ON BEHALF OF THE INSPIRE DUCHENNE STUDY TEAM

Initial Experience From the INSPIRE DUCHENNE Phase 1/2 Study of SGT-003 Microdystrophin Gene Therapy for Duchenne Muscular Dystrophy

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SGT-003 is an investigational product that has not been approved in any region.
No conclusions regarding safety and efficacy can be made.

Disclosures

Clinical trial support:

- Sarepta
- Dyne
- Avidity
- Ultragenyx
- Solid

Advisory boards:

- Armatus
- Encoded
- Insmed
- Dyne
- Solid

Past royalties:

- Astellas

Duchenne Muscular Dystrophy (Duchenne): Background

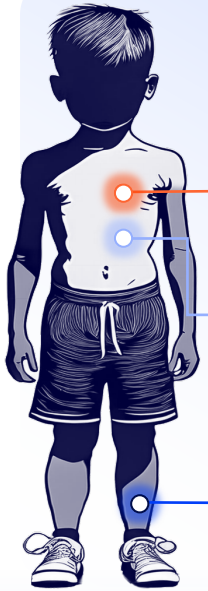
Duchenne is an X-linked recessive neuromuscular disorder caused by a lack of functional dystrophin[1]

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 AAVs to replace dystrophin[5]

- Microdystrophins can vary based on their unique compositions[6]



- Decreased heart function
- Cardiomyopathy

HEART FAILURE

- Weak diaphragm

RESPIRATORY FAILURE

- Loss of muscle mass
- Inflammation
- Fibrosis

LOSS OF AMBULATION

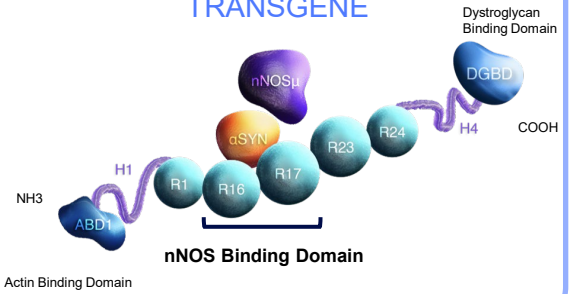
The impact of treatments on muscle integrity is key for patients with Duchenne[7]

AAV=adeno-associated virus.

1. Duan D, et al. *Nat Rev Dis Primers*. 2021;7(1):13. 2. Sheybani A, et al. *Pediatr Res*. 2022;92(6):1613-1620. 3. Voleti S, et al. *Pediatr Cardiol*. 2020;41(6):1173-1179. 4. Wagner KR, et al. *Biomark Med*. 2021;15(15):1389-1396. 5. Crudele JM, et al. *Hum Mol Genet*. 2019;28(R1):R102-R107. 6. Ramos JN, et al. *Mol Ther*. 2019;27(3):623-635. 7. Escobar-Huertas JF, et al. *Cytoskeleton (Hoboken)*. 2024;81(6-7):269-286.

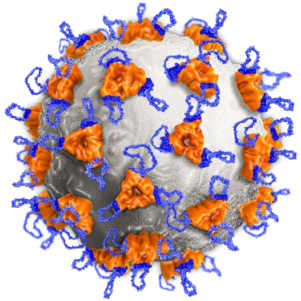
SGT-003: A Next-Generation AAV-Microdystrophin Gene Therapy Candidate[a]

SGT-003 MICRODYSTROPHIN TRANSGENE



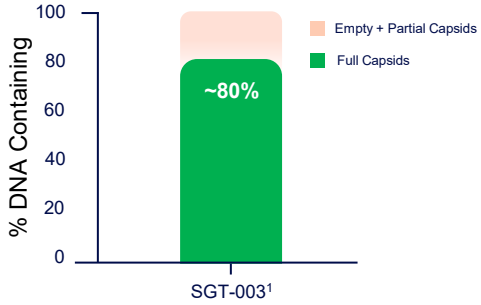
Unique inclusion of nNOS-binding domain designed with the goal of improving blood flow to prevent activity-induced ischemia and associated muscle injury[1]

SGT-003 AAV-SLB101 CAPSID



Rationally designed muscle-tropic capsid targeting multiple integrin receptors that are upregulated in dystrophic muscle[2]

SGT-003 FULL/EMPTY CAPSID RATIO



SGT-003 GMP manufacturing at ~80% full/empty capsid ratio (1000L scale)[3]

SGT-003's optimized transgene and next-generation capsid were selected to deliver a unique microdystrophin to muscles throughout the body while also de-targeting the liver[1,2]

αSYN=alpha-syntrophin; ABD1=actin-binding domain 1; DGBD=dystroglycan-binding domain; H=hinge; nNOS=neuronal nitric oxide synthase; R=spectrin-like repeat.
[a]SGT-003 is an investigational product that has not been approved in any region. No conclusions regarding safety and efficacy can be made.
1. Lai Y, et al. *J Clin Invest.* 2009;119(3):624-635. 2. Vu Hong A, *Nat Commun*. 2024;15(1):7965. 3. Data on file. Solid Biosciences. 2025.

INSPIRE DUCHENNE: Study Overview

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

Primary Objective: To investigate the safety and tolerability of a single 1.0E14 vg/kg IV dose of SGT-003

Primary Endpoint: Incidence of treatment-emergent adverse events through Day 360

Secondary Objective: To investigate the efficacy of a single IV dose of SGT-003

Secondary Endpoints:
- Expression: Microdystrophin protein levels at Days 90 and 360
- Motor function: TTR, 10MWR, NSAA, 4SC, 6MWT, SV95C at Day 540
- Pulmonary function: Percent predicted FVC, PEF, FEV1 at Day 540

KEY ELIGIBILITY CRITERIA

Age:	Cohort 1: Aged 4 to <7 years Cohort 2: Aged 7 to <12 years
***DMD* Genetic Variant Exclusions:**	Any deletion in exons 1 to 11 and/or 42 to 45, inclusive
Function:	Cohort 1: N/A Cohort 2: TTR and 10MWR 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/deflazacort) for ≥12 weeks

4SC=4-stair climb; 6MWT=6-minute walk test; 10MWR=10-meter walk/run; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; IV=intravenous; N/A=not applicable; NSAA=North Star Ambulatory Assessment; PEF=peak expiratory flow; SV95C=stride velocity 95th centile; TMA=thrombotic microangiopathy; TTR=time to rise.
Data on file. Solid Biosciences. 2025

INSPIRE DUCHENNE: Demographics for the First 6 Participants

As of a data cutoff of February 11, 2025, 3 participants have reached 90-day follow-up, and 2 participants have reached 180-day follow-up

Participant	Age at Dosing (Years)	Race/Ethnicity	Weight (kg)	Approx Time Elapsed Postdose (Months)[1]
1	5	White/Not Hispanic or Latino	19.6	8
2	5	White/Not Hispanic or Latino	26.4	7
3	7	White/Not Hispanic or Latino	27.8	5
4	6	White/Not Hispanic or Latino	22.0	<3
5	7	White/Not Hispanic or Latino	23.2	<3
6	7	Asian/Not Hispanic or Latino	18.9	<3

Day 90 data available

Data on file as of February 11, 2025. Solid Biosciences.

Vector Genome Copies in Day 90 Muscle Biopsies

PCR analysis demonstrated high vector genome copies in muscle

The AAV-SLB101 capsid efficiently transduces muscle
- PCR

Microdystrophin protein is expressed in muscle
- Western Blot
- Mass Spectrometry

Microdystrophin protein is localized throughout the muscle
- Immunofluorescence

Vector Genome Copies/Nucleus

Participant	Dose	Copies/Nucleus
1	1.0E14 vg/kg	19.8
2		28.6
3		7.6
Mean		18.7

PCR=polymerase chain reaction
Data on file as of February 11, 2025. Solid Biosciences.

SGT-003 Microdystrophin Expression in Day 90 Muscle Biopsies

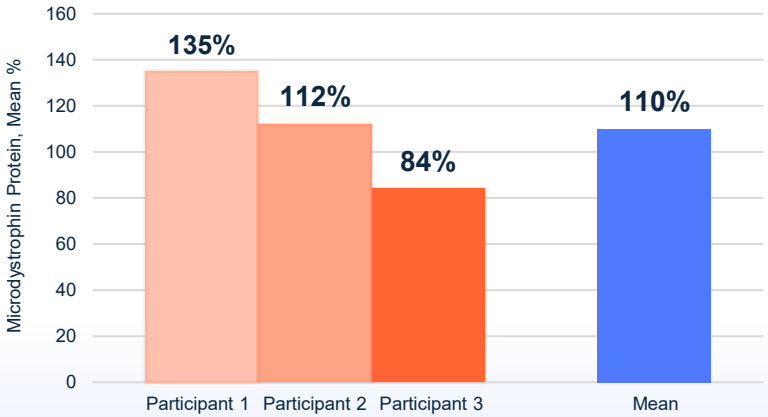
Western blot and mass spectrometry demonstrated high microdystrophin protein levels

The AAV-SLB101 capsid efficiently transduces muscle
- PCR

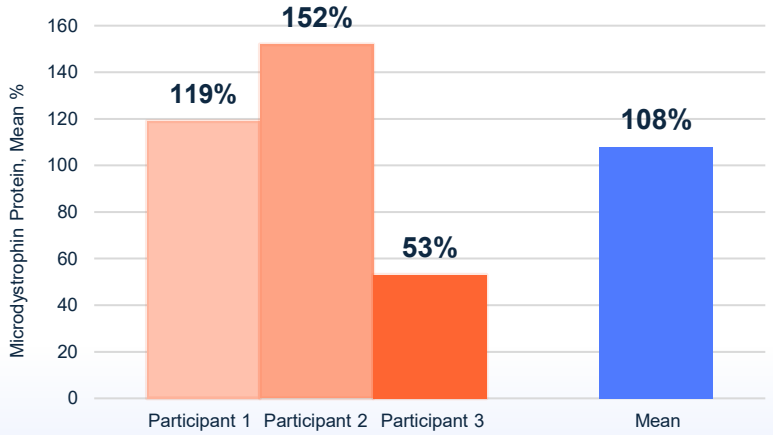
Microdystrophin protein is expressed in muscle
- Western Blot
- Mass Spectrometry

Microdystrophin protein is localized throughout the muscle
- Immunofluorescence

Microdystrophin Expression Measured by Western Blot[a]



Microdystrophin Expression Measured by Mass Spectrometry[a]



PCR=polymerase chain reaction
[a]Baseline Western blot and mass spectrometry were both 0% mean normal dystrophin.
Data on file as of February 11, 2025. Solid Biosciences.

SGT-003 Microdystrophin Protein Distribution in Day 90 Muscle Biopsies

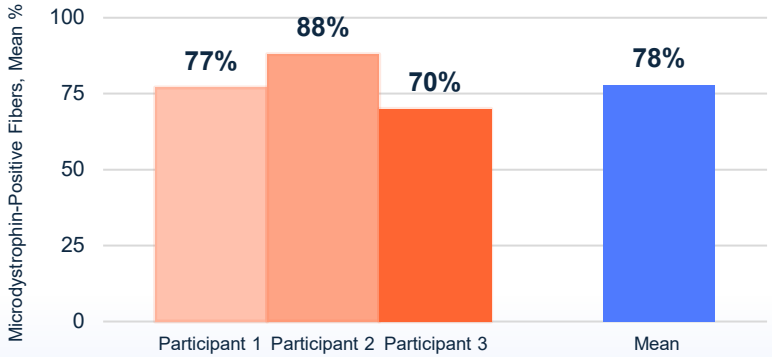
Immunofluorescence demonstrated microdystrophin protein in a high proportion of muscle fibers

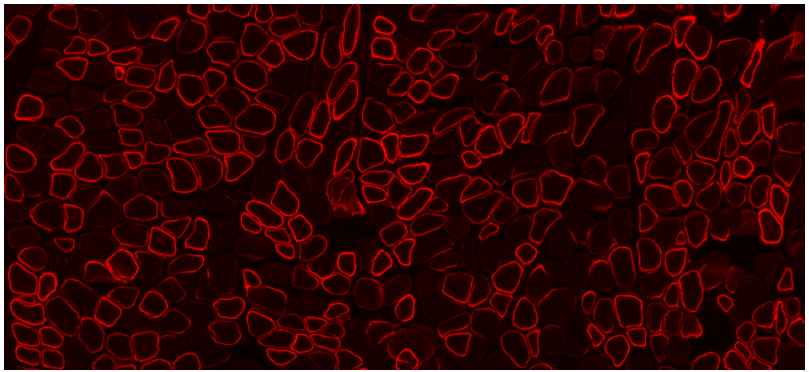
The AAV-SLB101 capsid efficiently transduces muscle
- PCR

Microdystrophin protein is expressed in muscle
- Western Blot
- Mass Spectrometry

Microdystrophin protein is localized throughout the muscle
- Immunofluorescence

Microdystrophin-Positive Fibers Measured by Immunofluorescence[a]





PCR=polymerase chain reaction
[a]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.
Participant 2 representative image is shown in the right panel.
Data on file as of February 11, 2025. Solid Biosciences.

Muscle Biopsies Showed Increases in Key Elements of the Dystrophin-Associated Protein Complex

Percent Positive Fibers – Microdystrophin[a]

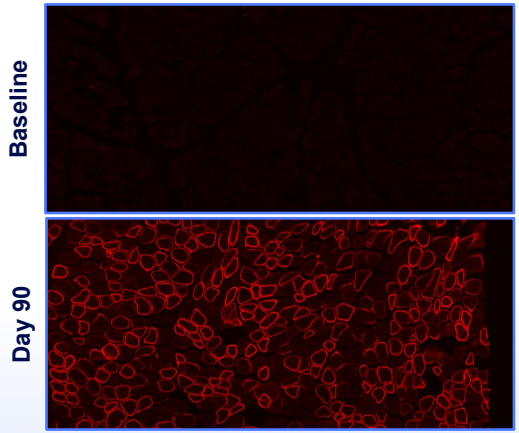
Participant	1	2	3	Mean
Day 90 Values	77%	88%	70%	78%
Baseline Values	0.8%	2.3%	1.3%	1.5%
Change From Baseline (Fold Change)	96x	38x	53x	53x

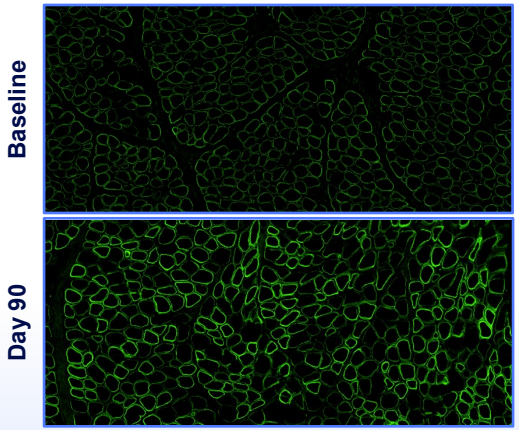
Percent Positive Fibers – β-sarcoglycan[a]

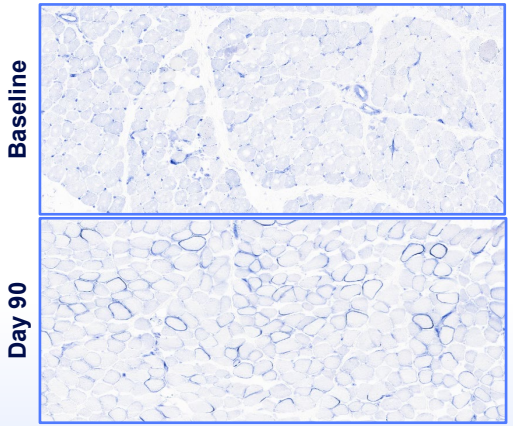
Participant	1	2	3	Mean
Day 90 Values	60%	88%	63%	70%
Baseline Values	0%	2.5%	1.5%	1.3%
Change From Baseline (Fold Change)	∞	34x	41x	52x

Percent Positive Fibers – nNOS activity[a]

Participant	1	2	3	Mean
Day 90 Values	48%	53%	25%	42%
Baseline Values	0%	1.5%	0.5%	0.7%
Change From Baseline (Fold Change)	∞	34x	49x	62x

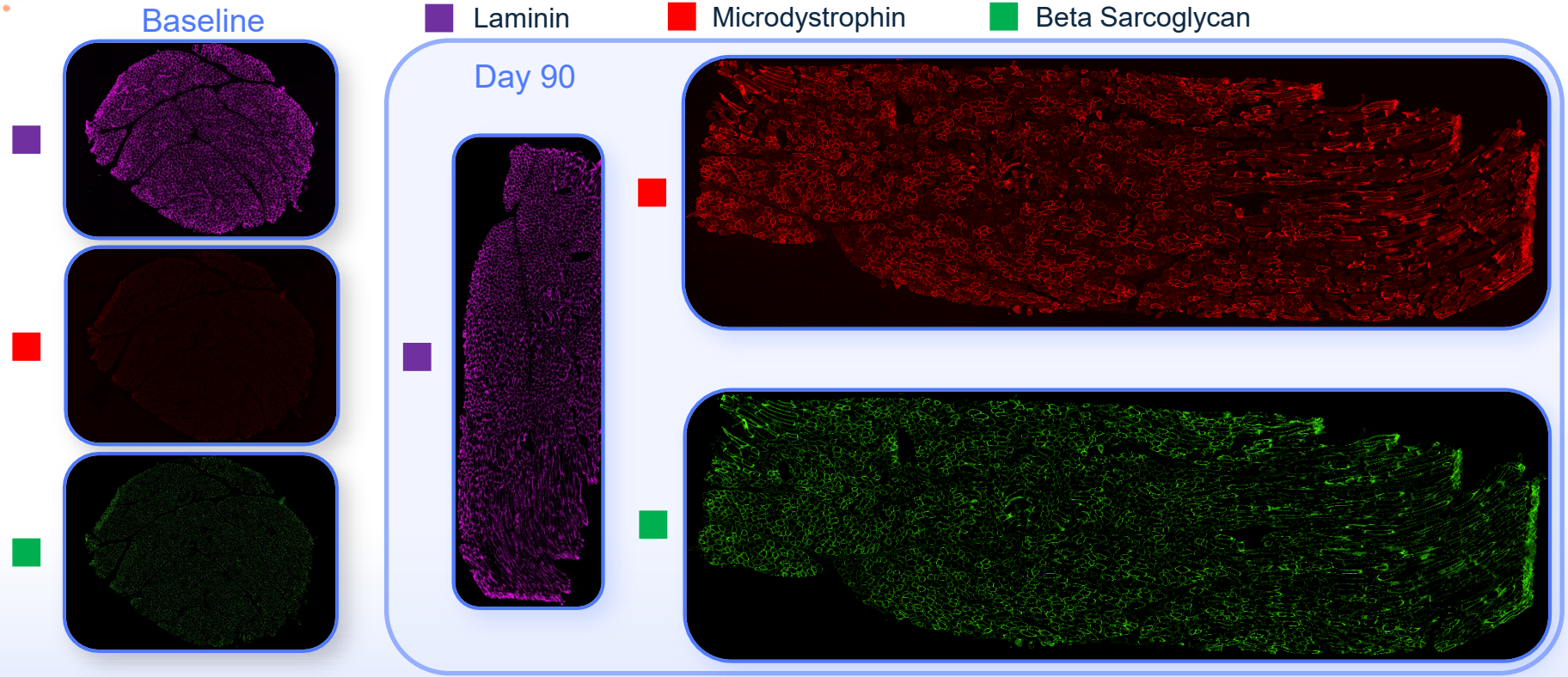






[a]Dystrophin-positive fibers are not adjusted for fat and fibrosis; these are absolute numbers. Participant 2 representative images are shown.
Data on file as of February 11, 2025. Solid Biosciences.

Full Slide Scans of Muscle Biopsy Sections Showed Uniform Increases in Key Elements of the Dystrophin-Associated Protein Complex[a]

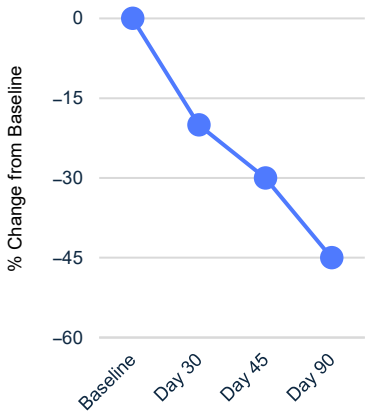


[a]Participant 2 representative images are shown. Laminin staining is used to demarcate muscle membranes.
Data on file. Solid Biosciences. 2025.

Improvements in Markers of Muscle Injury[1]

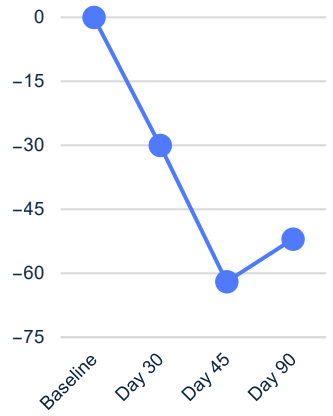
AST, **ALT**, **CK**, and **LDH** are released from muscle into circulation in Duchenne due to tissue damage and muscle injury[2-4]

SERUM AST (IU/L)[1,a]



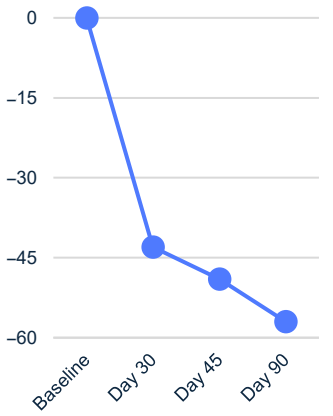
Serum AST (−45%)[1]

SERUM ALT (IU/L)[1,a]



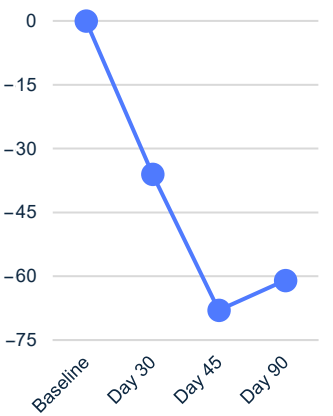
Serum ALT (−54%)[1]

SERUM CK (IU/L)[1,a]



Serum CK (−57%)[1]

SERUM LDH (IU/L)[1,a]



Serum LDH (−60%)[1]

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

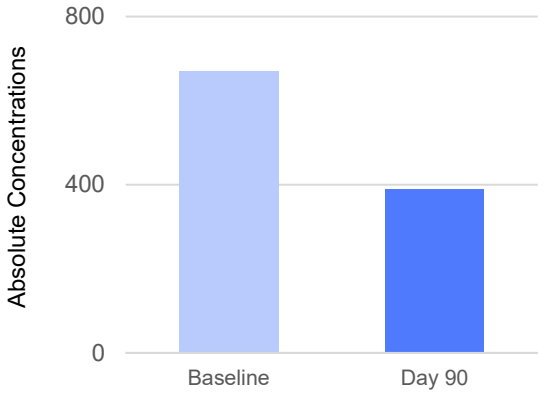
1. Data on file. Solid Biosciences. 2025. 2. Aulbach AD, Amuzie CJ. *A Comprehensive Guide to Toxicology in Nonclinical Drug Development.* 2nd ed. 2017. 3. Kim EY, et al. *Ann Rehabil Med.* 2017;41(2):306-312. 4. Farhana A, Lappin SL. *StatPearls* [Internet]. 2023.

Improvements in Markers of Muscle Breakdown and Dystrophic Regeneration[1]

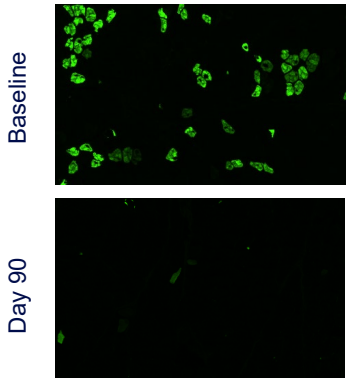
Titin is actively degraded and released into serum and urine when muscle is damaged[2]

eMHC is expressed in dystrophic muscle fibers that have recently undergone degeneration/regeneration[3]

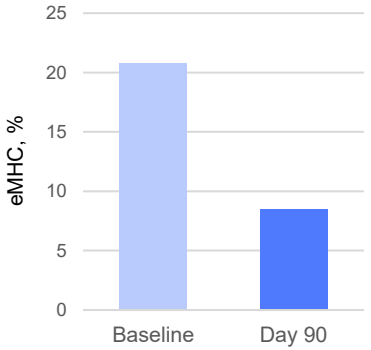
SERUM Titin (pmol/L)[1,a]



Histologic eMHC[1,b]



eMHC-Positive Fibers[1,a]



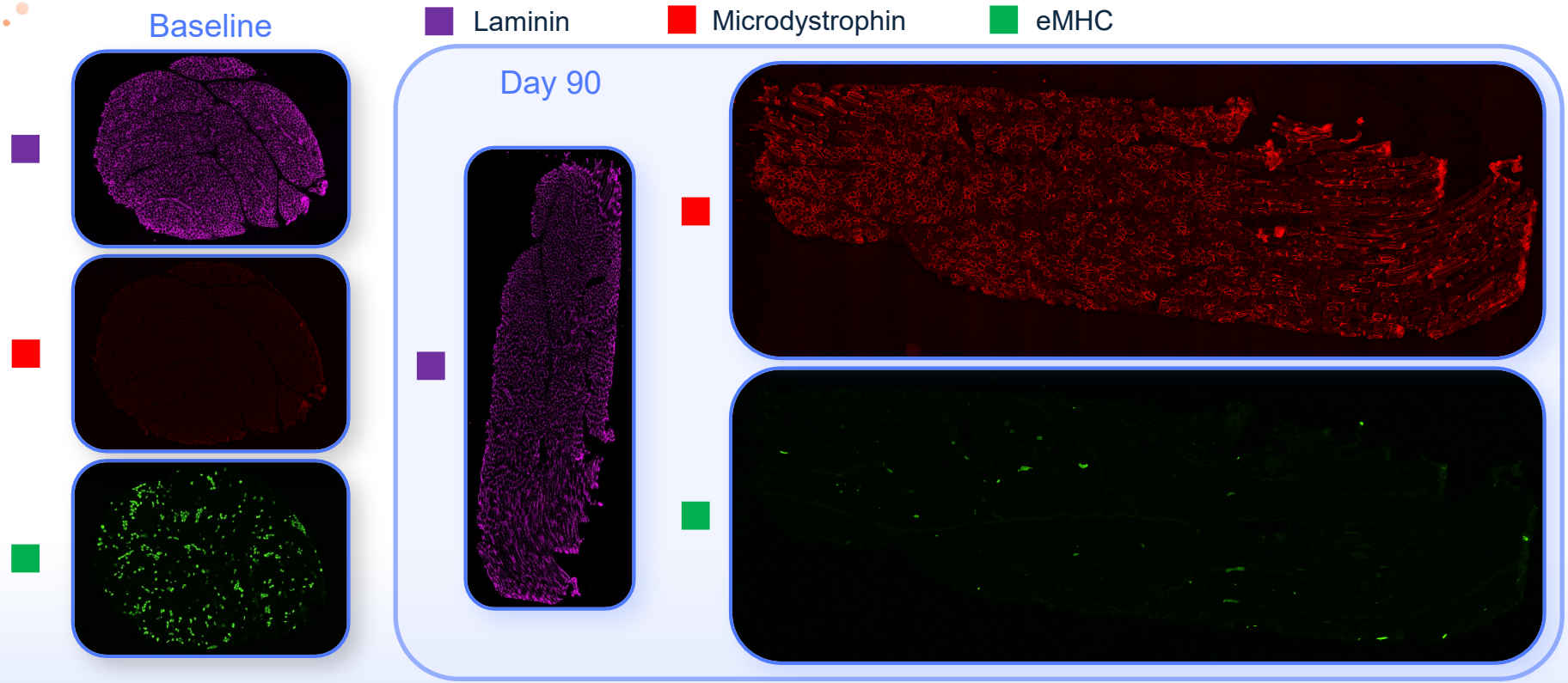
↓ Serum titin (−42%)[1]

↓ Histologic eMHC (−59%)[1]

eMHC=embryonic myosin heavy chain.
[a]Mean (n=3) absolute and percentage change from baseline results shown. [b]Participant 2 representative images are shown.

1. Data on file. Solid Biosciences. 2025. 2. Oshida N, et al. *Sci Rep*. 2019;9(1):19498. 3. Guiraud S, et al. *Hum Mol Genet*. 2019;28(2):307-319.

Full Slide Scans of Muscle Biopsy Sections Showed Uniform Improvements in eMHC, a Marker of Muscle Breakdown and Dystrophic Regeneration[a]

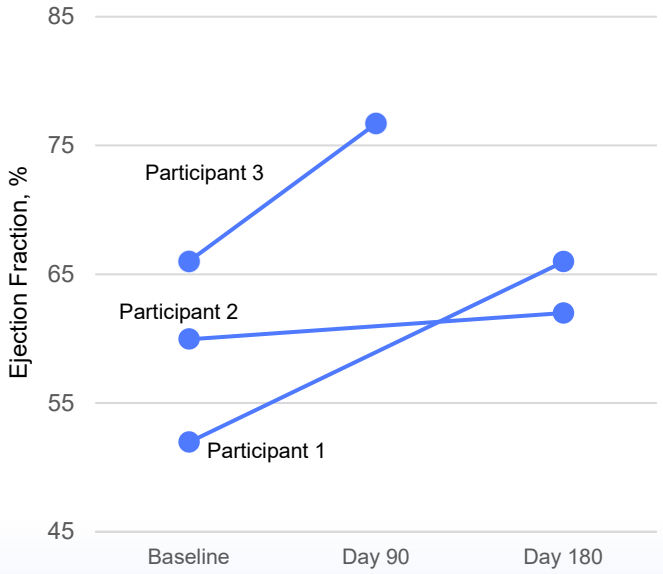


[a]Participant 2 representative images are shown. Laminin staining is used to demarcate muscle membranes

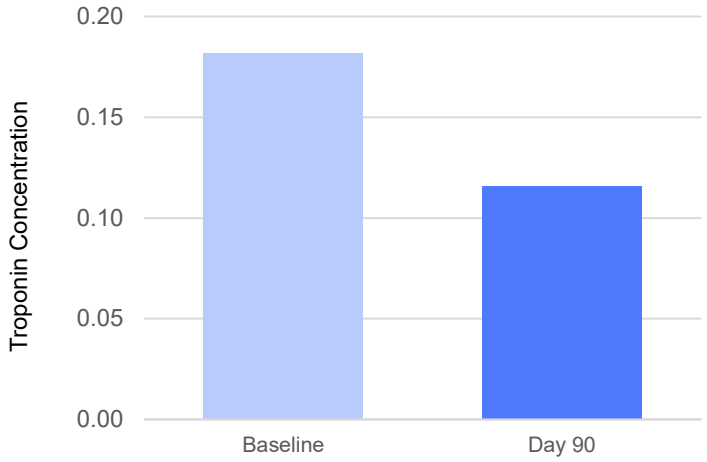
Data on file. Solid Biosciences. 2025.

Positive Changes Observed in Cardiac Markers[1]

Percent Left Ventricular Ejection Fraction (LVEF)[1,b]



SERUM Troponin (ng/mL)
Participant 3 (only)[1,a]



Serum Troponin (−36%)[1,a]

[a]Serum troponin data only from Participant 3 at Day 90: Participant 3 had elevated troponin levels at baseline. Troponin levels for Participants 1 and 2 were 0 at baseline. [b]Participant 3 has yet to reach the Day 180 follow-up as of the data cutoff. All 3 participants demonstrated LVEF above baseline at all follow-up timepoints.

1. Data on file as of February 11, 2025. Solid Biosciences. 2. Voleti S, et al. *Pediatr Cardiol*. 2020;41(6):1173-1179.

Safety Summary (Data Cutoff February 11, 2025; N=6 Participants)

MOST COMMON ADVERSE EVENTS

- Nausea (n=5)/vomiting (n=4)
  - All have resolved
- Fever (n=2)
  - All have resolved
- Infusion-related hypersensitivity reaction (n=1)
  - 1 CTCAE Grade 3 observed of prolonged fever: resolved
- Thrombocytopenia observed (n=3)
  - 1 CTCAE Grade 3 observed
  - All returned to within normal laboratory range with no clinical consequence (no bleeding)
  - No evidence of hemolysis (hemoglobin stable and no schistocytes on smears)
  - No eculizumab, no steroids or other agents used in response, and no hospitalizations or intervention

All Treatment Related Adverse Events Resolved With No Sequelae

- Began in days following treatment
- Resolved within weeks

Adverse Events of Special Interest

- Mild transient hs-troponin I elevation (n=1)
  - 1 CTCAE Grade 1 observed first week post-dosing[a]
  - No clinical evidence of myocarditis
  - No EKG or echocardiographic changes

No Serious Adverse Events

- No SUSARS
- No TMA/aHUS observed

No Adverse Events of Hepatic Transaminitis

- Consistent declines in AST and ALT
- No GGT increases

aHUS=atypical hemolytic uremic syndrome; CTCAE=Common Terminology Criteria for Adverse Events; EKG=electrocardiogram; GGT=gamma-glutamyl transferase; SUSAR=suspected unexpected serious adverse reaction; TMA=thrombotic microangiopathy.

[a]Participant 6: Troponin I was elevated at baseline, which increased during the first week of therapy and returned to baseline without intervention, and is now in the normal range of troponin (below baseline). This represents 2 participants in total (N=6) with troponin reduced below initial baseline values post-dose.

Data on file. Solid Biosciences. 2025.

INSPIRE DUCHENNE: Current Summary

INITIAL MUSCLE BIOPSY RESULTS FOR THE FIRST 3 PARTICIPANTS REACHING DAY 90

- Mean vector genome copies per nucleus: 18.7
- Mean microdystrophin expression: 110% of normal (Western blot), 108% of normal (mass spectrometry)
- Mean microdystrophin percent-positive fibers: 78%
- Mean β-sarcoglycan percent-positive fibers: 70%
- Mean nNOS-positive fibers: 42%

MUSCLE INTEGRITY BIOMARKER RESULTS FOR THE FIRST 3 PARTICIPANTS REACHING DAY 90

- Consistent improvements across 7 biomarkers

NO SERIOUS ADVERSE EVENTS IN THE 6 PARTICIPANTS TREATED (DATA CUTOFF FEBRUARY 11, 2025)

- Most common adverse events observed were nausea/vomiting and thrombocytopenia

Data on file. Solid Biosciences. 2025.

Acknowledgments

Thank you to the study participants and families!
Thank you to participating clinical sites, investigative teams, and study partners!

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Children's Hospital of The King's Daughters (Norfolk, VA)
- Crystal Proud, MD

University of California, Davis (Sacramento, CA)
- Craig McDonald, MD

University of California, Los Angeles (Los Angeles, CA)
- Perry Shieh, MD, PhD

The Hospital for Sick Children (Toronto, ON)
- Hernan Gonorazky, MD

INSPIRE DUCHENNE

Scan the QR code to navigate to the study posting (NCT06138639)