AAV-SLB101 in Duchenne Muscular Dystrophy: Nonclinical Safety, Characterization of Efficacy, and Preliminary Clinical Insights

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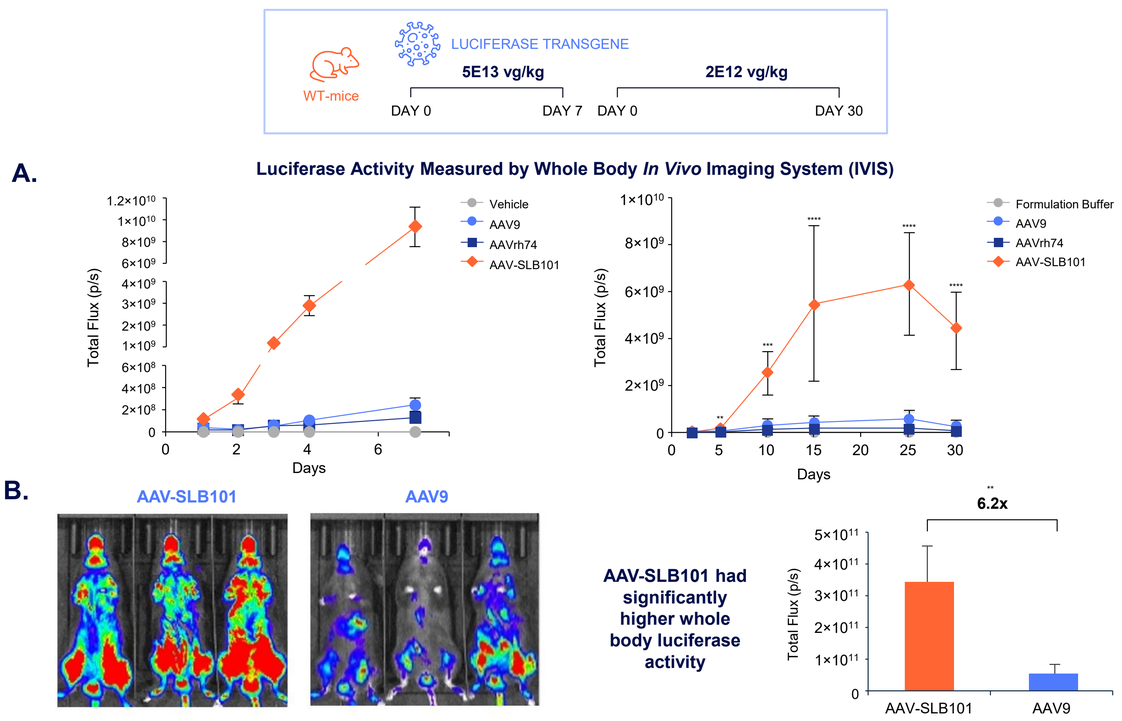
INTRODUCTION

- AAV-SLB101 is a proprietary, rationally designed muscle-tropic capsid used in Solid Biosciences' next-generation investigational gene therapy, SGT-003
- SGT-003 is currently being evaluated in the INSPIRE DUCHENNE (NCT06138639) Phase 1/2 clinical study for the treatment of Duchenne muscular dystrophy (Duchenne)
- AAV-SLB101-mediated transduction and expression of various reporter and therapeutic transgenes were compared to first generation (AAV9 and AAVrh74) vectors in wild type and Duchenne (*mdx*) mouse models
- SGT-003 transduction and microdystrophin expression were evaluated in muscle biopsies collected from INSPIRE DUCHENNE study participants

RESULTS

AAV-SLB101 ACHIEVED HIGHER AND MORE RAPID EXPRESSION COMPARED TO AAV9 AND AAVrh74 IN WILD TYPE MICE

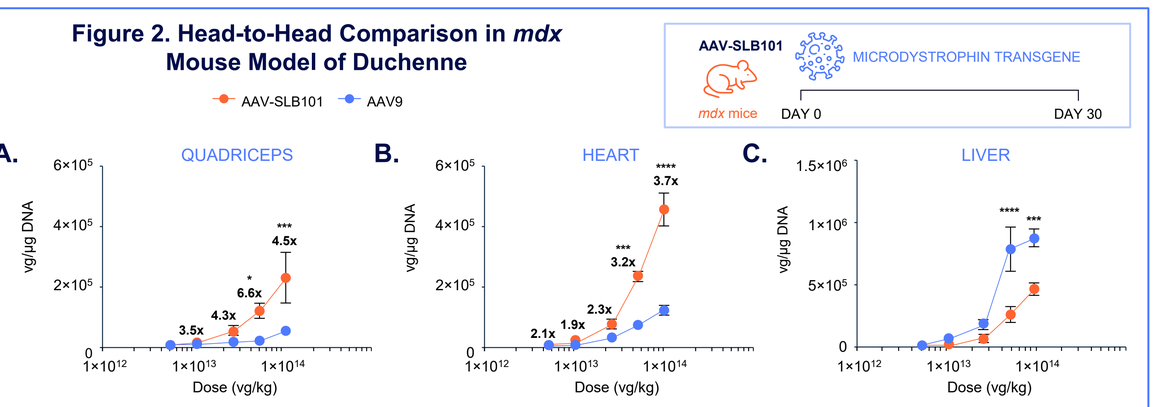
Figure 1. AAV-SLB101 Kinetics and Transduction Efficacy Compared to AAV9 and AAVrh74



A. Luciferase activity (whole body IVIS) was detected as early as 2 days post-dose and remained significantly higher for AAV-SLB101 vs AAV9 and AAVrh74. At Day 15, expression plateaued for all capsids, with higher levels maintained by AAV-SLB101-treated animals until Day 30. **B.** Luciferase activity (whole body IVIS) remained significantly higher for AAV-SLB101 vs AAV9 at Day 15 post AAV administration. Asterisks indicate statistical significance between groups (**p<0.01, ***P<0.001,****p<0.0001). WT, wild type.

AAV-SLB101 TRANSDUCED MUSCLES MORE EFFICIENTLY AND DISTRIBUTED LESS TO THE LIVER COMPARED TO AAV9

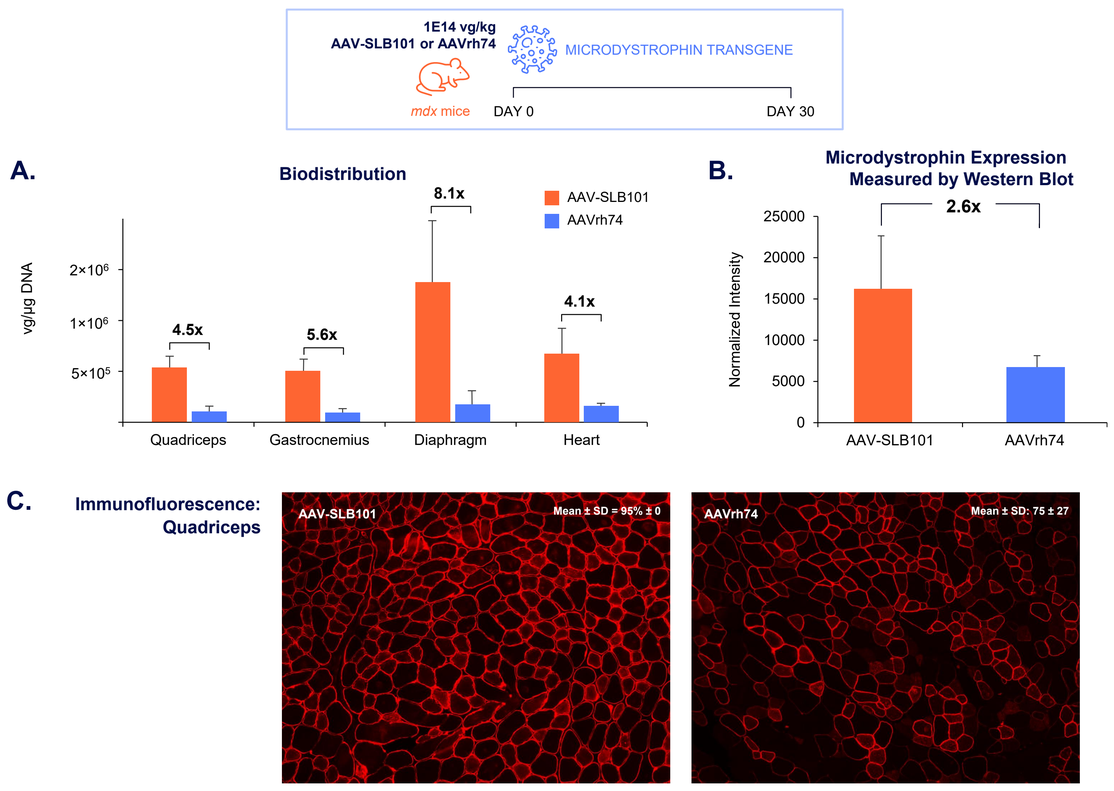
Figure 2. Head-to-Head Comparison in *mdx* Mouse Model of Duchenne



A and **B**. Higher biodistribution following AAV-SLB101 vs AAV9 treatment of mdx mice in disease-relevant tissues was observed in the quadriceps and heart. **C.** Decreased biodistribution of AAV-SLB101 vs AAV9 was observed in the liver. Asterisks indicate statistical significance (*p<0.05, ***p<0.001, ****p<0.0001) between groups with fold changes depicted.

AAV-SLB101 RESULTED IN HIGHER BIODISTRIBUTION AND EXPRESSION COMPARED TO AAVrh74

Figure 3. Head-to-Head Comparison in *mdx* Mouse Model of Duchenne

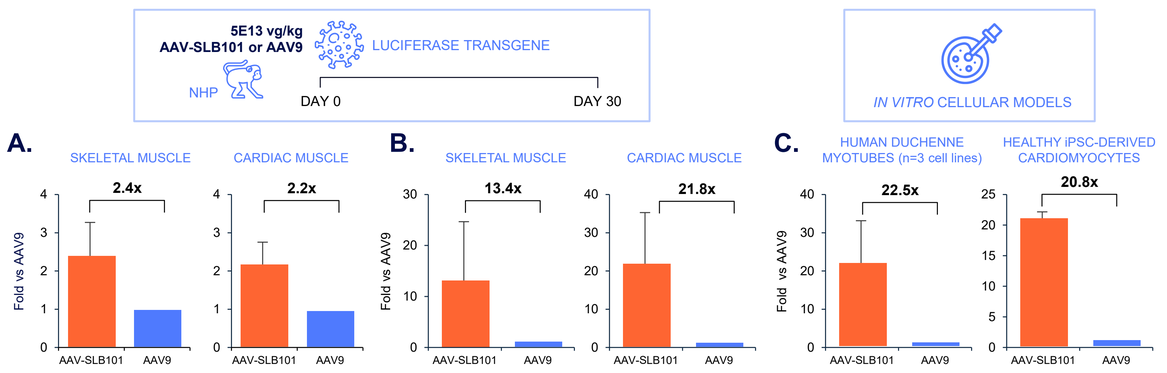


A. Higher biodistribution following AAV-SLB101 vs AAVrh74 treatment of *mdx* mice in quadriceps, gastrocnemius, diaphragm, and heart. **B.** Higher microdystrophin expression detected by Western blot in quadriceps of AAV-SLB101 vs AAVrh74-treated mice. **C.** Increased number of microdystrophin positive muscle fibers in quadriceps of AAV-SLB101 vs AAVrh74-treated mice. SD, standard deviation.

RESULTS *(cont'd)*

AAV-SLB101 TRANSDUCTION EFFICIENCY WAS MAINTAINED IN NHP STUDIES AND HUMAN CELL LINES COMPARED TO INITIAL RESULTS IN MICE

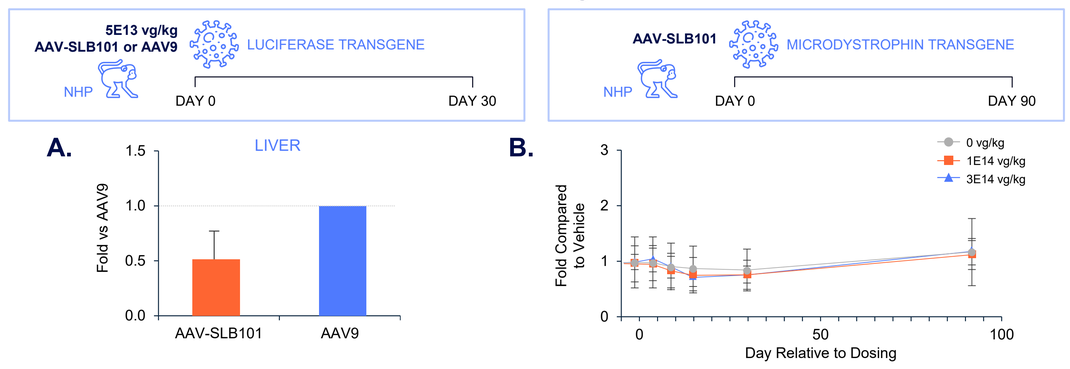
Figure 4. Transduction Efficiency of AAV-SLB101 Compared to AAV9 in Non-human Primates (NHPs) and Human Cell Models



A. Higher biodistribution (vector DNA) and **B.** luciferase activity following AAV-SLB101 vs AAV9 treatment of NHPs (n=3). Average fold differences calculated from the five skeletal muscle tissues sampled and three regions of cardiac tissue sampled**. C.** *In vitro* experiments showed increased luciferase activity of AAV-SLB101 in both Duchenne myotubes and healthy iPSC cardiomyocytes when compared to AAV9. Duchenne: Duchenne muscular dystrophy. iPSC: induced pluripotent stem cells, NHP: non-human primate.

REDUCTION TO LIVER MAY IMPROVE AAV-SLB101 SAFETY PROFILE

Figure 5. Reduced Liver Biodistribution Compared to AAV9 and Stable GGT Levels at Ascending Dose Levels of AAV-SLB101



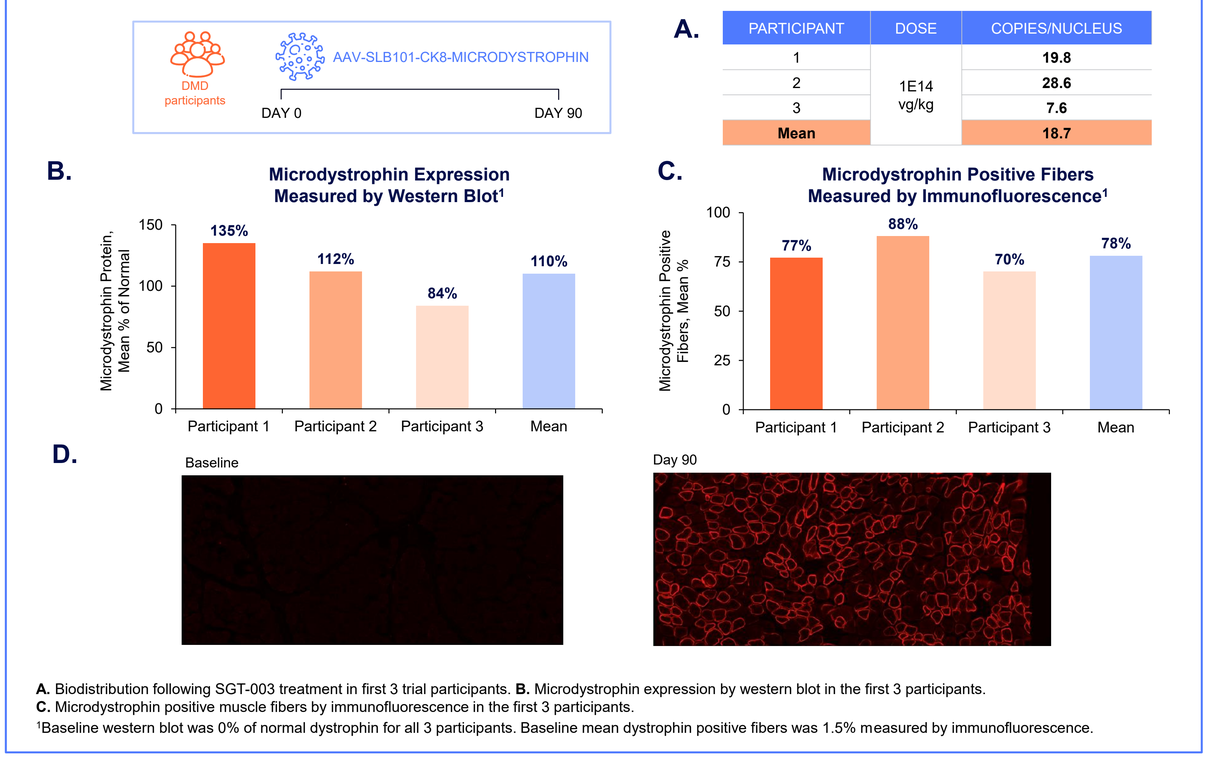
A. Reduced biodistribution was observed in the liver of NHPs treated with AAV-SLB101 when compared to those treated with AAV9. **B.** GGT levels remained stable 90 days post dose with AAV-SLB101 at doses up to 3E14 vg/kg in NHPs. These findings suggest that the decrease in biodistribution to the liver could be driving an increased safety profile of AAV-SLB101. GGT, gamma-glutamyl transferase; NHP, non-human primate.

INSPIRE DUCHENNE CLINICAL STUDY OF SGT-003: AAV-SLB101-CK8-MICRODYSTROPHIN

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.

Figure 6. Initial Data from INSPIRE DUCHENNE Clinical Trial of SGT-003



A. Biodistribution following SGT-003 treatment in first 3 trial participants. **B.** Microdystrophin expression by western blot in the first 3 participants.
C. Microdystrophin positive muscle fibers by immunofluorescence in the first 3 participants.
[1]Baseline western blot was 0% of normal dystrophin for all 3 participants. Baseline mean dystrophin positive fibers was 1.5% measured by immunofluorescence.

CONCLUSIONS

- Higher biodistribution and transgene expression were achieved when using AAV-SLB101 compared to both AAV9 and AAVrh74 in wild type mice and the *mdx* mouse model of Duchenne
- Higher biodistribution and microdystrophin expression were achieved with AAV-SLB101-CK8-microdystrophin compared to AAVrh74 in *mdx* DMD mice
- Reductions in AAV-SLB101 liver biodistribution were observed compared to AAV9 in both mice and NHPs
- High levels of biodistribution and microdystrophin expression were observed in muscle biopsies collected at Day 90 from the first 3 participants treated with SGT-003 in the INSPIRE DUCHENNE clinical study
  - No treatment-emergent SAEs reported (data cutoff Aug 12, 2025; n=15)
  - Encouraging liver safety profile that corresponds with observed nonclinical results

ACKNOWLEDGMENTS

This study was sponsored by Solid Biosciences Inc. (Charlestown, MA, USA). Medical editing assistance was provided by Elizabeth Schoelwer, PharmD, and Courtney Breuel, ELS, of the Propel Division of Woven Health Collective, LLC (New York, NY), and was funded by Solid Biosciences Inc.