# Update on INSPIRE DUCHENNE: A Phase 1/2 Study of SGT-003, an Investigational Next-Generation Microdystrophin Gene Therapy for Duchenne Muscular Dystrophy

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## INTRODUCTION

- Duchenne muscular dystrophy (Duchenne) is a chronic, progressive, and ultimately fatal X-linked recessive neuromuscular disorder caused by the absence of functional dystrophin protein[1]
- Dystrophin is required for maintaining muscle integrity and function[2-4]
  - Deterioration of muscle integrity leads to loss of essential membrane proteins and muscle fiber breakdown and leakage, resulting in progressive functional decline
- Shortened, functional microdystrophin transgenes can be packaged into adeno-associated viruses (AAVs) to replace dystrophin[5]
  - Microdystrophins vary based on their unique compositions[6]
- SGT-003 is a next-generation AAV-microdystrophin gene therapy with key features:
  - Microdystrophin transgene: unique inclusion of the neuronal nitric oxide synthase (nNOS)-binding domain helps improve blood flow to prevent activity-induced ischemia and associated muscle injury[7]
  - AAV-SLB101 capsid: rationally designed muscle-tropic capsid that leads to higher levels in muscle and reduced levels in the liver[8]
  - Full/empty capsid ratio: SGT-003 manufacturing uses a transient transfection process, focusing on maintaining high % full capsid ratios to improve purity

## OBJECTIVE

To evaluate the safety, tolerability, and efficacy of a single intravenous (IV) infusion of SGT-003 at 1E14 vg/kg in pediatric participants with Duchenne

## METHODS

- INSPIRE DUCHENNE (NCT06138639) is a single-dose-level, open-label Phase 1/2 study actively enrolling patients with DMD
  - A prophylactic prednisone regimen alone is being used as immunomodulation
- The primary safety endpoint is the incidence of treatment-emergent adverse events (TEAEs) through Day 360
- The primary efficacy endpoint is the change from baseline of microdystrophin protein levels at Day 90
- Secondary endpoints include:
  - Microdystrophin expression: 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

## RESULTS

- As of the August 12, 2025, data cutoff, 15 participants have received SGT-003 at ages ranging from 5 to 10 years (**Table 1**)

**Table 1. Demographics for the First 15 Participants**

| COHORT | ELIGIBLE AGE RANGE (YEARS) | AGES AT ENROLLMENT (YEARS) | WEIGHTS FOR DOSING (kg) | PARTICIPANTS ENROLLED (n) |
|---|---|---|---|---|
| 1 | 4 to < 7 | 5 to 6 | Up to 27.8 | 9 |
| 2 | 7 to < 12 | 7 to 10 | Up to 39.7 | 6 |
| Total | 4 to < 12 | 5 to 10 | Up to 39.7 | 15 |

### Safety Summary

- No reports of treatment-emergent serious adverse events (TESAEs)
- All treatment-related AEs resolved without sequelae (**Table 2**)
- Glucocorticoids alone used for immunosuppression
  - No need to administer any additional immunosuppression agents, including eculizumab or sirolimus
  - Avoiding the need for additional immunosuppressive agents such as eculizumab eliminates the associated infection risks and vaccination requirements, reducing treatment burden for both providers and patients[9]

**Table 2. SGT-003 Treatment-Emergent Adverse Events**

| SGT-003 TREATMENT-EMERGENT ADVERSE EVENTS (TEAES) | | TOTAL PARTICIPANTS (N=15) |
|---|---|---|
| *Data cutoff August 12, 2025* | | n (%) |
| **Serious Adverse Events (SAEs)** | | 0 (0) |
| **Adverse Events of Special Interest (AESIs)** | Hepatotoxicity | 1 (6.7)* |
| | Thrombotic Microangiopathy | 0 (0) |
| | Myocarditis | 0 (0) |
| | Myositis | 0 (0) |
| **Most Common Adverse Events (AEs)** | Nausea | 15 (100) |
| | Vomiting | 14 (93.3) |
| | Thrombocytopenia/Platelet Count Decreased | 10 (66.7) |
| | Decreased Appetite | 9 (60.0) |
| | Headache | 6 (40.0) |

*n=1 AESI of hepatotoxicity based on laboratory criteria; Grade 1 (mild) hypertransaminasaemia with no clinical symptoms.

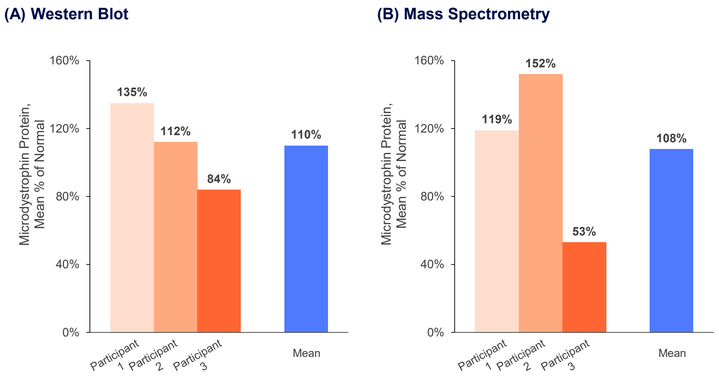
### Day 90 Muscle Biopsy Results

- In initial evaluations of muscle biopsies from the 3 participants who reached the Day 90 timepoint, qPCR analysis demonstrated high vector genome copies in muscle (**Table 3**)

**Table 3. Muscle Biodistribution Analysis by qPCR**

| PARTICIPANT | COPIES/NUCLEUS |
|---|---|
| 1 | 19.8 |
| 2 | 28.6 |
| 3 | 7.6 |
| Mean | 18.7 |

**Figure 1. High Microdystrophin Protein Levels at Day 90 in Muscle Biopsies as Measured by (A) Western Blot and (B) Mass Spectrometry**




Baseline values by Western blot and mass spectrometry were both 0% of normal dystrophin.

### Day 90 Muscle Biopsy Results (cont'd)

**Figure 2. High Percent Positive Fibers for (A) Microdystrophin, (B) β-sarcoglycan, and (C) nNOS Activity From Day 90 Muscle Biopsies**

**Microdystrophin[a]**

| PARTICIPANT | 1 | 2 | 3 | MEAN |
|---|---|---|---|---|
| Day 90 Values | 77% | 88% | 70% | 78% |
| Baseline Values | 0.8% | 2.3% | 1.3% | 1.5% |

**β-sarcoglycan[a]**

| PARTICIPANT | 1 | 2 | 3 | MEAN |
|---|---|---|---|---|
| Day 90 Values | 60% | 88% | 63% | 70% |
| Baseline Values | 0% | 2.5% | 1.5% | 1.3% |

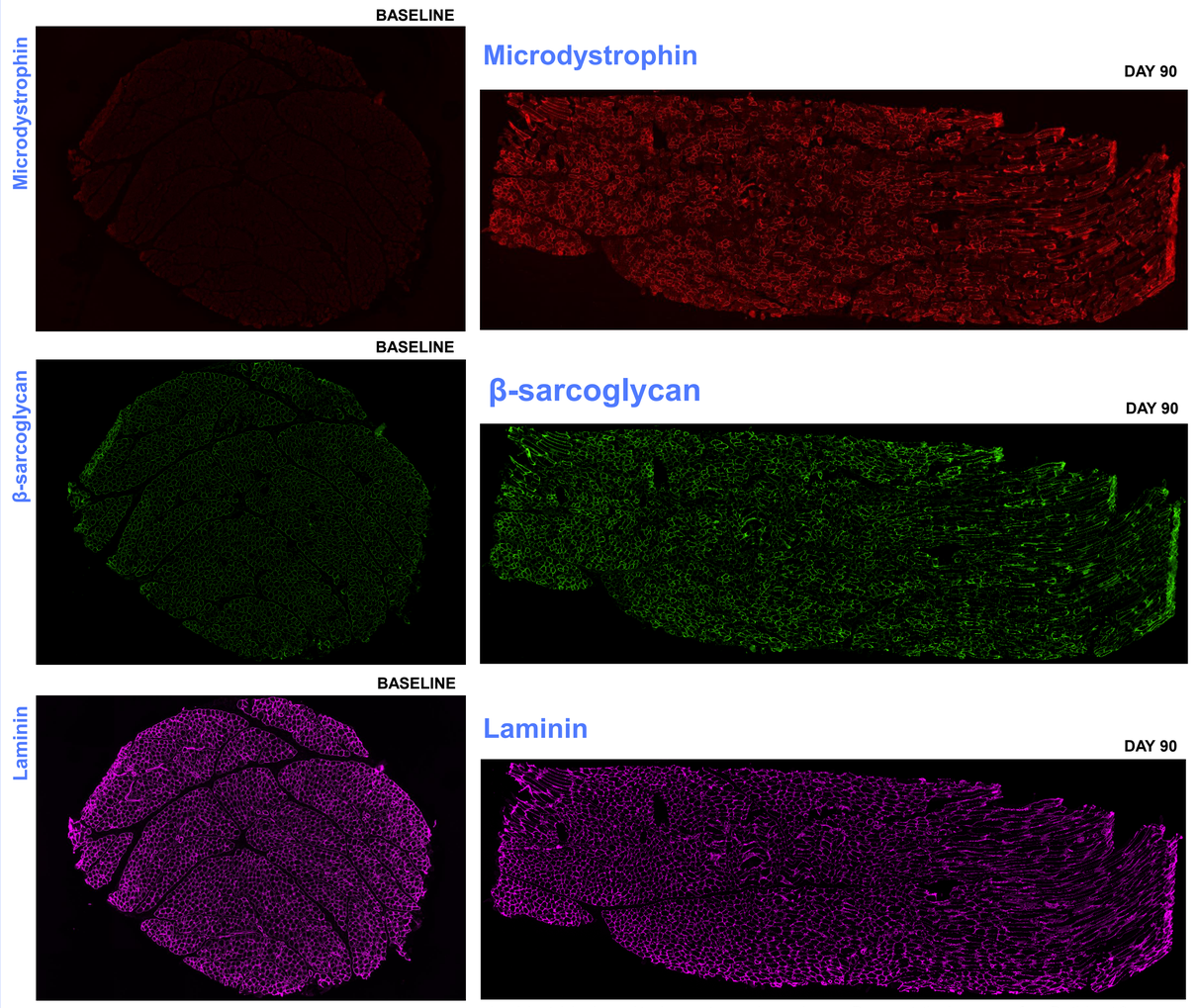
**nNOS Activity[a]**

| PARTICIPANT | 1 | 2 | 3 | MEAN |
|---|---|---|---|---|
| Day 90 Values | 48% | 53% | 25% | 42% |
| Baseline Values | 0% | 1.5% | 0.5% | 0.7% |

[a]Mean (n=3) absolute percent positive fibers results shown.

**Figure 3. Restoration of the Dystrophin-Associated Protein Complex (DAPC)**

- Muscle biopsies showed increases in key elements of the DAPC
- Representative images are from Participant 2

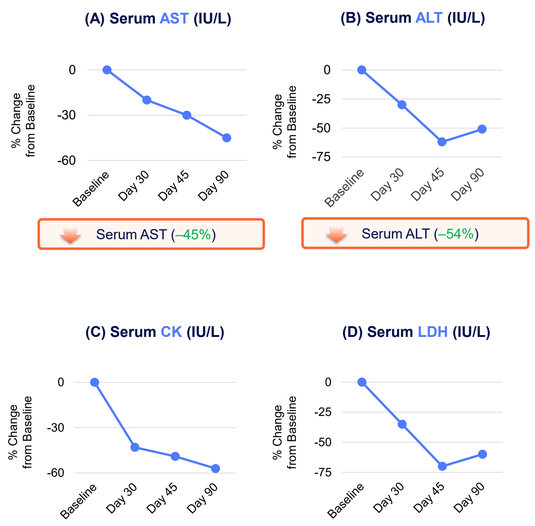



Laminin staining is used to demarcate muscle membranes. Representative images are from Participant 2.

### Day 90 Improvements in Markers of Muscle Integrity

**Figure 4. Reduced Markers of Muscle Injury: (A) AST, (B) ALT, (C) CK, and (D) LDH**

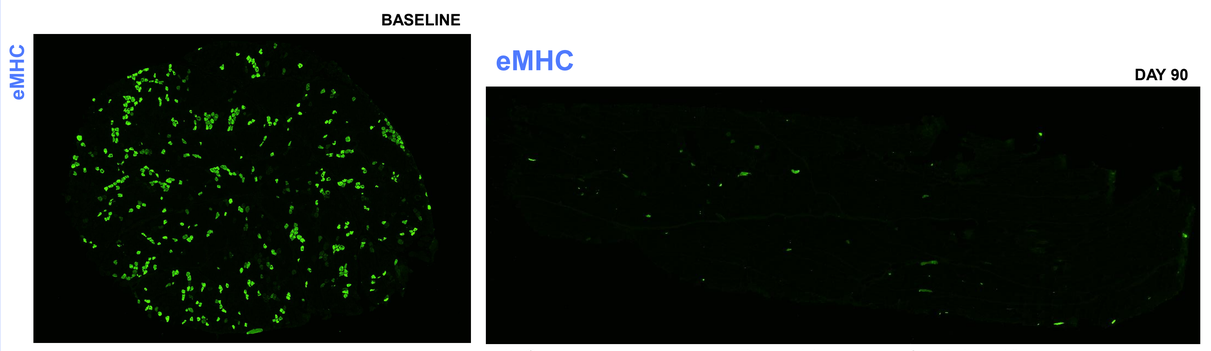
- AST, ALT, creatine kinase (CK), and lactate dehydrogenase (LDH) are released from muscle into circulation in Duchenne due to tissue damage and muscle injury[10-12]
- SGT-003 demonstrated improvements in all 4 serum biomarkers evaluated[1] (**Figure 4**)



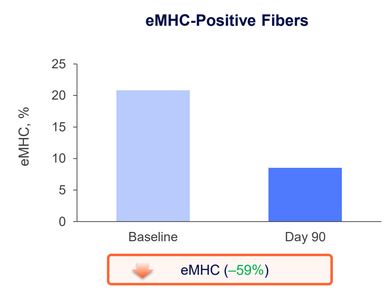

Mean (n=3) change from baseline results shown. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase.

**Figure 5. Improvements in Markers of Muscle Breakdown and Dystrophic Regeneration**

- Muscle biopsies showed decreases in the embryonic form of myosin heavy chain (eMHC), a marker of actively degenerating / regenerating muscle



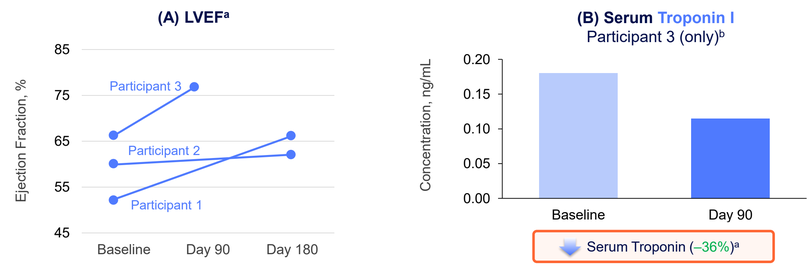

eMHC: embryonic myosin heavy chain. Representative images are from Participant 2.




Mean (n=3) absolute and percent change from baseline results shown.

**Figure 6. Positive Changes in Cardiac Markers: (A) LVEF and (B) Serum Troponin I**

- Positive changes were observed in cardiac markers following treatment with SGT-003 (**Figure 6**)




[a]Participant 3 had not reached the Day 180 follow-up at this data cutoff (February 11, 2025). [b]Serum troponin data only from Participant 3 at Day 90: Participant 3 had elevated troponin levels at baseline. Absolute and percent change from baseline results shown. Troponin levels for Participants 1 and 2 were below the limit of quantification at baseline. LVEF: left ventricular ejection fraction.

## CONCLUSIONS

- Initial muscle biopsy results for the first 3 participants reaching Day 90:
  - High levels of vector genome copies per nucleus
  - High protein levels and distribution of SGT-003 microdystrophin
  - DAPC proteins, uniquely including enzymatically active nNOS, were restored to the membrane
- Muscle integrity biomarker results for the first 3 participants reaching Day 90:
  - Consistent improvements across all biomarkers of muscle integrity evaluated
- No treatment-emergent SAEs in the 15 participants treated with a data cutoff of August 12, 2025

## REFERENCES

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