AAV-SLB101: A Next-Generation Rationally Designed Capsid Demonstrates Highly Potent Cardiac Tropism and Initial Clinical Safety

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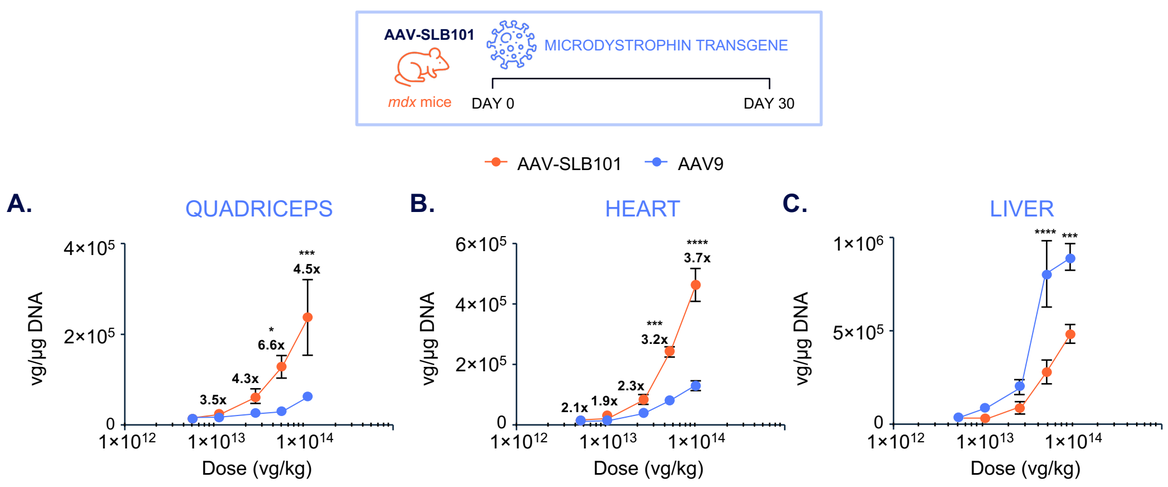
INTRODUCTION

- 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 with those of 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
- Cardiac structure and function, as well as biomarkers of cardiac injury, were monitored

RESULTS

AAV-SLB101 SHOWED IMPROVED MUSCLE TRANSDUCTION AND LOWER LIVER DISTRIBUTION COMPARED WITH AAV9

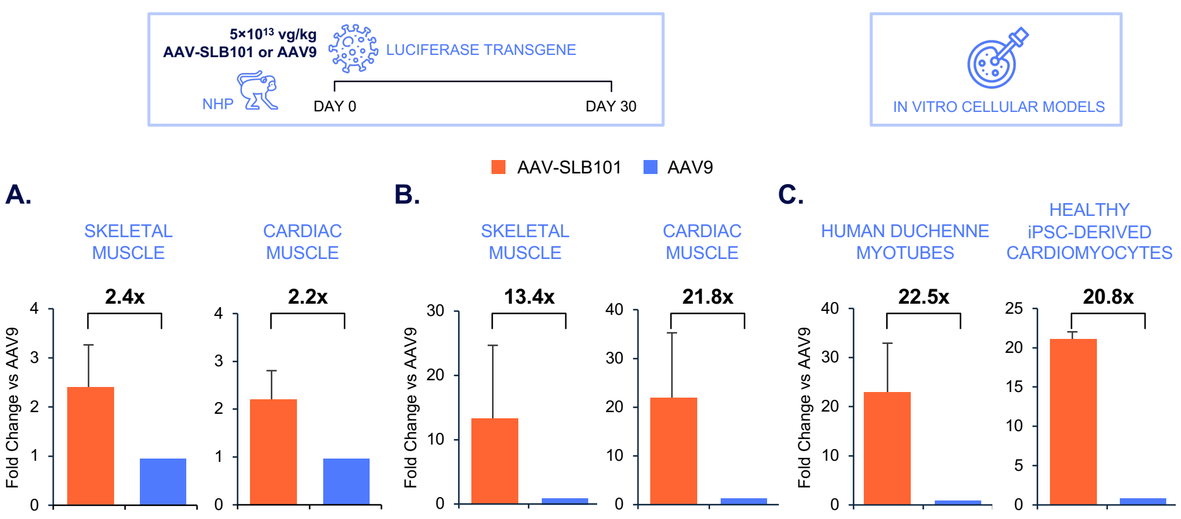
Figure 1. Head-to-Head Comparison in *mdx* Mouse Model of Duchenne[1]



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 TRANSDUCTION EFFICIENCY WAS MAINTAINED IN NON-HUMAN PRIMATE (NHP) STUDIES AND HUMAN CELL LINES COMPARED WITH INITIAL RESULTS IN MICE

Figure 2. Transduction Efficiency of AAV-SLB101 Compared With AAV9 in NHPs and Human Cell Models[1]



A. Higher biodistribution (vector DNA) and **B.** luciferase activity were observed following AAV-SLB101 vs AAV9 treatment in NHPs (n=2 per group). Average fold differences calculated from the 5 skeletal muscle tissues sampled and 3 regions of cardiac tissue sampled**. C.** In vitro experiments showed increased luciferase activity of AAV-SLB101 in both Duchenne myotubes (n=3 cell lines per treatment) and healthy iPSC cardiomyocytes when compared with that of AAV9. iPSC, induced pluripotent stem cell; NHP, non-human primate.

INSPIRE DUCHENNE CLINICAL STUDY OF SGT-003: AAV-SLB101-CK8-MICRODYSTROPHIN[2]

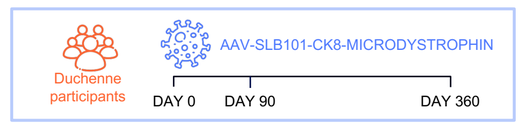
COHORT	ELIGIBLE AGE RANGE (YEARS)	AGES AT ENROLLMENT (YEARS)	WEIGHTS FOR DOSING (kg)	PARTICIPANTS ENROLLED (n)
1	4 to <7	4 to 6	≤27.8	13
2	7 to <12	7 to 10	≤39.7	8
3	0 to <4	1 to 3	≤17.0	2
Total	0 to <12	**1 to 10**	**≤39.7**	**23**

SGT-003 TREATMENT-RELATED ADVERSE EVENTS *Data cutoff October 31, 2025*		TOTAL PARTICIPANTS (N=23) n (%)
Serious Adverse Events		1 (4.3)*
Most common treatment-related adverse events	Nausea	17 (73.9)
	Vomiting	16 (69.6)
	Decreased appetite	11 (47.8)
	Thrombocytopenia/platelet count decreased	11 (47.8)
	Headache	6 (26.1)

*One (n=1) CTCAE Grade 3 serious adverse event of immune-mediated myositis. The myositis was not associated with muscle pain or weakness. The participant responded promptly to steroid treatment, with all clinical symptoms noted at presentation resolving and with creatine kinase levels declining well below baseline.

RESULTS *(cont'd)*

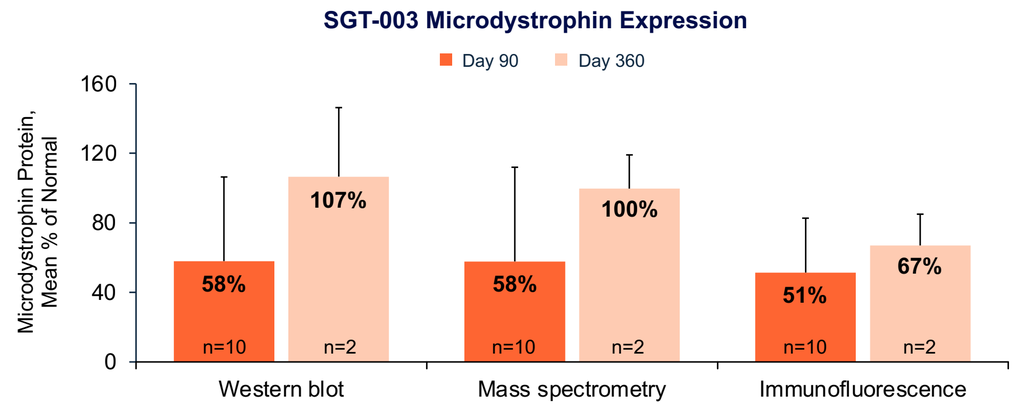
Figure 3. Data From INSPIRE DUCHENNE Clinical Trial of SGT-003[2]



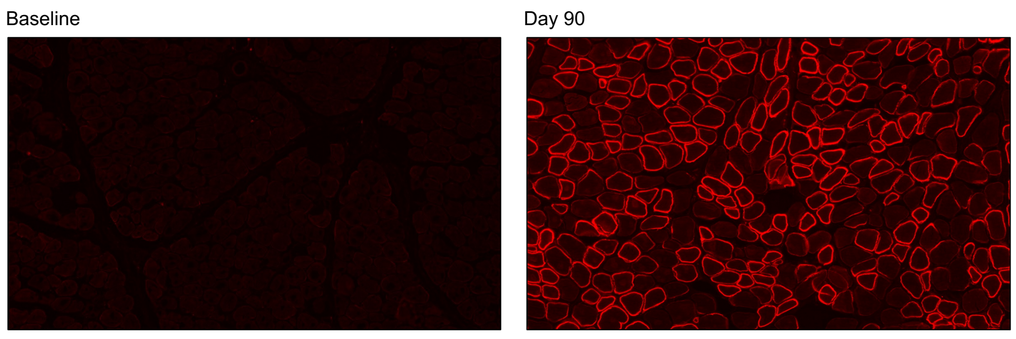
A.

DOSE (vg/kg)	VECTOR COPIES/NUCLEUS DAY 90 (n=10)	VECTOR COPIES/NUCLEUS DAY 360 (n=2)
1×10^{14}	13	12

B.



C.



A. Microdystrophin transduction at Day 90 and Day 360. **B.** Microdystrophin expression by western blot, mass spectrometry, and immunofluorescence. Baseline western blot and mass spectrometry were both 0% mean normal dystrophin. Baseline mean dystrophin-positive fibers were 1.5% measured by immunofluorescence. Dystrophin-positive fibers are not adjusted for fat and fibrosis; these are absolute numbers. **C.** Example microdystrophin biopsy at baseline and Day 90.

Figure 4. Signals of SGT-003 Cardiac Treatment Effect From INSPIRE DUCHENNE[2]

A. The mean ± SD normal LVEF range is 60% to 69% for this age-matched population.[3] **B.** Observations of improved cardiac function, as measured by LVEF using echocardiography, were primarily driven by participants with low to low-normal LVEF at baseline. **C.** Troponin reductions observed in participants who entered the trial with elevated baseline levels may indicate early signals of an SGT-003 cardiac treatment effect.

CONCLUSIONS

- Higher biodistribution and transgene expression were achieved when using AAV-SLB101 compared with AAV9 in key tissues for Duchenne, including skeletal muscle and heart
- Reductions in AAV-SLB101 liver biodistribution were observed compared with that of AAV9 in both mice and NHPs
- High levels of biodistribution and microdystrophin expression were observed in muscle biopsies collected from participants treated with SGT-003 in the INSPIRE DUCHENNE clinical study
- Though collected for safety, early data may indicate signals of potential benefit through reduction in cardiac troponin and increased systolic function, as measured by LVEF using echocardiography
  - Improvements in systolic function appear to be driven largely by those participants with low to low-normal systolic function at baseline

ACKNOWLEDGMENTS

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REFERENCES

1. Data on file. Solid Biosciences. 2025. 2. Data on file. Solid Biosciences. 2025. Data cutoff September 29, 2025. 3. Romanowicz J, et al. *J Am Soc Echocardiogr*. 2023;36(3):310-323.

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