SGT-003: Initial Safety Evaluation of a Next-Generation Investigational Gene Therapy for Duchenne Muscular Dystrophy

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INTRODUCTION

- Adeno-associated virus (AAV) gene therapy offers a promising approach for Duchenne muscular dystrophy because AAV vectors can deliver genetic material with high precision; however, the high systemic-doses often required for neuromuscular indications can be associated with safety risks, such as acute liver injury
- SGT-003 incorporates innovations in both vector biology and scalable manufacturing to address these limitations
- AAV-SLB101 is a rationally designed muscle-tropic capsid that engages integrin receptors that are upregulated in dystrophic muscle[1]
- SGT-003 delivers a microdystrophin transgene that includes the neuronal nitric oxide synthase (nNOS) binding domain, which promotes local vasodilation in muscle during periods of energy demand, such as activity, to mitigate ischemic muscle injury[2]
- Preclinical studies showed increased skeletal and cardiac muscle biodistribution and decreased liver biodistribution using AAV-SLB101, compared to naturally occurring capsids
- SGT-003 is manufactured using a 1000 L suspension-based transient transfection process that focuses on maintaining a high % of full capsids for purity

OBJECTIVE

To evaluate preliminary safety and tolerability data from the ongoing INSPIRE DUCHENNE Phase 1/2 study (NCT06138639) of SGT-003, a next-generation AAV gene therapy candidate utilizing the rationally designed AAV-SLB101 capsid for the treatment of Duchenne muscular dystrophy

METHODS

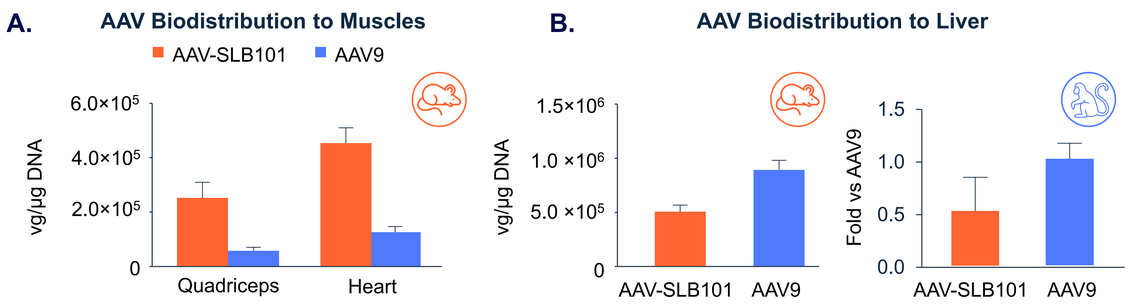
- INSPIRE DUCHENNE is a single-dose-level, open-label Phase 1/2 study actively enrolling patients with Duchenne muscular dystrophy
- Participants receive a single IV infusion of 1E14 vg/kg of SGT-003
- Prophylactic corticosteroids only used for immunomodulation

- **Primary Safety Endpoint:** Incidence of treatment-emergent adverse events (TEAEs) through Day 360
- **Primary Efficacy Endpoint:** 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; Stride Velocity 95th Centile; 10-Meter Walk/Run; North Star Ambulatory Assessment, 4-Stair Climb Test, 6-Minute Walk Test

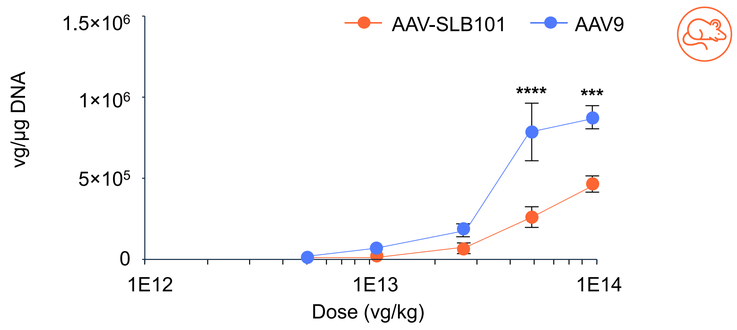
RESULTS

Figures 1. AAV-SLB101 Resulted in Increased Skeletal and Cardiac Muscle Biodistribution and Reduced Liver Biodistribution Versus AAV9

IMPROVED MUSCLE TRANSDUCTION | **DECREASED LIVER TRANSDUCTION**



DECREASED LIVER TRANSDUCTION ACROSS DOSE RANGES



Asterisks indicate statistical significance between groups (***p<0.001, ****p<0.0001).
AAV: adeno-associated virus.

- In the *mdx* mouse, AAV-SLB101 showed increased biodistribution to the quadriceps and heart and decreased biodistribution to the liver compared to AAV9 (**Figure 1A-1B**)
- In non-human primates, AAV-SLB101 showed lower liver transduction compared to AAV9 (**Figure 1B**)
- Across escalating doses, AAV-SLB101 consistently demonstrated reduced liver biodistribution relative to AAV9 in the *mdx* mouse model (**Figure 1C**)
- The no observed adverse effect level (NOAEL) was 3E14 vg/kg (highest dose level tested) in *mdx* mice and non-human primates; no adverse effects were identified in either species at or below this dose level
- SGT-003–related changes in *mdx* mice included decreases in ALT AST, and CK up to the NOAEL dose level at Days 4, 29, and 92, compared to untreated *mdx* animals that showed higher levels associated with their Duchenne phenotype

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase

REFERENCES

1. Vu Hong A, et al. *Nat Commun*. 2024;15(1):7965. **2.** Lai Y, et al. *J Clin Invest*. 2009;119(3):624-35.

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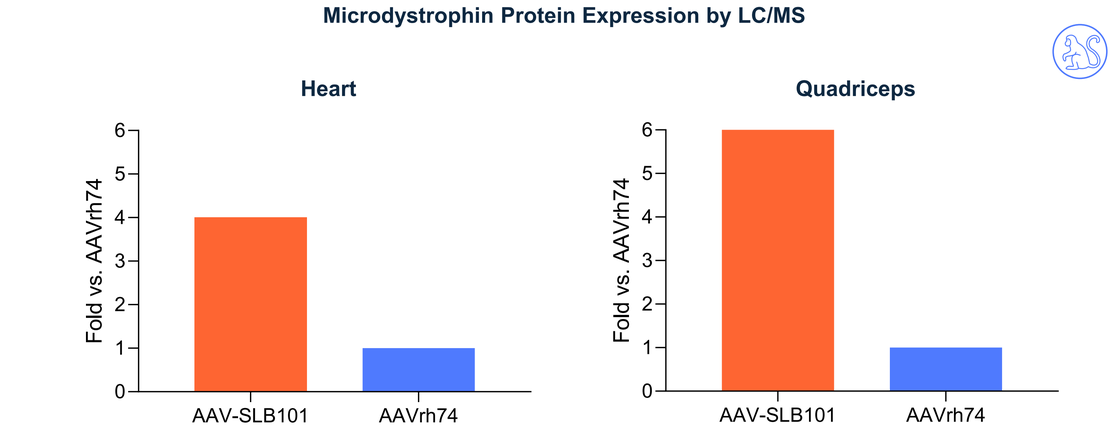
RESULTS *(cont'd)*

Figures 2. AAV-SLB101 Resulted in Higher Microdystrophin Expression Versus AAVrh74

ROBUST MUSCLE-TROPIC EXPRESSION IN NON-HUMAN PRIMATES

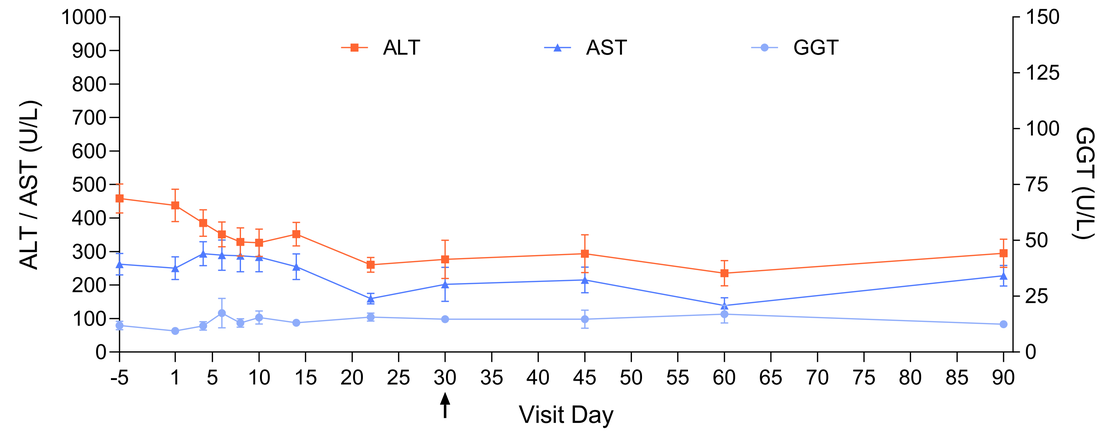


n=3 for AAV-SLB101; n=2 for AAVrh74
LCMS: liquid chromatography mass spectrometry.

- AAV-SLB101 drove robust muscle-tropic transgene expression in non-human primates administered equivalent 1E14 vg/kg doses of CK8-microdystrophin packaged in either AAV-SLB101 or AAVrh74
- Heart and quadriceps tissues showed multiple fold higher microdystrophin protein levels in animals administered CK8-microdystrophin using AAV-SLB101 compared to AAVrh74

Figure 3. Liver Enzymes Remain Stable After Treatment With SGT-003 in INSPIRE DUCHENNE

STABLE LIVER BIOMARKERS



ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase.

- Mean (n=15) absolute levels of ALT, AST, and GGT for participants having reached each timepoint. Arrow indicates steroid tapering that begins at Day 30. Data cutoff August 12, 2025

SGT-003 TREATMENT-EMERGENT ADVERSE EVENTS (TEAES) *Data cutoff August 12, 2025*		TOTAL PARTICIPANTS (N=15) 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. No bilirubin elevation. No events of drug induced liver injury.

- Treatment with SGT-003 has been well-tolerated in all participants to date
- No SAEs, suspected unexpected serious adverse reactions (SUSARs), or thrombotic microangiopathy (TMA) / atypical hemolytic uremic syndrome (aHUS) observed
- Glucocorticoids alone used for immunosuppression
  - Tapering of steroids back to baseline levels begins at Day 30 and occurs over the following 4 weeks

CONCLUSIONS

- SGT-003 has shown a favorable safety profile in the first 15 participants treated in the INSPIRE DUCHENNE study (data cutoff August 12, 2025)
- No treatment-emergent SAEs have been reported
- AAV-SLB101 is one of the first rationally designed capsids to decrease liver biodistribution and improve skeletal and cardiac muscle delivery
- The positive initial safety profile observed in the INSPIRE DUCHENNE study may be due to the unique tissue tropism of the AAV-SLB101 capsid

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