# Systemic Delivery of SGT-003 Microdystrophin Gene Therapy Using the Novel Capsid AAV-SLB101 Ameliorates Muscle Pathology and Rescues Muscle Function in the *mdx* Mouse Model of Duchenne Muscular Dystrophy

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## Introduction

- Duchenne muscular dystrophy (DMD) is a rare, X-linked neuromuscular disease caused by mutations in the *DMD* gene that prevent the production of functional dystrophin protein.
- The lack of functional dystrophin protein results in severe, progressive muscle wasting and premature death.
- Solid Biosciences' next generation therapeutic gene therapy candidate SGT-003 utilizes a novel adeno-associated virus vector (AAV-SLB101) and contains a codon-optimized human microdystrophin transgene driven by the muscle-specific CK8 promoter.
- This unique microdystrophin transgene contains the R16/R17 nNOS binding domain that has been shown to be required for proper nNOS membrane localization and function, which is essential for increasing blood flow to the muscle during exercise to prevent damage resulting from functional ischemia.
- To test the efficacy of SGT-003, systemic injections were evaluated in *mdx* mice at escalating doses.
- A No Observed Adverse Effect Level (NOAEL) of 3.0E14 vg/kg (highest dose tested) was observed in *mdx* mice and cynomolgus monkeys. There were no adverse SGT-003-related gross or microscopic findings.
- Three months post-SGT-003 treatment, functional efficacy was observed at doses ≥ 6.0E12 vg/kg.
- A plateau in functional efficacy and microdystrophin expression was observed at SGT-003 doses ≥ 3.0E13 vg/kg.

## Study Design

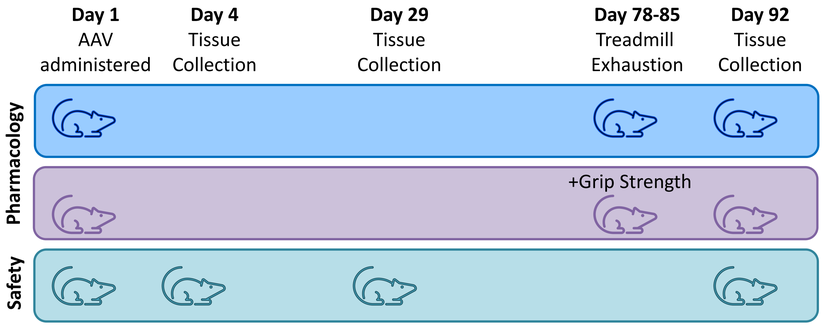



**Figure 1.** Three studies were performed in *mdx* mice to evaluate SGT-003 pharmacology and toxicology. All studies were 92 days in duration. Tissue was collected at interim days 4 and 29 in the toxicology study to evaluate expression kinetics.

## SGT-003 Biodistribution

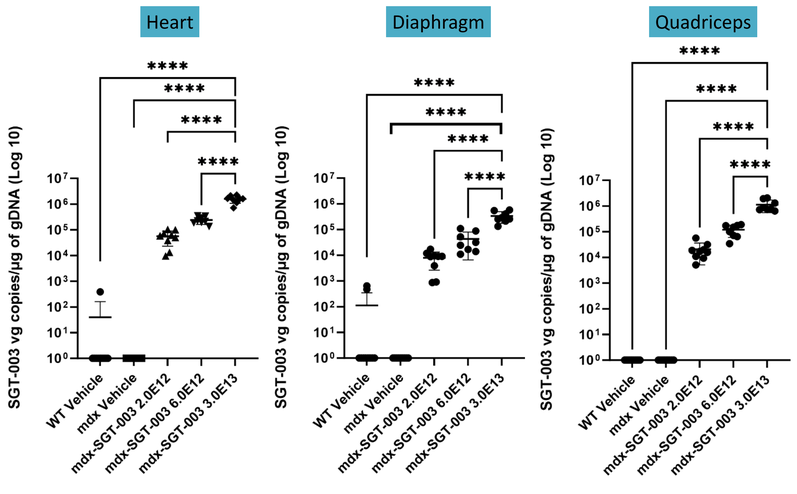



**Figure 2.** SGT-003 biodistribution measured by qPCR demonstrated dose-dependent levels of vector genomes per ug DNA in heart, diaphragm, and quadriceps.

## Microdystrophin Protein Expression

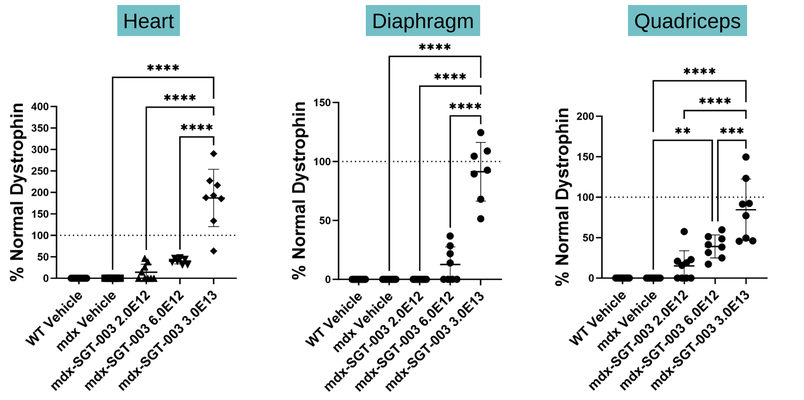
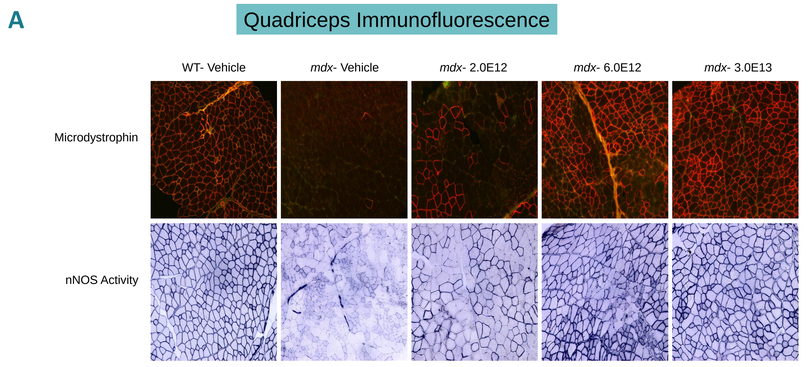



**Figure 3.** A dose-dependent increase in microdystrophin protein expression measured by mass spectrometry was observed in heart, diaphragm, and quadriceps. % Normal Dystrophin was calculated by dividing each sample concentration by the average concentration of five individual human adult muscle samples.

## Microdystrophin Protein Localization



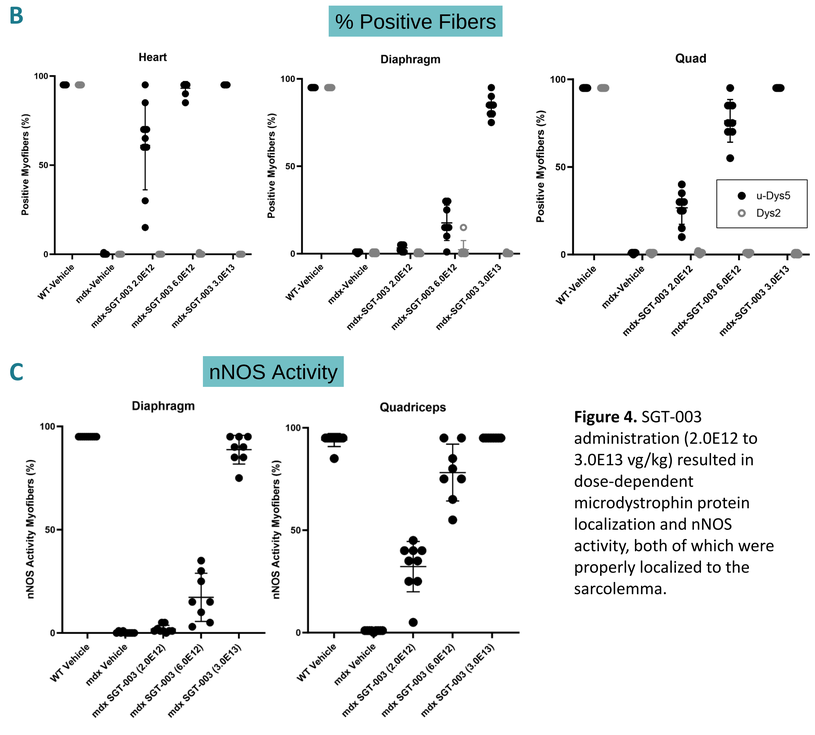




**Figure 4.** SGT-003 administration (2.0E12 to 3.0E13 vg/kg) resulted in dose-dependent microdystrophin protein localization and nNOS activity, both of which were properly localized to the sarcolemma.

## High Dose Protein Localization and Functional Efficacy

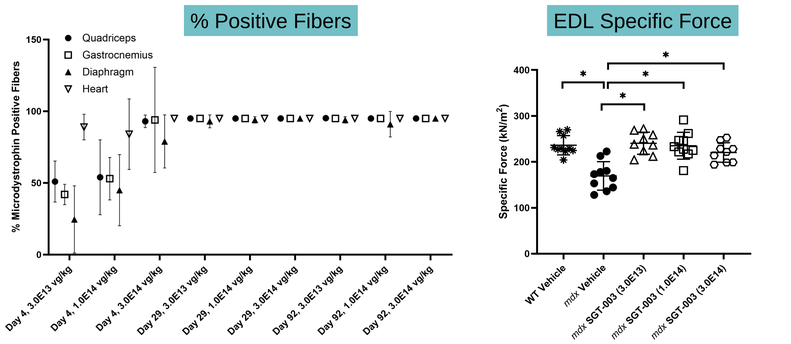



**Figure 5.** Membrane localization of microdystrophin in heart, diaphragm, gastrocnemius, and quadriceps at days 4, 29, 92 and specific force production of the EDL muscle at SGT-003 doses 3.0E13 to 3.0E14 vg/kg.

## Functional Efficacy and Biomarker Data

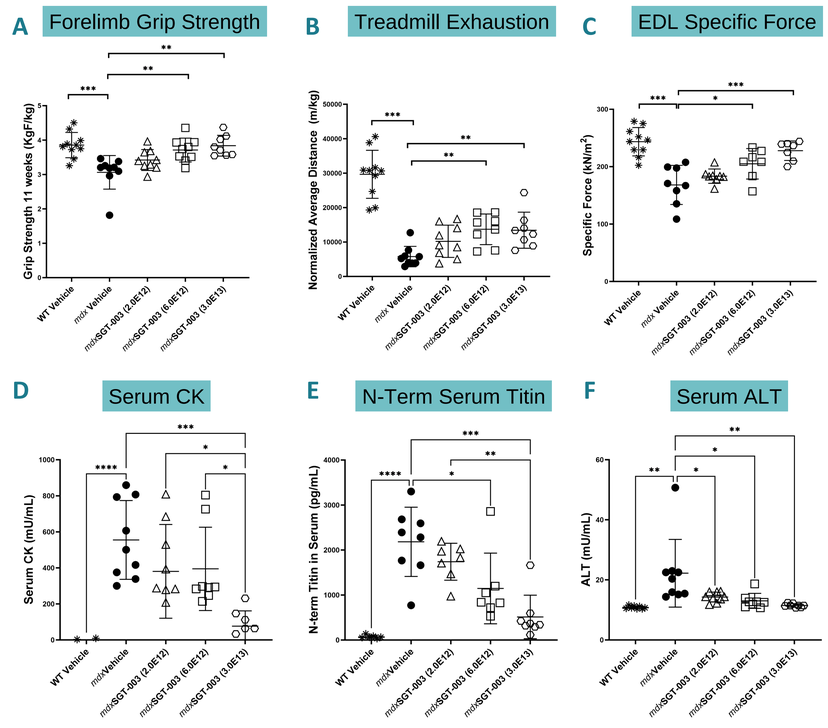



**Figure 6.** The minimal effective dose of SGT-003 was 6.0E12 vg/kg.

## Conclusions

- Three months post-SGT-003 treatment, functional efficacy was observed at doses ≥ 6.0E12 vg/kg as measured by forelimb grip strength, EDL specific force production, and treadmill exhaustion. A plateau in functional efficacy was observed at SGT-003 doses ≥ 3.0E13 vg/kg.
- Serum biomarkers showed improvements in sarcolemmal membrane integrity at doses ≥ 6.0E12 vg/kg.
- Microdystrophin protein, as well as nNOS enzymatic activity, were detected at the sarcolemma.
- Improvements in muscle pathology were also observed in response to microdystrophin expression.
- Overall, these data provided proof of concept for the use of SGT-003 in the treatment of DMD and supported initiation of a Phase I/II clinical study in boys with DMD.

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