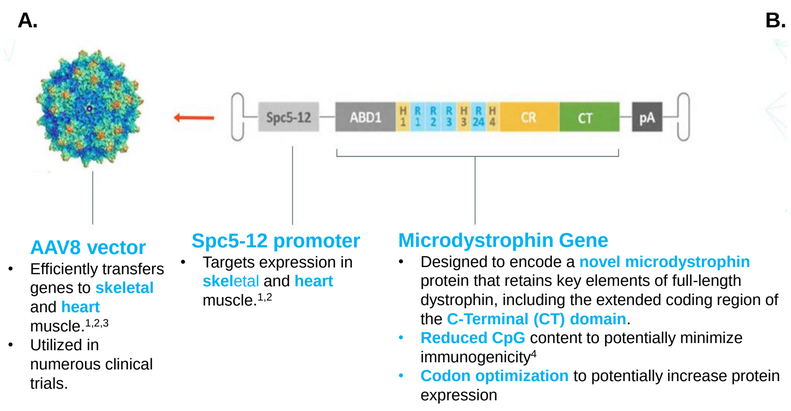
Introduction

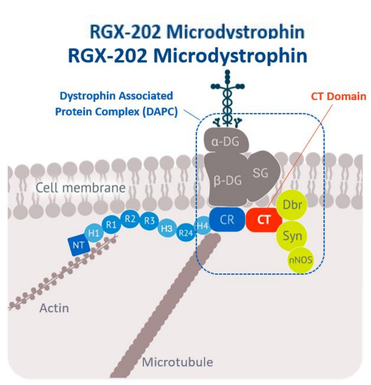
Duchenne Muscular Dystrophy (Duchenne) is a rare, X-linked, progressive muscle disease due to pathogenic variants in the *DMD* gene, which encodes for the sarcolemmal protein, dystrophin. The absence of functional dystrophin results in muscle cell damage during contraction, inflammation, fibrofatty replacement of muscle tissue, and ultimately cell death. This reflects clinically in progressive weakness of skeletal muscle, eventual loss of ambulation, and weakness of cardiac muscle and the diaphragm which can present as cardiomyopathy and respiratory failure.

RGX-202

RGX-202 is an investigational, one-time gene therapy for the treatment of Duchenne muscular dystrophy (Duchenne; Figure 1A). The CT domain retains key elements of full-length dystrophin that recruit several key proteins to the muscle cell membrane (Figure 1B).

Figure 1: RGX-202





Abbreviations: DgBD: Dystroglycan binding domain; SBD: Syntrophin binding domain; DbBD: Dystrobrevin binding domain; CR: Cysteine rich domain' nNOS BD: Neuronal nitrogen oxide synthase binding domain; CT: carboxyl terminus; pA: polyA signal; H: hinge; R: rod

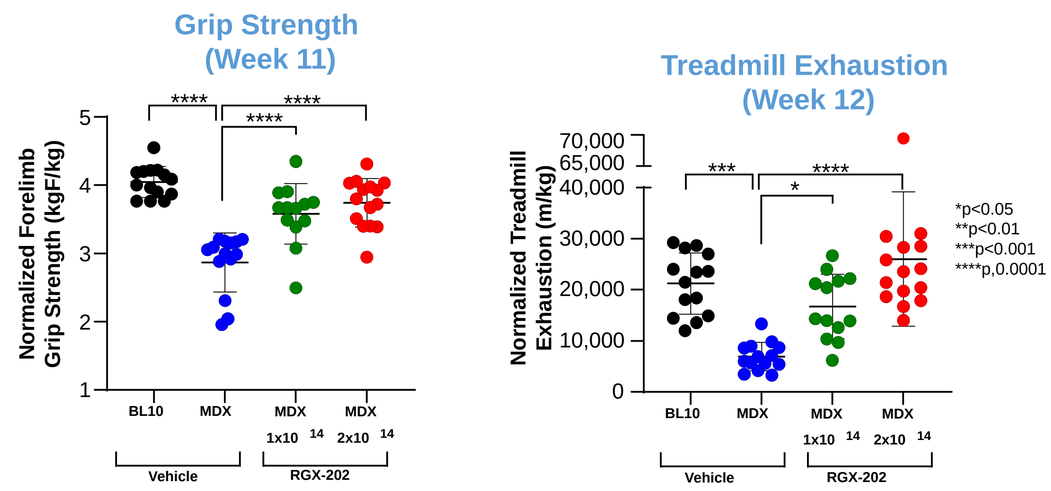
Abbreviations: Syn: Syntrophin; Dbr: Dystrobrevin; CR: Cysteine rich domain; nNOS: Neuronal nitric oxide synthase; DG: Dystroglycan; H: hinge; R: repeat

Preclinical Data

Methods

A thirteen-week pharmacology study evaluated the effectiveness of intravenously (IV) administered commercial-ready RGX-202 at either $1x10^{14}$ or $2x10^{14}$ GC/kg in six-week-old male *mdx* mice compared to vehicle treated *mdx* or BL10 wildtype mice. Muscle function was determined via forelimb grip strength and treadmill exhaustion (an assessment that integrates function of all major muscle including skeletal, respiratory, cardiac and diaphragm muscle to support exercise) at 11 or 12 weeks, respectively.

Figure 2: Forelimb Grip Strength and Treadmill Exhaustion



Data was checked for normality; a Two-way ANOVA with a Tukey post-hoc analysis (α = 0.05) was performed to correct for multiple comparisons. Both RGX-202 doses ($1x10^{14}$ and $2x10^{14}$ GC/kg) were significantly different from *mdx* vehicle treated animals for both forelimb grip strength and treadmill exhaustion; by comparison, RGX-202 treated animals were not significantly different from wild type vehicle treated controls.

Results

RGX-202 administration resulted in dose-dependent improvements in muscle function in *mdx* mice. The $1x10^{14}$ GC/kg dose of RGX-202 showed significant improvements compared to non-treated mdx mice; the $2x10^{14}$GC/kg dose restored both grip strength and treadmill performance to vehicle treated BL10 wildtype mice.

Interim Clinical Results

REGENXBIO is assessing the safety, tolerability, and clinical efficacy of a one-time IV dose of RGX-202 as a potential gene therapy treatment for boys with Duchenne muscular dystrophy. An immunosuppressive regimen of eculizumab, sirolimus and corticosteroids is administered through week 12. Participants were assessed for safety and RGX-202 microdystrophin expression. Capillary western blot (JESS) was used to measure the levels of RGX-202 microdystrophin (µDys) from biceps brachii biopsies collected at baseline and 12 weeks post RGX-202 administration. Immunofluorescence was used to detect the localization of RGX-202 microdystrophin to the sarcolemma.

The characteristics of three boys with Duchenne dosed with RGX-202 at $1x10^{14}$ GC/kg are presented in Table 1.

Table 1: Participant Key Baseline Characteristics

Participant	Age at Dosing	Weight at Dosing
1	4 yrs	17.8 kg
2	10 yrs	28.3 kg
3*	6 yrs	26.8 kg

* For participant 3, only safety data available due to recent dosing.

Interim Safety

RGX-202 at a dose of $1x10^{14}$ GC/kg was well-tolerated in three patients as of September 20, 2023, with no serious adverse events. Time post-administration ranged from 2-25 weeks.

Interim Biomarkers

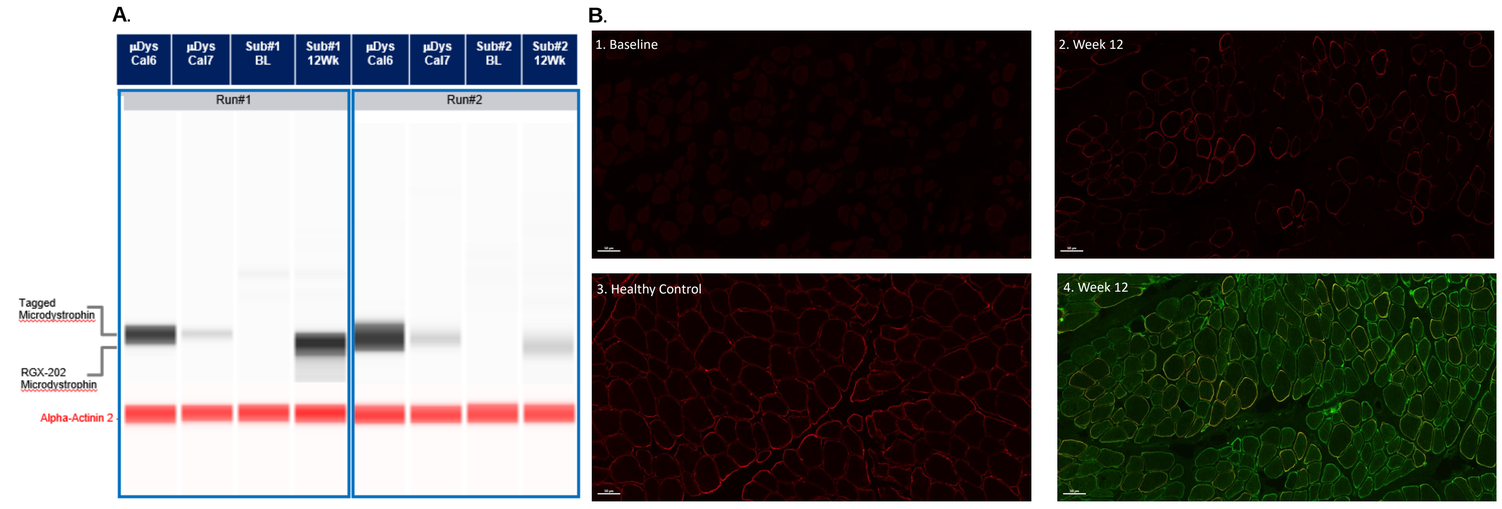
Table 2: Serum Creatine Kinase

	Participant 1		Participant 2	
	Avg Baseline	Week 10	Avg Baseline	Week 10
CK levels (U/L)	15,278	8,692	17,437	9,756
% Reduction	43%		44%	

Elevated creatine kinase (CK) levels are associated with muscle injury and are uniformly elevated in patients with Duchenne. Two patients who have completed their 10-week visit showed a decrease in serum CK levels with a mean reduction of CK of 43.5%.

Figure 3: RGX-202 Microdystrophin Expression at 12 Weeks

RGX-202 microdystrophin was readily detectable by both JESS and immunofluorescence (IF) with RGX-202 microdystrophin localized to the sarcolemma.



A. Western blot (JESS) B. Representative IF images of biopsied sections from biceps muscle from participant 1 at baseline (1), week 12 post RGX-202 administration (2), and healthy control (3) stained with antibody against dystrophin and RGX-202 microdystrophin (red). Co-staining in participant 1 with antibody against merosin demonstrated localization of RGX-202 microdystrophin to the sarcolemma (4) at week 12 post RGX-202 administration.

Conclusions

- RGX-202 resulted in dose-dependent improvement in muscle function in *mdx* mice.
- RGX-202 has been well tolerated in 3 participants up to 25 weeks post-administration of RGX-202. The prophylactic immune suppression for gene therapy with RGX-202 has been well tolerated.
- RGX-202 leads to readily detectable RGX-202 microdystrophin levels at 12 weeks and a decrease in creatine kinase levels at 10 weeks post-administration of RGX-202.

References:

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