



# IGNITE DMD Phase I/II ascending dose study of SGT-001 microdystrophin gene therapy for DMD: Update on long-term outcomes

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**WMS 2021 Congress**

# Disclosures

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- Advisory capacity: NS Pharma, Sarepta Therapeutics, Regenxbio, PTC Therapeutics, and Scholar Rock
- Speaker: Genentech/Roche, Biogen, Avexis

# Forward-Looking Statements

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# Agenda

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- Overview of SGT-001 microdystrophin gene therapy for DMD
- IGNITE DMD study design
- Safety update
- Long-term muscle biopsy update
- Long-term functional data update
- Key takeaways

# Duchenne Muscular Dystrophy Is a Devastating Muscle-Wasting Disease



Caused by Mutations in the *DMD* Gene



1:3500-5000 Newborn Males Affected



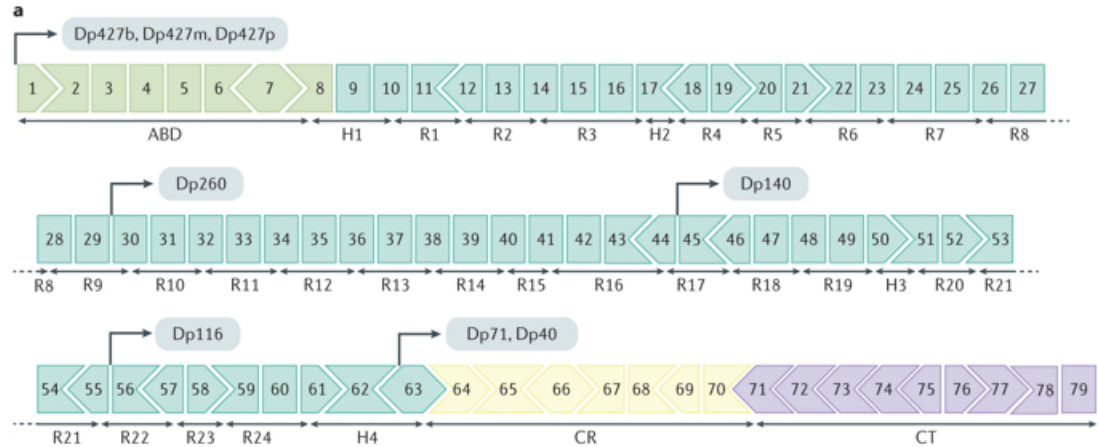
Skeletal and Cardiac Muscle Manifestations



Progressive & Irreversible



No Meaningful Treatment Options



**b** Normal dystrophin: ABD connects to extracellular matrix with CR domain



**c** Duchenne muscular dystrophy: dystrophin cannot fulfil linker function because cysteine domain is lacking



**d** Becker muscular dystrophy: dystrophin is partially functional, crucial domains are present

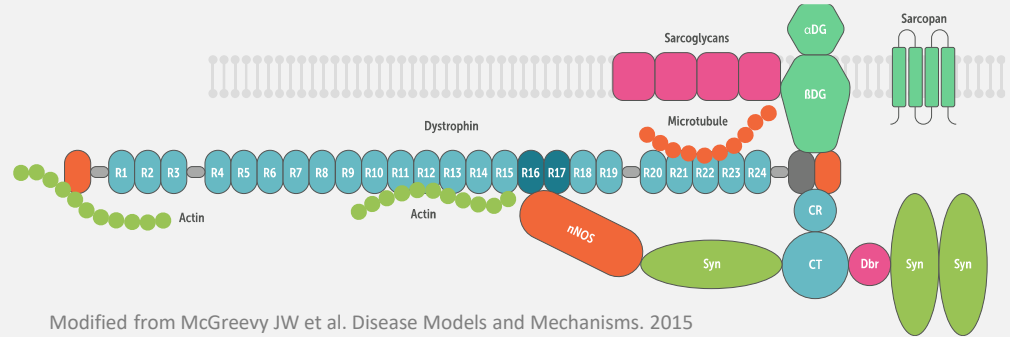


*Schematic depiction of DMD gene and dystrophin protein. Duan et al. Nature Reviews Disease Primers 2021*

# SGT-001 Microdystrophin Gene Therapy to Replace Absent Dystrophin

## Dystrophin and the Glycoprotein Complex

- Stabilizes the muscle membrane
- Acts as a molecular shock absorber
- Prevents muscle tissue damage and death
- Absent in Duchenne muscular dystrophy (DMD)

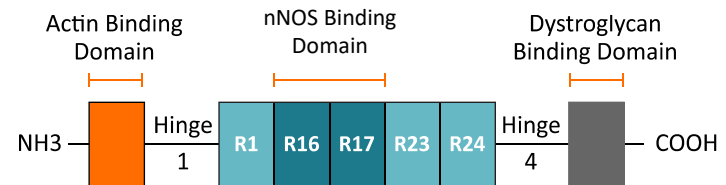


Modified from McGreevy JW et al. Disease Models and Mechanisms. 2015

## SGT-001: AAV9-CK8-Microdystrophin

- AAV gene transfer therapy
- Systemically delivers a unique rationally designed microdystrophin
  - Shortened form of dystrophin able to be packaged into an AAV vector
  - **Uniquely includes the nNOS binding domain**
    - Important for prevention of activity-induced ischemia and associated muscle injury
    - Presence correlated with milder phenotypes of Becker muscular dystrophy (BMD)
  - Acts as a functional surrogate of full-length dystrophin

## SGT-001 Microdystrophin Retains key dystrophin protein functional domains



nNOS: neuronal nitric oxide synthase

# IGNITE DMD Study Design: Two Dose Levels Initially Assessed; 2E14 vg/kg Selected

## Interim Analysis of Subjects in IGNITE DMD

- n=3 subjects analyzed as controls
- n=3 subjects at 5E13 vg/kg\*
- n=3 subjects at 2E14 vg/kg
- 2 additional subjects dosed at 2E14 vg/kg\*\*

## Inclusion Criteria

- Ambulatory children; mutation agnostic
- Ages 4-17 years; upper weight limit of 18 kg for next two patients dosed; up to 30 kg (~66 lbs) for remainder of the clinical trial
- Primary focus on children with the potential to include adolescent patient population in the future
- Anti-AAV9 antibodies below protocol-specified thresholds
- For more information, please visit [clinicaltrials.gov](https://clinicaltrials.gov/NCT03368742)  
[NCT03368742](https://clinicaltrials.gov/NCT03368742)

\*Data at 1.5 year timepoint not collected for 5E13 cohort subjects due to COVID-19

\*\*One year and later timepoints not yet reached for additional subjects dosed

Dose Cohort	Patient #	Age at Baseline (years)
2E14 vg/kg	Pt 4	10.7
	Pt 5	6.8
	Pt 6	7.7

## Primary Endpoints (Baseline to 1 Year):

- Incidence of adverse events
- Change in microdystrophin protein levels in muscle biopsies by Western Blot

## Select Secondary Endpoints (Baseline to 1 Year):

- Six Minute Walk Distance
- North Star Ambulatory Assessment (NSAA)
- Pulmonary Function Tests
- Quality of Life as measured by Pediatric Outcomes Data Collection Instrument (PODCI)

## Overview of IGNITE DMD Safety Findings

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### Most Common Drug Related Clinical Adverse Reactions\*

*(updated to include Subjects 7 and 8)*

Nausea	(8/8)
Vomiting	(7/8)
Fever	(6/8)

- The most common drug related laboratory abnormalities were thrombocytopenia/decreased platelets, anemia, proteinuria, and increases in fibrin, D dimer, soluble C5b9 and LDH\*\*
- Activation of the terminal pathway (sC5b9) of the classical complement system occurred in all subjects resulting in 3 serious adverse events (SAEs) : Systemic Inflammatory Response Syndrome (2); thrombocytopenia (1).
- Two other SAEs: immune hepatitis 4 weeks post dosing which resolved rapidly after a transient increase of corticosteroids (1); Giardiasis, determined to be unrelated to SGT-001 (1)
- All SAEs are resolved
- No other drug-related adverse events have occurred in any of the 8 subjects after 90 days to 3.5 years of observation

\*Less common adverse reactions include cytokine release syndrome, generalized edema, acute kidney injury and thrombotic microangiopathy

\*\*Less common laboratory abnormalities include increased CPK, decreased complement, increased liver enzymes, increased troponin, decreased hemoglobin, increased haptoglobin urinary casts and leukocytosis

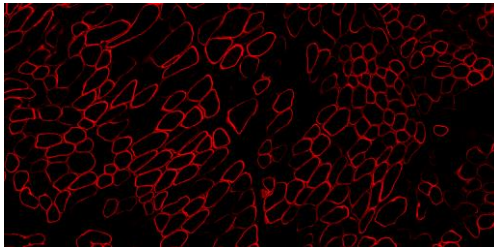


## MUSCLE BIOPSY ANALYSIS

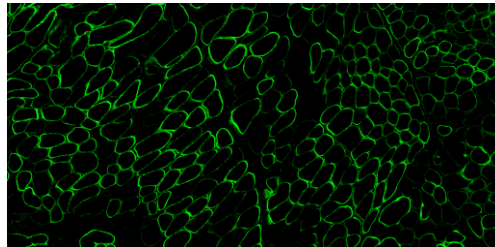
# Durable Microdystrophin Expression and Protein Function Observed in Long-Term Biopsies

	Microdystrophin Expression			
	% Positive Fibers (Immunofluorescence)		% of Normal Dystrophin (Western Blot)	
	3 Months	Last Timepoint	3 Months	Last Timepoint
Pt 4	10-20%	10-30% (24 months)	BLQ	BLQ (24 months)
Pt 5	50-70%	85% (18 months)	17.5%	69.8% (18 months)
Pt 6	50-70%	50-60% (12 months)	8.0%	20.3% (12 months)

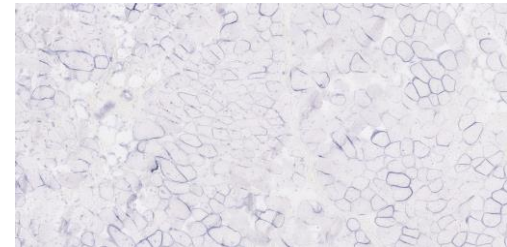
Microdystrophin



$\beta$ -Sarcoglycan

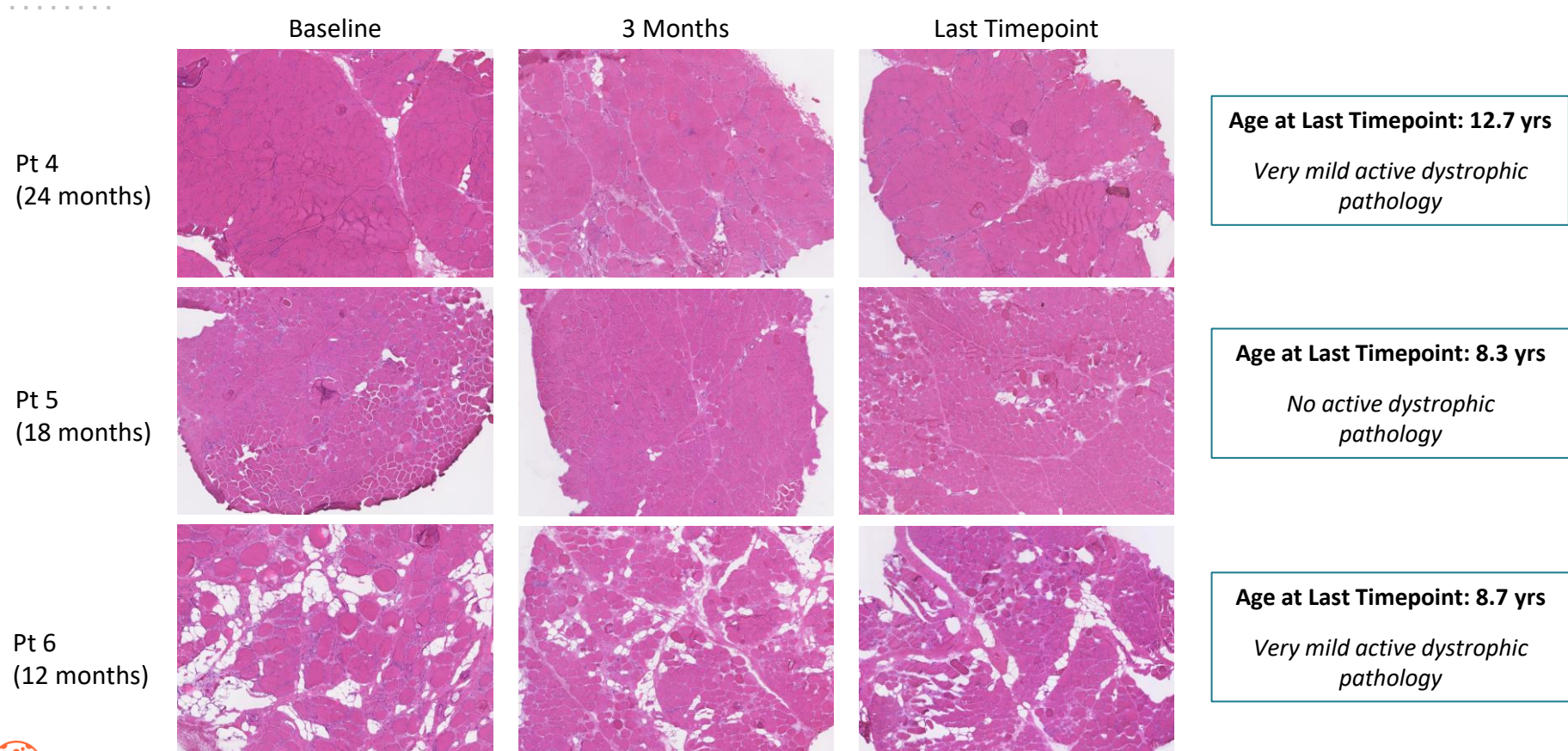


nNOS Activity



## MUSCLE BIOPSY ANALYSIS

### Limited Dystrophic Pathology Progression Over 12-24 Months

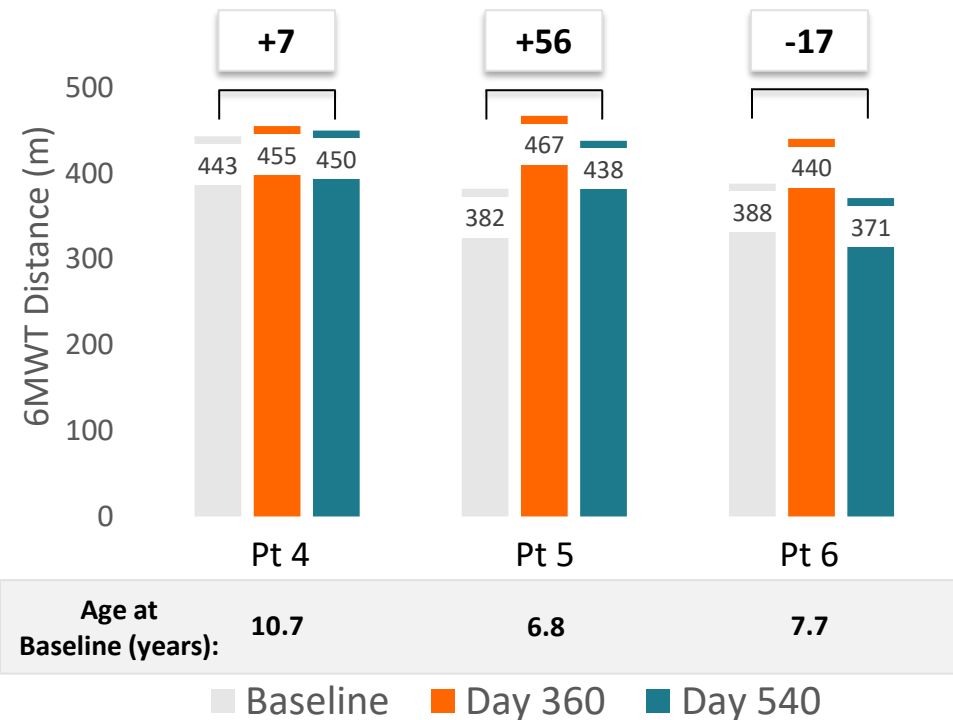


## FUNCTIONAL ASSESSMENTS

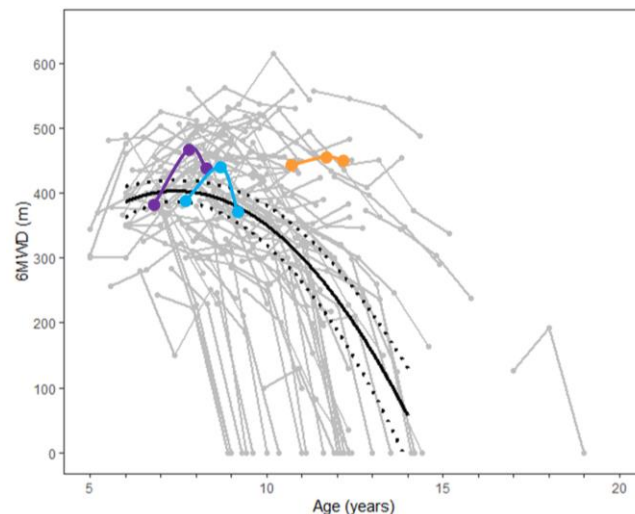
# 6MWT Distances are Maintained 1.5 Years Post-Treatment

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Mean Change from Baseline to Day 540:  $+15.3 \pm 37.2$  m | Difference of +78.8 m Compared to Natural History over 1.5 Years



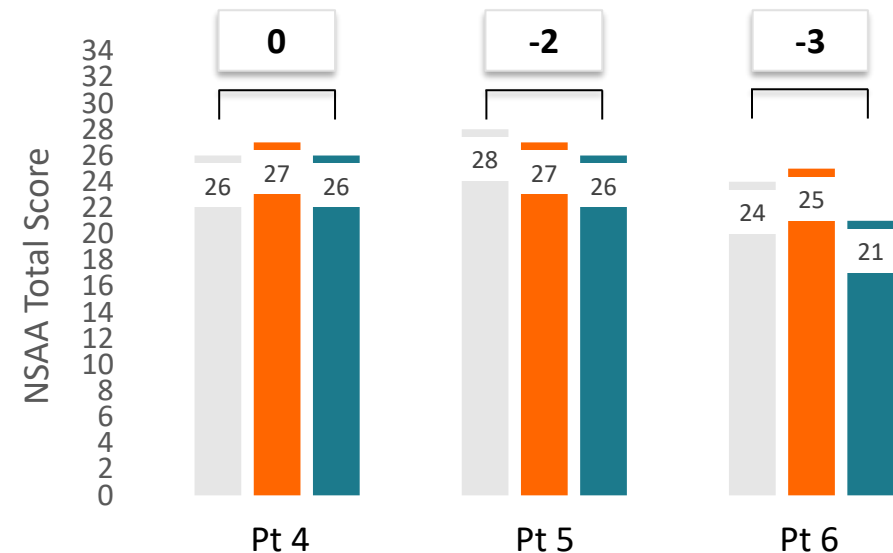
## Individual Patient Trajectories



## FUNCTIONAL ASSESSMENTS

# NSAA Scores Show Minimal Change 1.5 Years Post-Treatment

Mean Change from Baseline to Day 540:  $-1.7 \pm 1.5$  Units | ***Difference of +2.8 Units Compared to Natural History over 1.5 Years***



Age at Baseline (years):

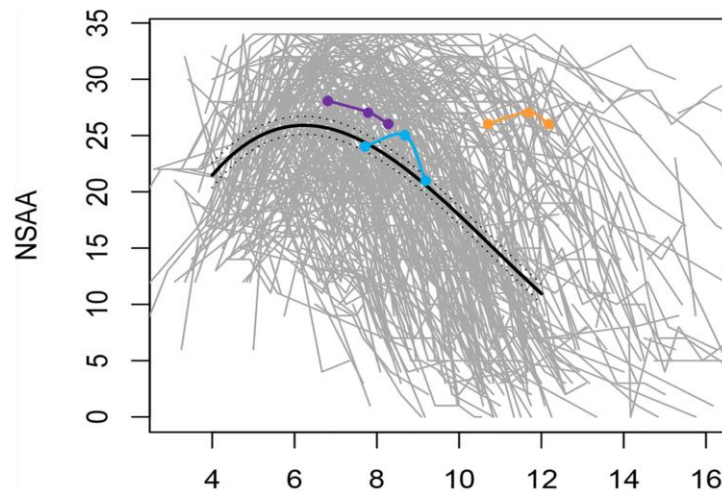
10.7

6.8

7.7

■ Baseline ■ Day 360 ■ Day 540

## Individual Patient Trajectories



Data overlaid on Muntoni et al 2019

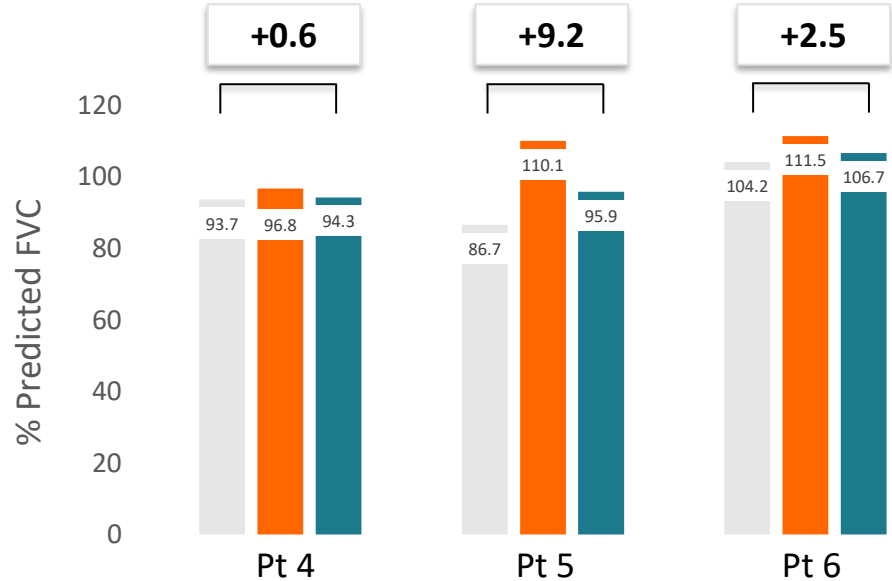
DMD Natural History

-4.5 unit expected decline over 1.5 years after age 6.3

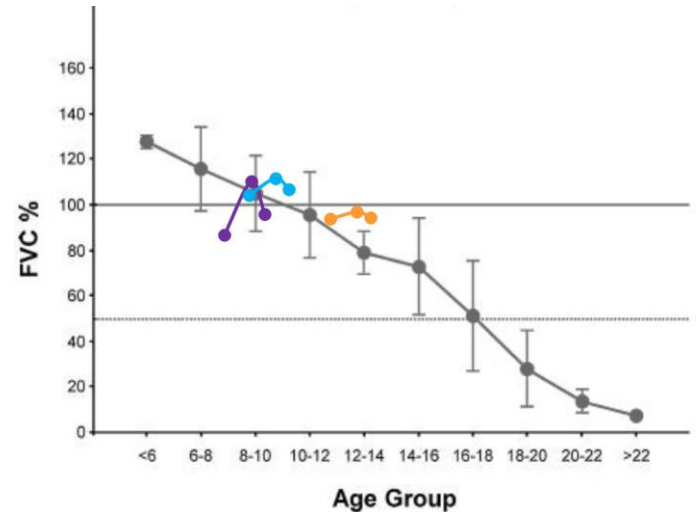
## FUNCTIONAL ASSESSMENTS

# % Predicted FVC Continues to Show Stability or Improvement 1.5 Years Post-Treatment

Mean Change from Baseline to Day 540:  $+4.1 \pm 4.5\%$  | Difference of  $+11.6\%$  Compared to Natural History over 1.5 Years



## Individual Patient Trajectories



Data overlaid on Mayer et al 2015

DMD Natural History

-7.5% expected decline over 1.5 years after age 6

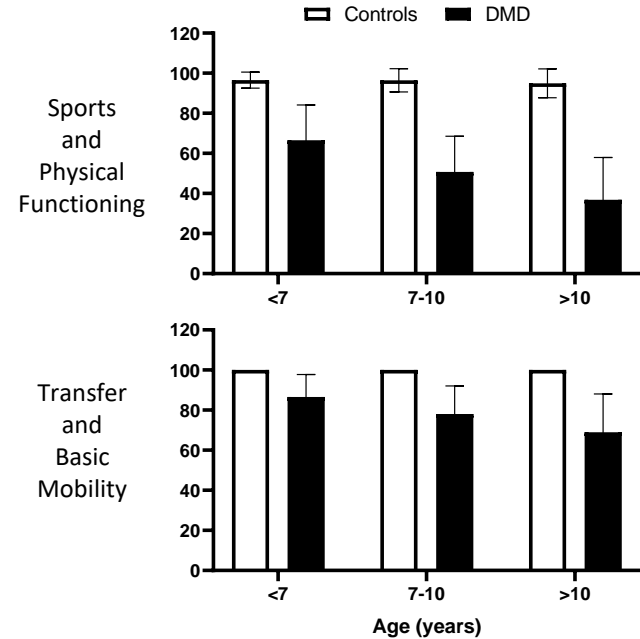
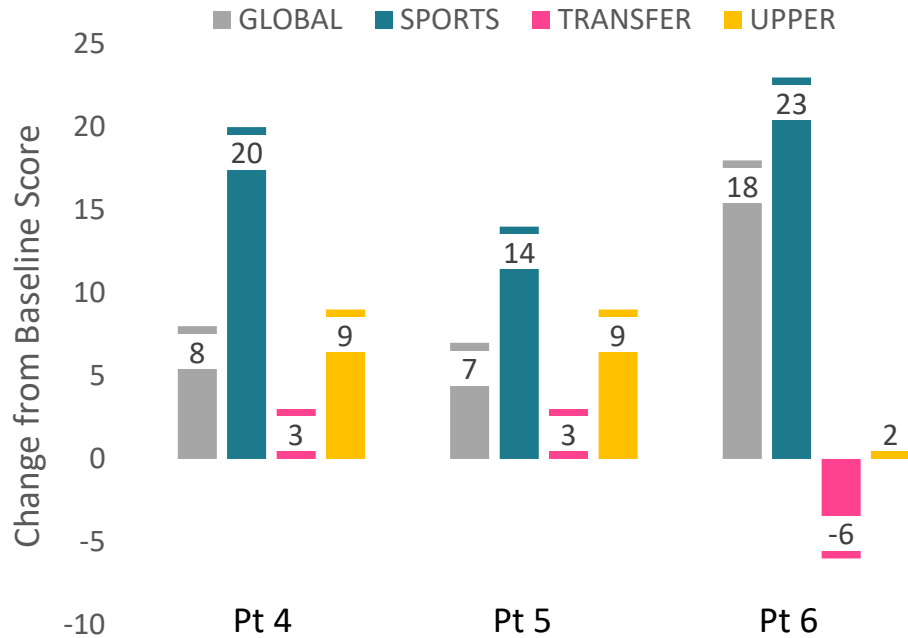


■ Baseline ■ Day 360 ■ Day 540

Interim data presented | FVC: forced vital capacity

## PATIENT REPORTED OUTCOMES

# Sustained Meaningful Improvements in SGT-001 Treated Subjects at 1.5 Years by PODCI



Modified from McDonald et al 2010, Henricson et al 2013  
DMD Natural History

- 7.6 point expected decline over 1.5 years in Global scale
- 4.7 point expected decline over 1.5 years in Sports scale
- 14.9 point expected decline over 1.5 years in Transfer scale

# Key Takeaways From Interim Analysis of IGNITE DMD

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## Durable expression and function of microdystrophin protein in biopsies collected $\geq 12$ months post-administration of SGT-001

- ✓ Sustained or increased microdystrophin protein levels and percent positive muscle fibers
- ✓ Sarcolemmal restoration of key dystrophin associated proteins  $\beta$ -sarcoglycan and nNOS



## Encouraging evidence of functional benefit 1.5 years post-treatment vs natural history

- ✓ 6-Minute Walk Test (6MWT)
- ✓ North Star Ambulatory Assessment Total Score (NSAA)
- ✓ Forced Vital Capacity (FVC) normalized for age, height, and weight



## Meaningful improvement in patient reported outcomes that assess motor function and fatigue

- ✓ Pediatric Outcomes Data Collection Instrument (PODCI)

**Totality of data supports continued dosing in IGNITE DMD at 2E14 vg/kg dose**





Thank You



Questions & Answers