Comprehensive Evaluation of Muscle Integrity Biomarkers to Assess Therapeutic Efficacy in Duchenne Muscular Dystrophy

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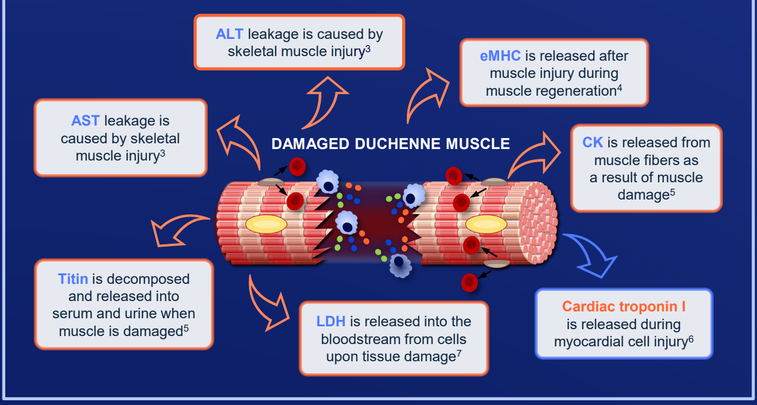
INTRODUCTION

- Duchenne muscular dystrophy (Duchenne) is a progressive neuromuscular disorder caused by the lack of functional dystrophin in muscle[1]
- Dystrophic muscle demonstrates substantial instability due to the lack of dystrophin. As a result, a hallmark of Duchenne is elevated serum creatine kinase (CK), an enzyme typically located in muscle fibers.[1]
- While this elevation is well established, the utility of CK to monitor treatment effects may be strengthened by additional markers that are also impacted by muscle instability[2]
- A biomarker panel composed of additional proteins typically located in muscle and markers of muscle turnover was evaluated to characterize muscle integrity (**Figure 1**) in three patients treated with SGT-003 enrolled in the INSPIRE DUCHENNE Phase 1/2 clinical trial

Figure 1. Exploratory Assessment of Biomarkers Associated with Muscle Integrity, Resilience, and Preservation



INSPIRE DUCHENNE: STUDY OVERVIEW

- Single-dose level, open-label, Phase 1/2 study
- Patients with Duchenne
- Prophylactic prednisone regimen as immunomodulation
- Actively enrolling: US, Canada, Italy, and UK
- NCT06138639

PRIMARY OBJECTIVE: To investigate the safety, tolerability, and efficacy of a single 1E14 vg/kg intravenous (IV) dose of SGT-003

PRIMARY SAFETY ENDPOINT: Incidence of treatment-emergent adverse events through Day 360

PRIMARY EFFICACY ENDPOINT: Change from baseline of microdystrophin protein levels at Day 90

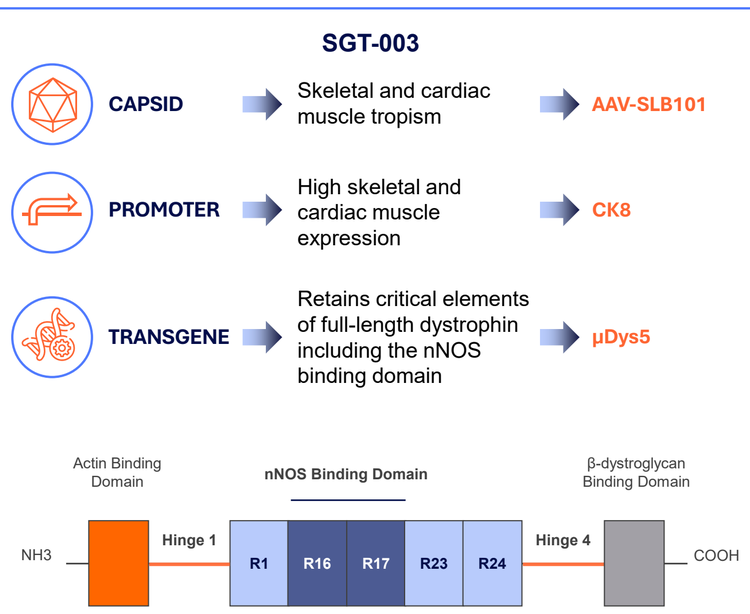
SECONDARY ENDPOINTS INCLUDE:

- Expression: Microdystrophin protein levels at Day 360 and distribution at Day 90 and Day 360
- Motor function: Time to rise, 10-meter walk/run, North Star Ambulatory Assessment, 4-stair climb, 6-minute walk test, stride velocity 95th centile

KEY ELIGIBILITY CRITERIA

- **Antibodies:** Negative for AAV9 antibodies
- **Prior Treatments:** No history of gene therapy; ≥12-week washout from exon skipping therapies, vamorolone, and/or givinostat
- **Steroid Regimen:** On a stable dose of daily oral steroids (prednisone or deflazacort) for ≥12 weeks
- **Age:** Cohort 1: 4 to <7 years, Cohort 2: 7 to <12 years; Cohort 3: <4 years
- ***DMD* Genetic Variant Exclusions:** Any deletion in exons 1 to 11 and/or 42 to 45, inclusive
- **Function:** Cohorts 1, 3: None; Cohort 2: Time to rise and 10-meter walk/run criteria

OVERVIEW OF SGT-003



SGT-003 is an AAV-based microdystrophin gene transfer therapy being evaluated in the INSPIRE DUCHENNE Phase 1/2 clinical trial. SGT-003 was designed to deliver a unique, rationally designed dystrophin surrogate that includes the nNOS binding domain to replace absent protein in skeletal and cardiac muscles throughout the body using the muscle-tropic capsid, AAV-SLB101.

nNOS: neuronal nitric oxide synthase.

REFERENCES:

1. Escobar-Huertas JF, et al. *Cytoskeleton (Hoboken)*. 2024; epub ahead of print. **2.** Kim EY, et al. *Ann Rehabil Med*. 2017;41(2):306-312. **3.** Aulbach AD, Amuzie, CJ. *A Comprehensive Guide to Toxicology in Nonclinical Drug Development (Second Edition)*. 2017. **4.** Guiraud S, et al. *Hum Mol Genet*. 2019;28(2):307-319. **5.** Oshida N, et al. *Sci Rep*. 2019;9(1):19498. **6.** Hiramuki Y, et al. *Sci Rep*. 2025;15(1):1778. **7.** Farhana A, Lappin SL. *StatPearls* [Internet]. 2023. **8.** ELEVIDYS prescribing information. Sarepta Therapeutics, Inc; Cambridge, MA. August 2024. **9.** Mendell JR, et al. *Nat Med*. 2025 Jan;31(1):332-341. **10.** Sarepta Therapeutics EMBARK Part 2 conference call, January 27, 2025. **11.** Oshida N, et al. *Sci Rep*. 2019;9(1):19498. **12.** Guiraud S, et al. *Hum Mol Genet*. 2019;28(2):307-319. **13.** Hiramuki Y, et al. *Sci Rep*. 2025;15(1):1778.

PRECLINICAL DATA PROVIDE INSIGHT INTO IMPACT OF MICRODYSTROPHIN ON CIRCULATING BIOMARKERS OF MUSCLE INTEGRITY

Figures 2-4. Mice lacking dystrophin were treated with SGT-003 and positive changes in the circulating biomarker profile were noted at 92 days post-dosing. Circulating markers correlated with microdystrophin levels and functional readouts.

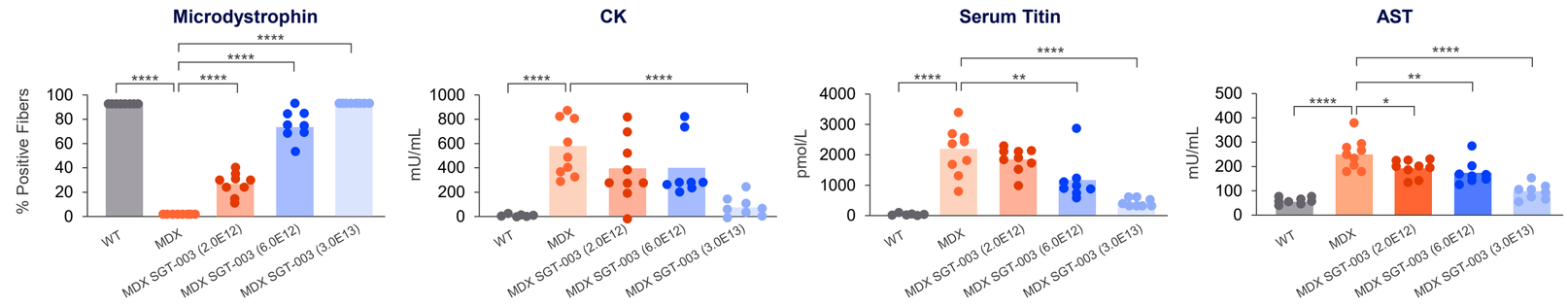


Figure 2. Microdystrophin was measured by immunofluorescence in quadriceps muscles 92 days post treatment with SGT-003. Serum was taken at Day 92 and CK, titin, and AST were measured. Declines in all three were observed in a dose dependent manner in mice treated with ascending doses of SGT-003. *p<0.05, **p<0.01, ****p<0.0001.

AST: aspartate aminotransferase; CK: creatine kinase.

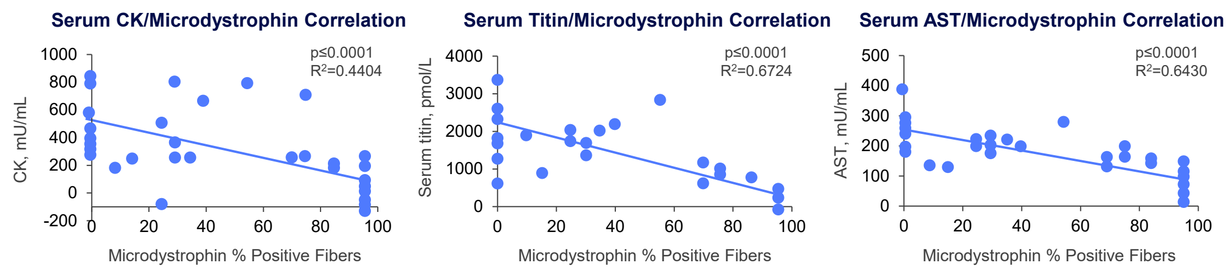


Figure 3. Correlations were observed between circulating biomarkers and microdystrophin expression in the muscle.

AST: aspartate aminotransferase; CK: creatine kinase.

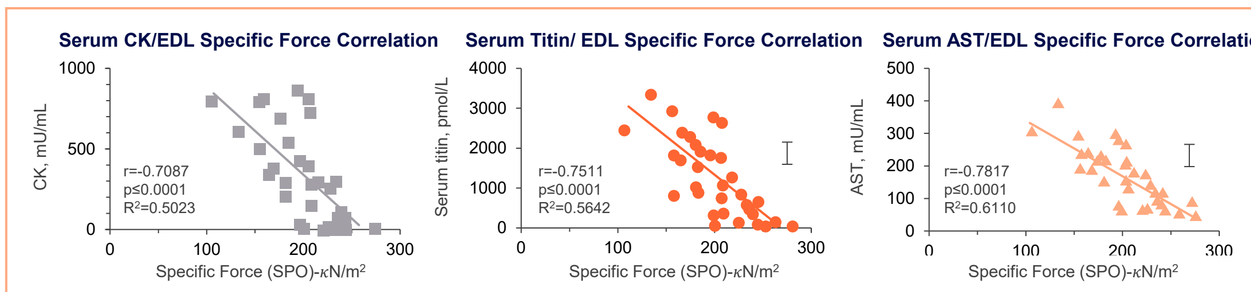


Figure 4. Circulating markers correlated to EDL specific force at Day 92 in mice treated with SGT-003.

AST: aspartate aminotransferase; CK: creatine kinase; EDL: extensor digitorum longus.

INITIAL CLINICAL DATA FROM THE INSPIRE DUCHENNE STUDY OF SGT-003 SHOWED ROBUST MICRODYSTROPHIN EXPRESSION AND IMPROVEMENTS IN BIOMARKERS OF MUSCLE INTEGRITY

EFFICIENT TRANSDUCTION OBSERVED IN SKELETAL MUSCLE

Participant	Dose	Copies/Nucleus
1	1E14 vg/kg	19.8
2		28.6
3		7.6
Mean		18.7

Figure 5. SGT-003 biodistribution indicated robust skeletal muscle transduction across the first three participants in the study.

PROTEIN EXPRESSION ACHIEVED IN SKELETAL MUSCLE

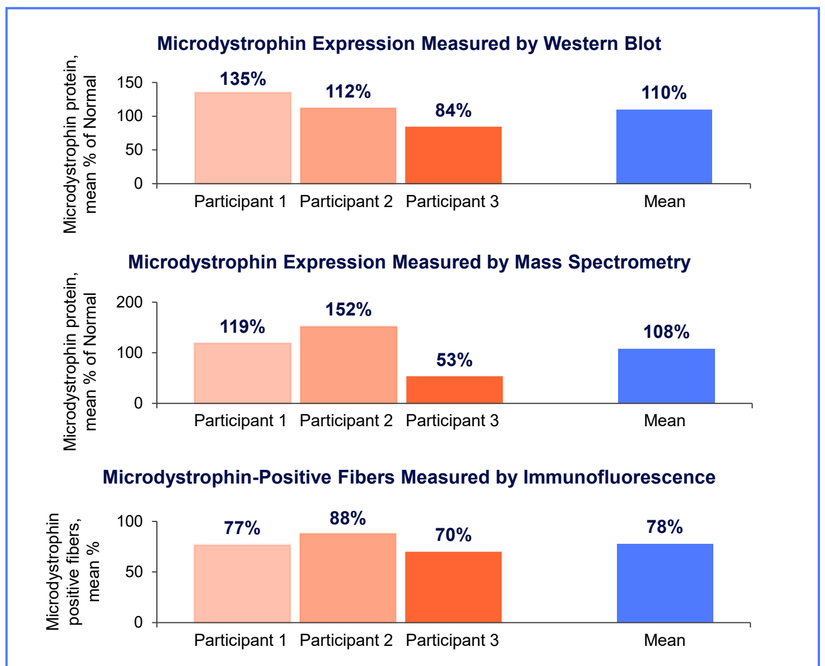


Figure 6. Comprehensive orthogonal measurements show high levels of microdystrophin expression.[b,9,10]

[a]Baseline Western blot and mass spectrometry were both 0% mean normal dystrophin. Baseline mean dystrophin positive fibers were 1.5% measured by immunofluorescence.

MARKERS OF MUSCLE INJURY WERE DECREASED WITH SGT-003

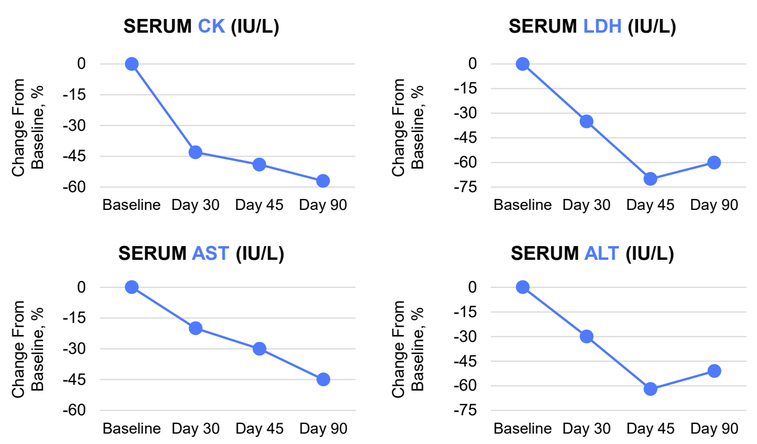


Figure 7. Levels of serum CK, LDH, AST, and ALT are increased in dystrophic serum due to release from the muscle into the circulation when muscle is damaged. Treatment with SGT-003 resulted in decreases over time for the first three participants in the study for all four markers, suggesting a decline in muscle injury.

Mean (n=3) change from baseline results shown. ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; LDH: lactate dehydrogenase.

REDUCTION IN MARKERS OF MUSCLE BREAKDOWN AND MUSCLE PRESERVATION

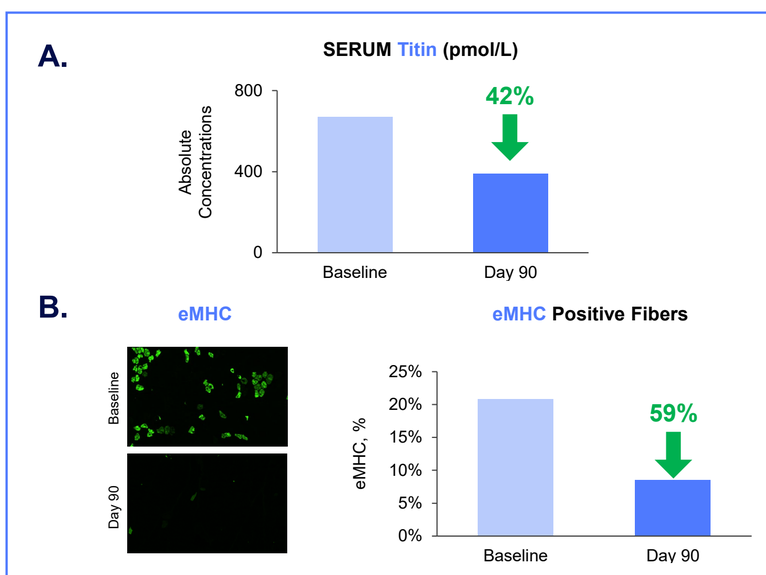


Figure 8. Reduced titin combined with reduced eMHC suggests that SGT-003 has interrupted muscle breakdown and preserved muscle fibers at Day 90 for the first three participants in the study. **A.** Titin is actively degraded and fragments and released into serum when muscle is damaged.[11] A decrease suggests that SGT-003 treatment results in a reduction in muscle breakdown. **B.** eMHC is expressed in dystrophic muscle that is undergoing degeneration / regeneration.[12] A decrease suggests that SGT-003 helps in muscle preservation and resilience.

eMHC: embryonic myosin heavy chain

DECREASE IN CARDIAC INJURY MARKER (n=1, DAY 90)

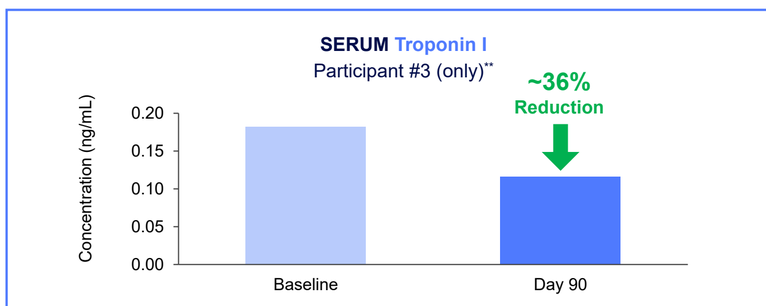


Figure 9. Cardiac troponin I is released during myocardial cell injury and levels can be spontaneously increased in patients with Duchenne.[13] Reductions were observed with SGT-003 treatment in one participant, suggesting potential impact to the cardiac profile. **Serum troponin data only from Participant 3 who had elevated levels at baseline. Troponin I levels for Participants 1 & 2 were 0 at baseline.

CONCLUSIONS

- Analyses of data generated from mouse models of Duchenne treated with SGT-003 demonstrate that microdystrophin positive fibers correlate with improvements in circulating biomarkers
- In the INSPIRE DUCHENNE Phase 1/2 study of SGT-003, the first three participants showed improvements in multiple markers of muscle integrity in both skeletal muscle biopsies and serum
- One study participant with a baseline troponin I elevation demonstrated a decrease at 90 days after SGT-003 treatment
- Improved muscle integrity, as indicated by a coordinated biomarker profile, may support a slowing of disease progression and better long-term clinical outcomes
- Monitoring of multiple Duchenne biomarkers represents a comprehensive approach to assess disease trajectory
- Biomarker data from the ongoing INSPIRE DUCHENNE study will continue to be analyzed to further evaluate the potential SGT-003 treatment effect

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