SRP-9001 (delandistrogene moxeparvovec) for Treatment of Duchenne Muscular Dystrophy

May 12, 2023

Cellular Tissue and Gene Therapy Advisory Committee

Sarepta Therapeutics

Introduction

Patrick O'Malley

Vice President, Regulatory Affairs

Sarepta Therapeutics

SRP-9001 Proposed Indication and Dosing

SRP-9001 is indicated for the treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene

SRP-9001 is contraindicated in patients with any deletion that fully includes exons 9 – 13 in the DMD gene

Dosing & Administration

SRP-9001 administered intravenously as one-time infusion at dose of 1.33×10^{14} vector genomes (vg) per kg of body weight

SRP-9001 administration is not recommended in patients with elevated anti-AAVrh74 total binding antibody titers (≥ 1:400)

SRP-9001 Meets Criteria for Accelerated Approval

Criteria	Support	Result
Treats serious condition	▪ DMD is serious, devastating, and fatal condition with high unmet need ▪ Progression is inevitable and irreversible and leads to early mortality	✓
Provides meaningful advantage over available therapies	▪ Current treatment options that introduce functional dystrophin limited to specific DMD mutations ▪ Standard of care has recognized limitations and does not address underlying cause of disease	✓
Demonstrates effect on an endpoint reasonably likely to predict clinical benefit	▪ SRP-9001 dystrophin protein expression is reasonably likely to predict clinical benefit (product design, biological, and empirical data showing direct change in underlying pathophysiology of disease, combined with durable functional effect over 4 years of follow-up)	✓
Confirmatory study (SRP-9001-301)	▪ Phase 3 study ongoing in same population as Studies 101, 102, and 103 (cohort 1) ▪ Fully enrolled as of Sept 2022	✓

Phase 3 Confirmatory Study Fully Enrolled

- Study 301
  - Global, double-blind, randomized, placebo-controlled, two-part study
  - 125 patients, 4 – 7 years old
  - Informed by previous studies
  - Primary endpoint change in NSAA from Baseline to Week 52
    - NSAA well recognized clinical endpoint for standard approval[1]
  - Part 1 study report expected early 2024

Study status provides reassurance of achieving timely completion

NSAA = North Star Ambulatory Assessment

1. Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry, February 2018

SRP-9001 Dystrophin Protein Expression Is Reasonably Likely to Predict Benefit

Biological Plausibility

- Monogenic disease where low levels of residual or restored dystrophin shown to confer significant benefit
- Functional shortened dystrophins that conserve key structural domains observed in nature
- SRP-9001 dystrophin rationally designed based on observations in nature and decades of research and development

Empirical Evidence

- Demonstration of:
  - Transduction
  - Expression
  - Localization
  - Biological function
  - Relationship with motor function and clinical outcomes

SRP-9001 dystrophin expression is surrogate endpoint and therapeutic agent

SRP-9001 Clinical Studies Supporting Accelerated Approval

BLA Core Studies

STUDY 101
N = 4
Open-label

4 – 7 years old
Ambulatory

STUDY 102
N = 41
Double-blind, randomized, placebo-controlled

4 – 7 years old
Ambulatory

STUDY 103
N = 40
Open-label

3 – 20 years old
Ambulatory and Non-ambulatory

External Control

Comparator pools drawn from 3 external sources to contextualize trial results according to pre-specified analysis plan

Disease Background and Unmet Need	**Jerry Mendell, MD** Professor of Pediatrics and Neurology Nationwide Children's Hospital and The OSU College of Medicine
Evidence for Surrogacy	**Louise Rodino-Klapac, PhD** Executive Vice President, Head of R&D, and Chief Scientific Officer Sarepta Therapeutics
Clinical Trial Results	**Stefanie Mason, MD** Clinical Development Lead SRP-9001 Sarepta Therapeutics
External Control Analyses	**James Signorovitch, PhD** Co-Founder, Collaborative Trajectory Analysis Project (cTAP) in Duchenne Managing Principal, Analysis Group
External Control Results	**Craig McDonald, MD** Professor and Chair, Department of Physical Medicine and Rehabilitation Professor of Pediatrics, Director MDA Neuromuscular Disease Clinics, University of California Davis Health
Summary of Safety	**Eddie Darton, MD, JD** Executive Medical Director, Safety Evaluation & Risk Management Sarepta Therapeutics
Clinical Perspective	**Craig McDonald, MD**

External Responders

Francesco Muntoni, MD, FRCPCH
Dubowitz Neuromuscular Centre and MRC Centre for Neuromuscular Diseases
UCL Great Ormond Street Institute of Child Health
Great Ormond Street Hospital for Children

Howard Worman, MD
Professor of Medicine and Pathology and Cell Biology
Vagelos College of Physicians and Surgeons
Columbia University

Kay Davies, PhD
Dr Lee’s Professor of Anatomy, Emerita
Department of Physiology, Anatomy, and Genetics
University of Oxford

Chris Mullin, MS
Director, Global Strategy Services
NAMSA

Kan Hor, MD
Director of Cardiac MRI at The Heart Center
Nationwide Children's Hospital
Associate Professor of Clinical Pediatrics
The Ohio State University College of Medicine

Disease Background and Unmet Need

Jerry Mendell, MD

Curran-Peters Chair of Pediatric Research
Professor of Neurology and Pediatrics
Nationwide Children's Hospital and The Ohio State University College of Medicine in Columbus, Ohio

DMD: Most Common Childhood Form of Muscular Dystrophy

- Well-characterized, rare, fatal, X-linked monogenic neuromuscular disease
  - Affecting ~1 in 5,000 newborn males
  - Caused by mutations in *DMD* gene leading to lack of functional dystrophin
- Lack of functional dystrophin is sole cause of DMD
  - Dystrophin is key structural protein that protects against muscle damage during normal contraction
  - Without functional dystrophin, normal activity leads to muscle cell damage, inflammation, fibrosis, and irreversible muscle loss

Al-Zaidy SA, et al. 2017

Children with Duchenne Suffer Irreparable Harm Highlighting Urgent Need for Effective Therapies

Based on US incidence and prevalence

~ 400 lose ambulation each year

2,000 more will lose ambulation over 5 years

Median survival 28 years

> 400 patients in US die each year

2,228 patients will die over 5 years

McDonald et al. 2018; Passamano et al. 2012; Broomfield et al. 2021; Paramsothy et al. 2022

Damage Starts In Utero, Is Progressive, and Leads to Early Death

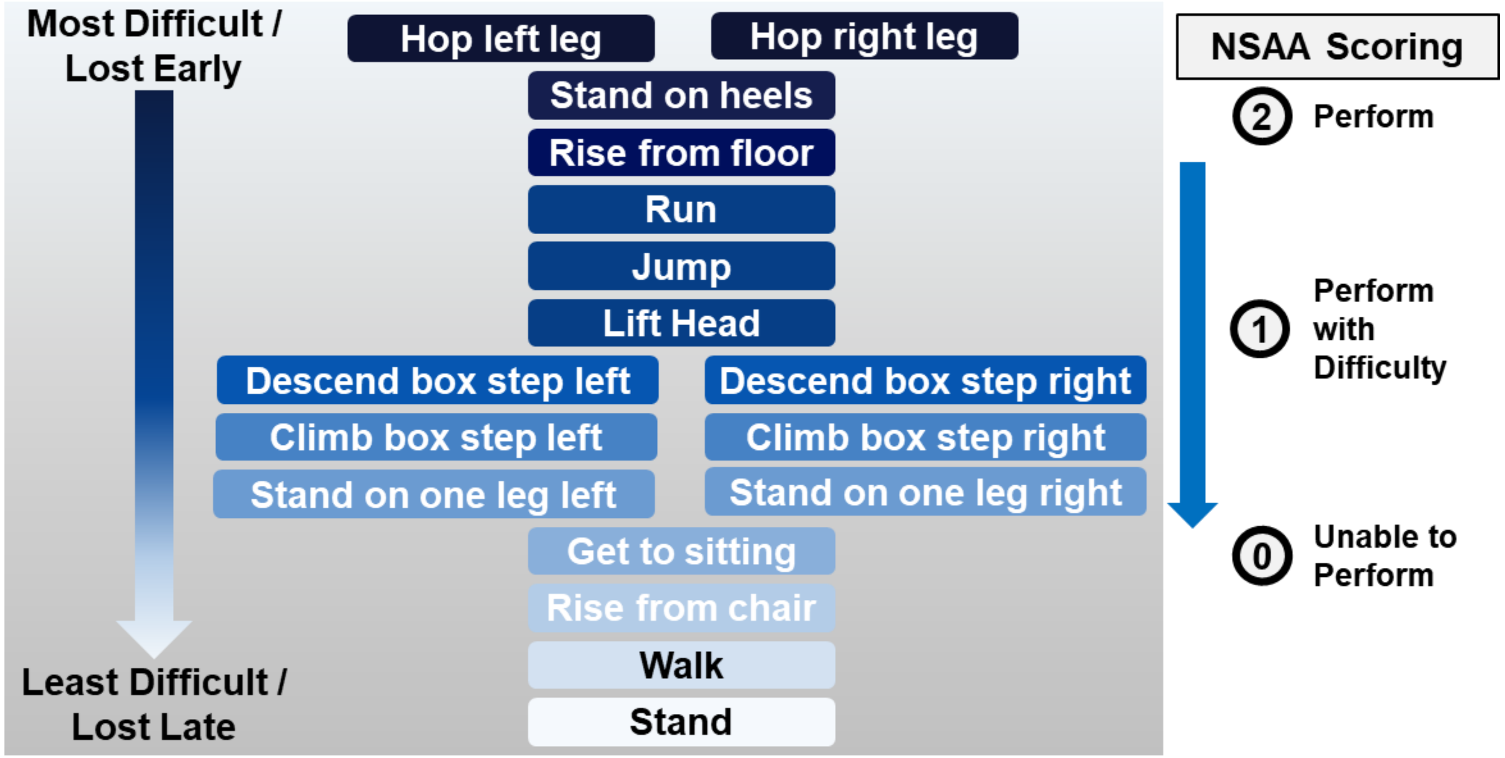
Birth – 2 years of age

- **Birth**
  Creatine Kinase
  > 2,000 (U/L)
- **Poor head control**
- **Can't sit without support**
- **Standing, cruising late**
- **Walk**
  15 – 18 months
- Autistic spectrum, delayed speech

3 – 4 yoa	5 – 7 yoa	8 – 11 yoa	Early Teens	Teens	Teens to Twenties
▪ Increased CK ▪ Genetic diagnosis	▪ Motor delay ▪ Toe walking ▪ Difficulty stair climbing ▪ Positive Gowers' sign	▪ Walking difficulty ▪ Tires easier ▪ Wheelchair at times ▪ Frequent falls	▪ Loss of ambulation ▪ Full-time wheelchair use ▪ Increased arms weakness	▪ Reduced forced vital capacity ▪ Need for ventilatory support ▪ Reduced activities of daily living	▪ Cardiac dysfunction ▪ Heart failure ▪ Death

NSAA: Well-Established and Validated Measure of Global Function

- Composite evaluation of motor function across 17 test items with increasing difficulty
- Healthy boys obtain score of 34 by 4 years of age
- Boys with DMD achieve peak score of 26 around age 6 years

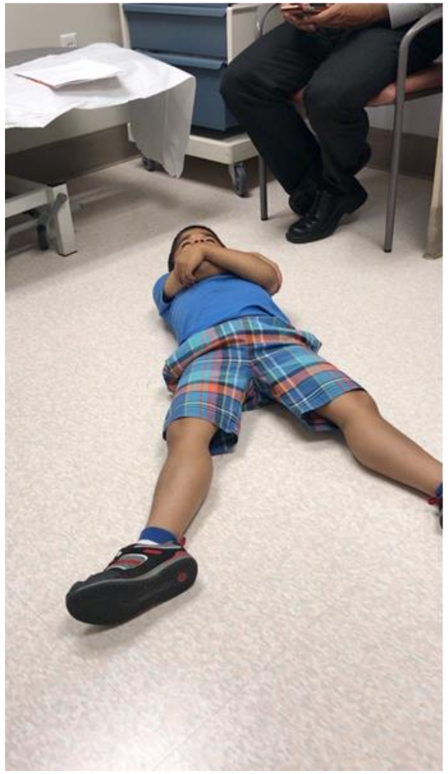


Zambon et al. 2022

Change of 1 Point Is Clinically Meaningful

Example NSAA Item: Rise from Floor

NSAA Score = 2
Stands easily



NSAA Score = 1
Stands with difficulty

NSAA Score = 0
Cannot stand

Videos shown with patient consent

Unmet Needs Remain Challenging Due to Limited Treatment Options

- DMD is progressive and universally fatal disease
- Supportive care is mainstay of treatment
- Corticosteroids delay time to loss of ambulation, but do not address underlying cause of DMD and associated with significant side effects
- RNA-based treatment provide small increases in dystrophin related only to specific mutations amenable to exon skipping (30%)
- Supportive care and medical intervention have improved life expectancy, but quality of life severely compromised

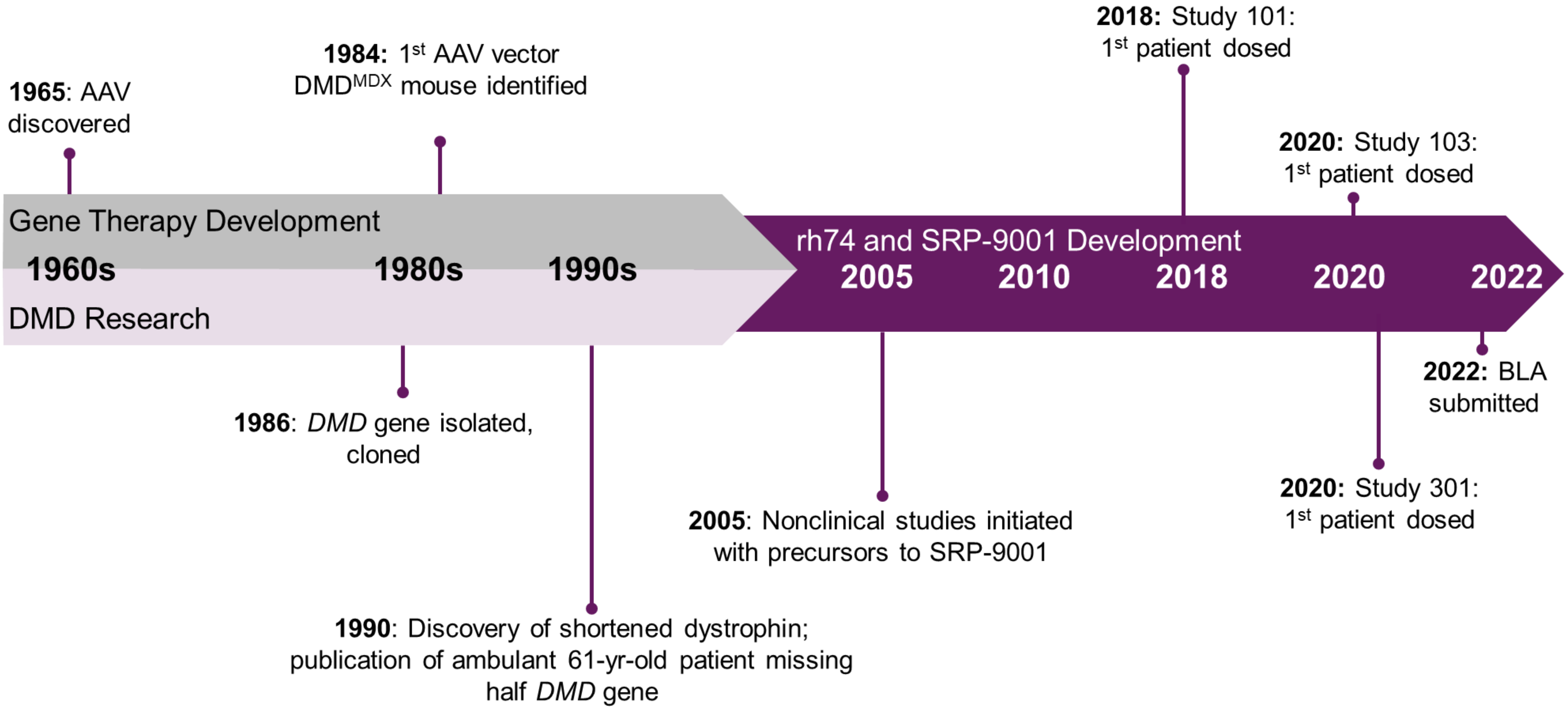
Gene therapy addresses underlying cause of DMD and has potential to stabilize disease progression

Evidence for Surrogacy

Louise Rodino-Klapac, PhD

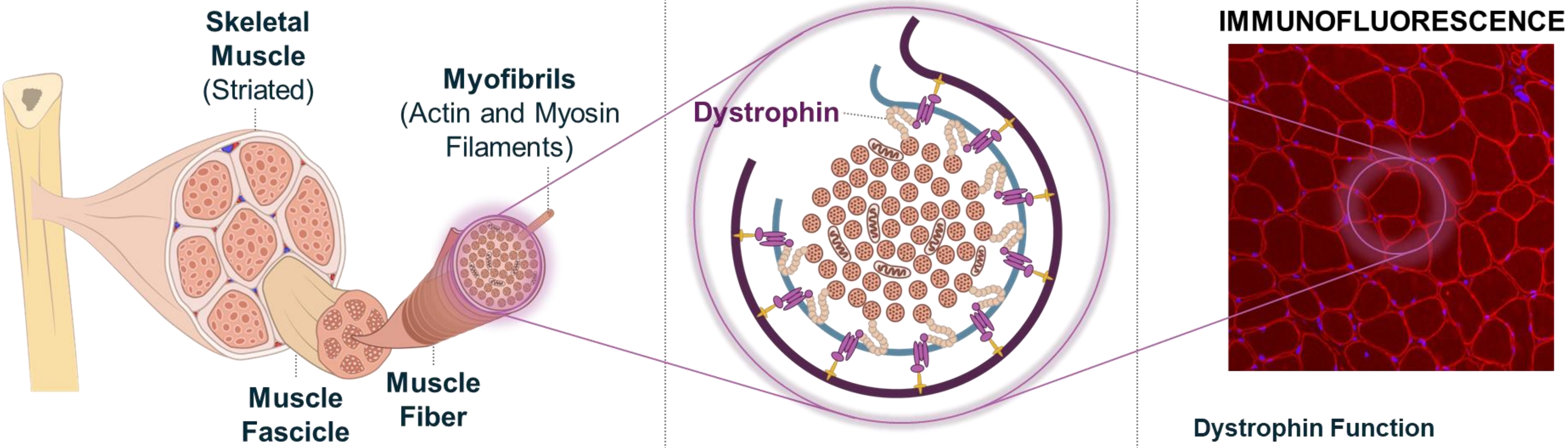
Executive Vice President, Head of R&D, and
Chief Scientific Officer
Sarepta Therapeutics

Key DMD, AAV, and SRP-9001 Milestones



AAV = adeno-associated virus

Dystrophin: Essential Muscle Protein

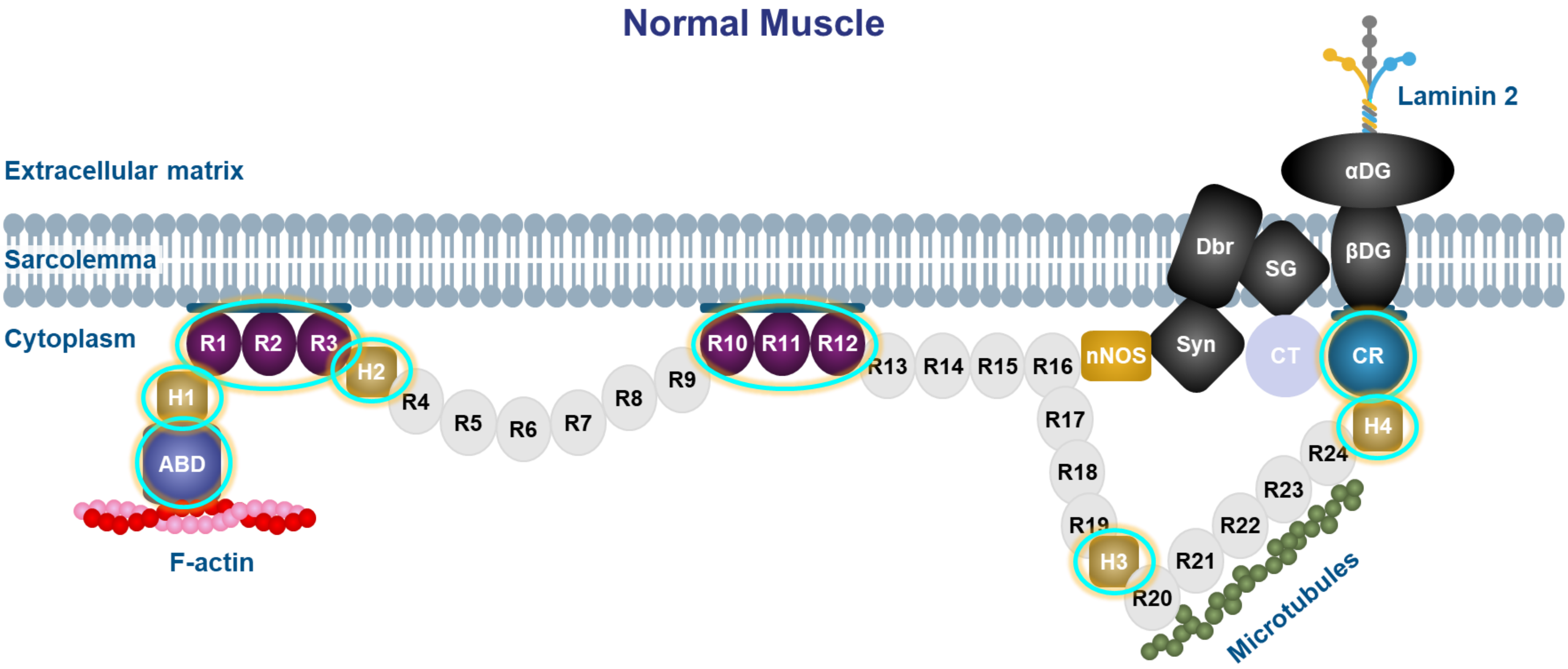


Dystrophin Function

- Flexible link between contractile machinery within muscle fiber and extracellular matrix
- Protects against contraction-induced injury to muscle fibers

Image adapted from Biga et al. 2020

Anatomy of Dystrophin: Key Functional Domains

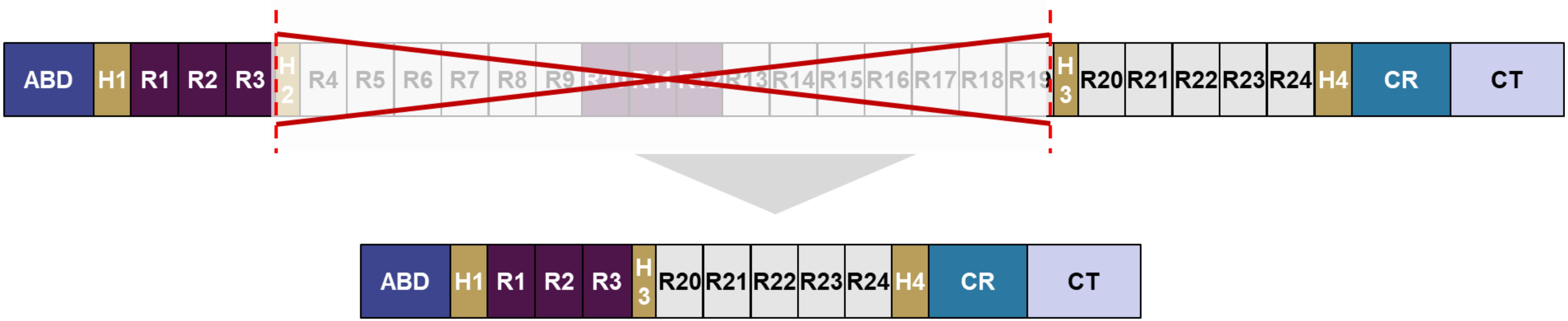


αDG = α-dystroglycan; ABD = actin binding domain; βDG = β-dystroglycan; CR = cystine rich; CT = C terminus; Dbr = dystrobrevin; H = hinge; nNOS = neuronal nitric oxide synthase; R = repeat; SG = sarcoglycan; Syn = syntrophin

Adapted from Zhao et al. 2016

Natural History Demonstrates that Large Portions of Dystrophin Protein Are Less Critical

- First discovered by Professor Kay Davies in 1990
  - Mild Becker muscular dystrophy (BMD) patient who, surprisingly, could still ambulate at age 61
- Genetic testing confirmed patient missing nearly half their dystrophin protein
  - Missing 46% of dystrophin coding region (Del 17 – 48)[1], specifically large stretch of spectrin-like repeats in middle

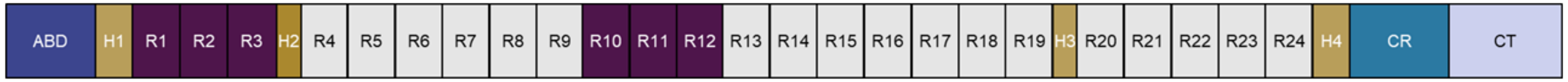


1. England et al. 1990

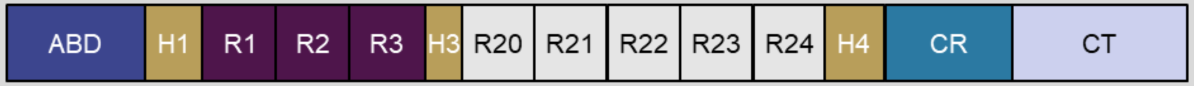
Evidence includes 2 additional mildly affected individuals in the pedigree

Shortened Dystrophins Leading to Sustained Ambulation and/or Increased Survival

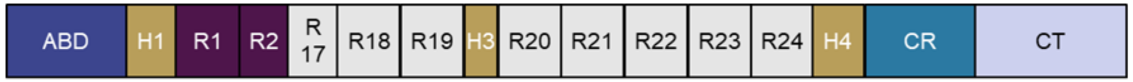
Full-length dystrophin



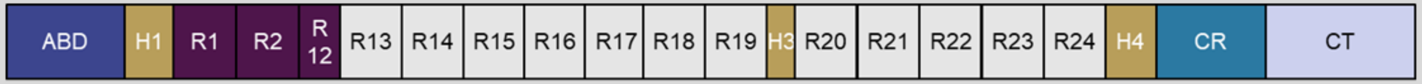
KE Davies Patient[1]
- Still ambulant at age 61



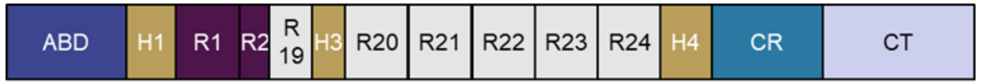
Patient 1[2]
- Age of loss of ambulation unknown
- Alive at 68



Patient 2[2]
- Age of loss of ambulation unknown
- Alive at 64

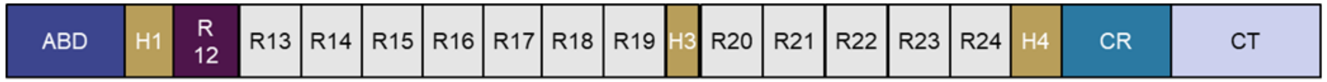


Patient 3[3]
- Still ambulant at age 37



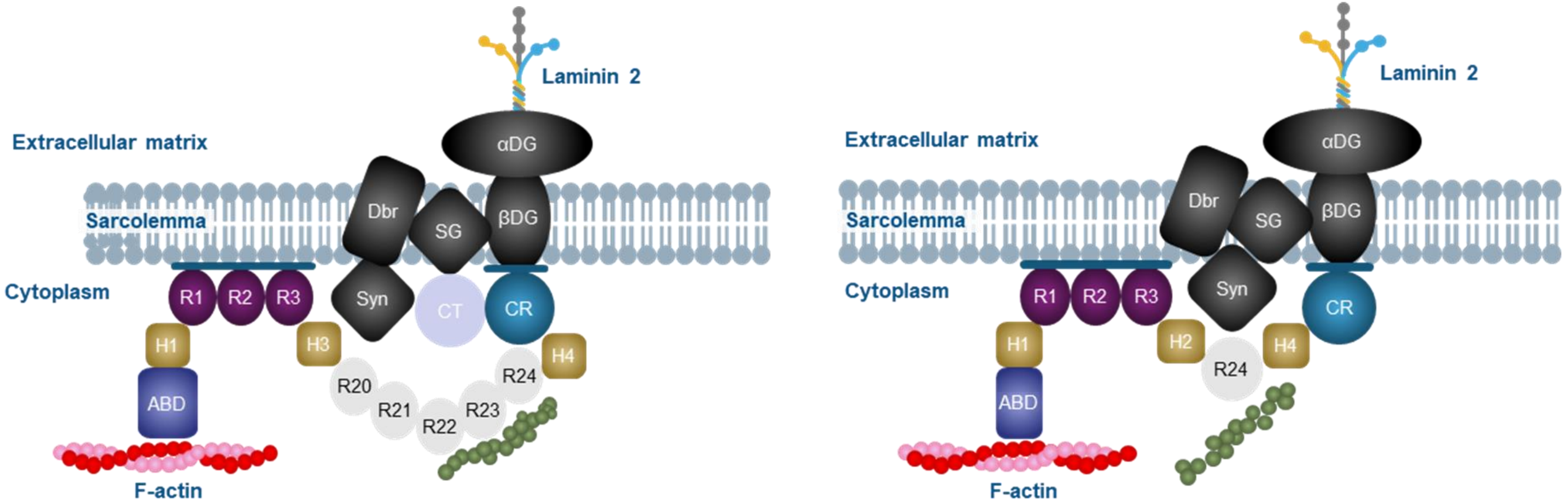
Patient 4[4]
- Age of loss of ambulation unknown
- Alive at 46

Patient 5[5]
- Still ambulant at age 26



1. England et al. 1990; 2. Unpublished case; 3. Passos-Bueno 1994; 4. Morandi 1993; 5. Koenig 1989

SRP-9001 Dystrophin Design Follows Structure of Natural, Highly Functional, Shortened Dystrophins



Includes key functional regions

Iterative experiments to find optimal structure

Efficacy demonstrated nonclinically and clinically

Image adapted from Zhao et al. 2016

Nonclinical Studies Reinforce Key Domains Important for Dystrophin Function

	Tetanic Force (N/cm^2) **Mean** (SE)	**Construct Candidates**
Wild-type (full dystrophin protein)	**21.5** (0.5)	
Dys$^{\Delta R4\text{-}23/\Delta CT}$-*mdx*	**20.4** (0.9)	
Dys$^{\Delta H2\text{-}R19/\Delta CT}$-*mdx*	**20.3** (0.9)	
Dys$^{\Delta R2\text{-}R15/\Delta R18\text{-}23/\Delta CT}$-*mdx*	**19.7** (0.8)	
Dys$^{\Delta H2\text{-}R15}$-*mdx*	**17.8** (0.8)	
mdx	**13.1** (0.5)	*No dystrophin*

Nelson et al. 2018

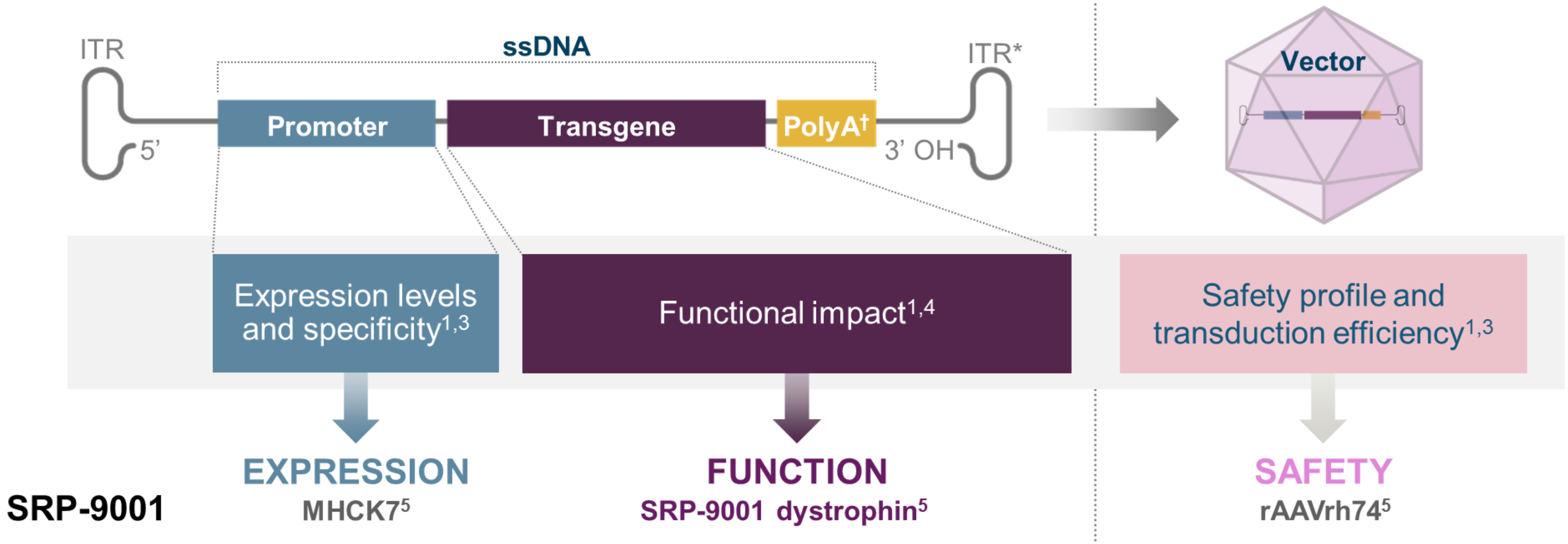
SRP-9001 Dystrophin Resulted in Superior Specific Force Compared to Other Tested Constructs

	Specific Force (mN/mm^2), **Mean** (SE)	**Construct Candidates**
Wild-type (full dystrophin protein)	**284.2** (14.2)	ABD H1 R1 R2 R3 H2 R4 R5 R6 R7 R8 R9 R10 R11 R12 R13 R14 R15 R16 R17 R18 R19 H3 R20 R21 R22 R23 R24 H4 CR CT
SRP-9001	**232.7** (12.3)	MHCK7 Promotor; ABD H1 R1 R2 R3 H2 R24 H4 CR
MCK.micro-dys	**195.5** (15.6)	MCK Promotor; ABD H1 R1 R2 R3 H2 R24 H4 CR
Micro-dys C-term	**163.7** (19.7)	MHCK7 Promotor; ABD H1 R1 R24 H4 CR CT
Dual vector	**188.8** (21.0)	MHCK7 Promotor; ABD H1 R1 R2 R3 R16 R17 H3 R20 R21 R22 R23 R24 H4 CR CT
Untreated *mdx*	**154.7** (10.1)	

Potter et al. 2019

MHCK7 = alpha-myosin heavy-chain creatine kinase 7 promoter/enhancer; MCK = muscle creatine kinase

SRP-9001: AAV-Based Investigational Gene Transfer Therapy for Treatment of DMD[1,2]



*ITRs are required for genome replication and packaging; †PolyA signals the end of the transgene to the cellular machinery that transcribes (ie, copies) it.

AAV = adeno-associated virus; AAVrh74 = recombinant human adeno-associated virus 74; ITR = information transfer rate; ssDNA = single-stranded DNA

1. Asher et al. 2020; 2. US National Library of Medicine 2013; 3. Zheng and Baum 2008; 4. Chandler and Venditti 2016; 5. Mendell et al. 2020

Empirical Evidence for Surrogacy

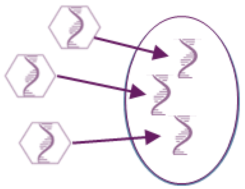
Nonclinical

Biological Cascade Through Which SRP-9001 Exerts Effect Is Demonstrable Through Series of Well-Validated Endpoints

Biological Endpoints

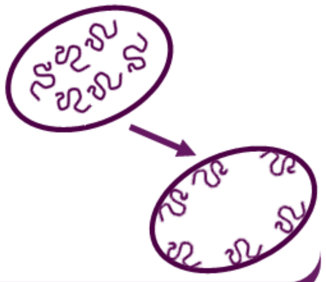
Transduction Efficiency

Vector Genome Copy Number



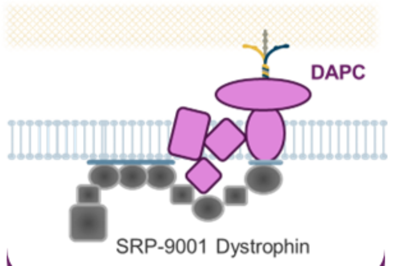
SRP-9001 Dystrophin Expression

Western Blot % Normal Expression



SRP-9001 Dystrophin Localization and Restoration of DAPC

IF Fiber Intensity and PDPF



Normalization of Muscle Microenvironment

Muscle Histology and Serum CK

Relationship to Functional Benefit

Functional Benefit

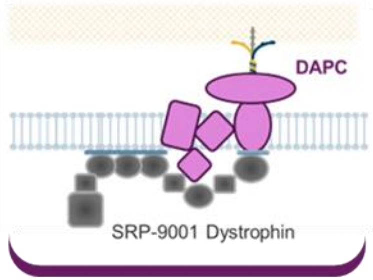
NSAA

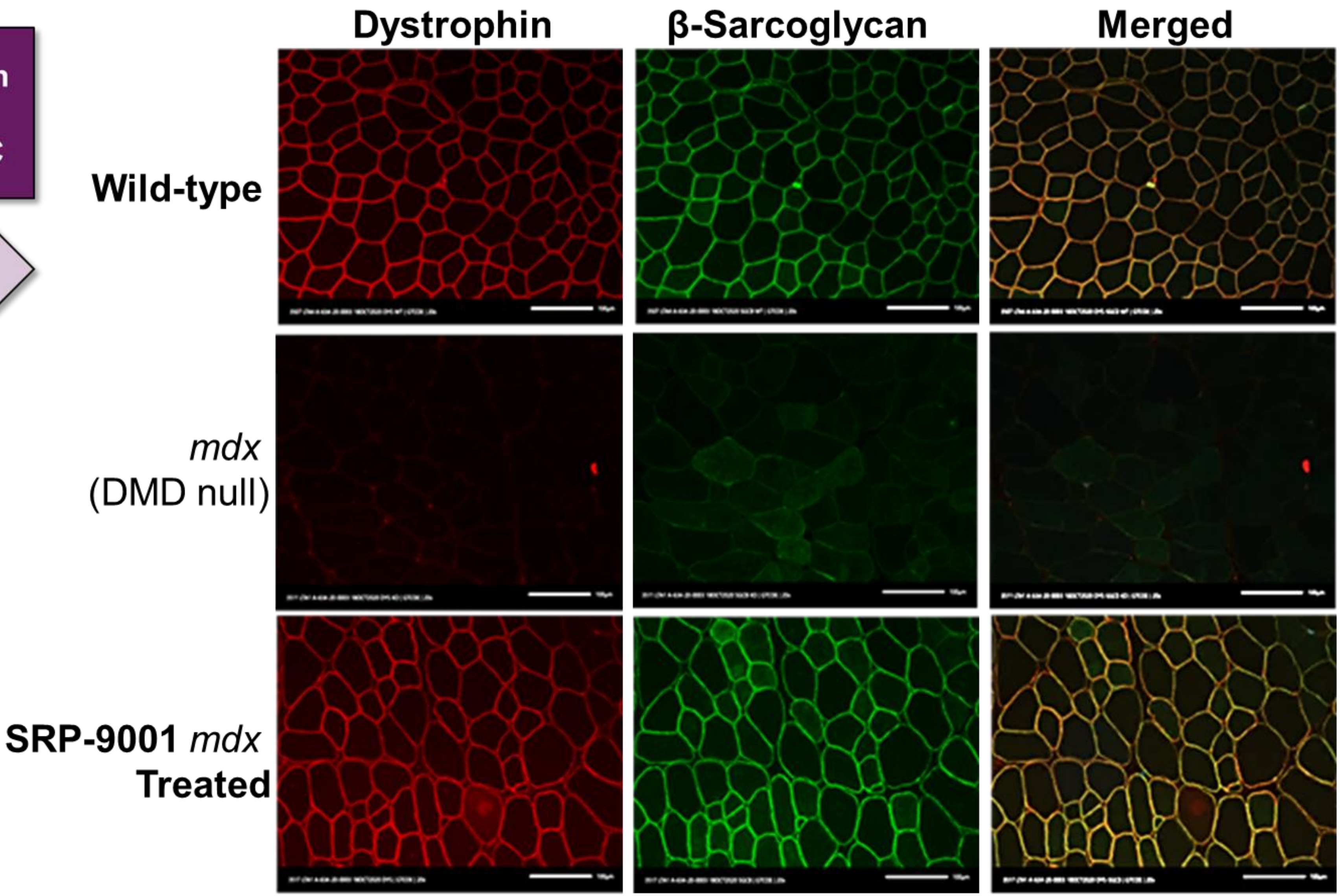
CK = creatine kinase; DAPC = dystrophin associated protein complex; IF = immunofluorescence; PDPF = percent dystrophin positive fibers

SRP-9001 Protein Expression Stabilizes Sarcolemma Leading to DAPC Restoration in DMD^{MDX} Mice

SRP-9001 Dystrophin Localization and Restoration of DAPC

IF Fiber Intensity and PDPF





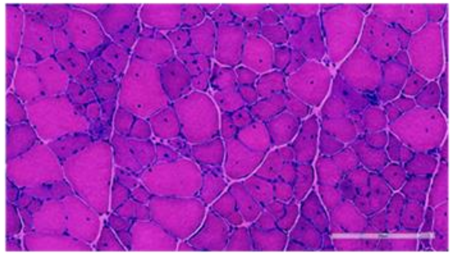
Images at 20X magnification

Membrane Stabilization Leads to Improved Muscle Health, Reduced CK, and Functional Improvement

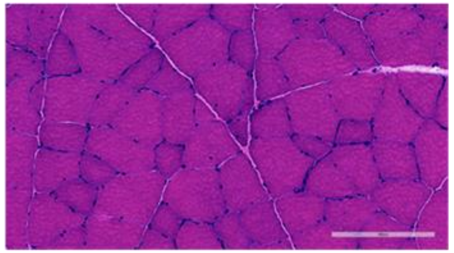
Normalization of Muscle Microenvironment

Muscle Histology

DMD^{MDX} Untreated

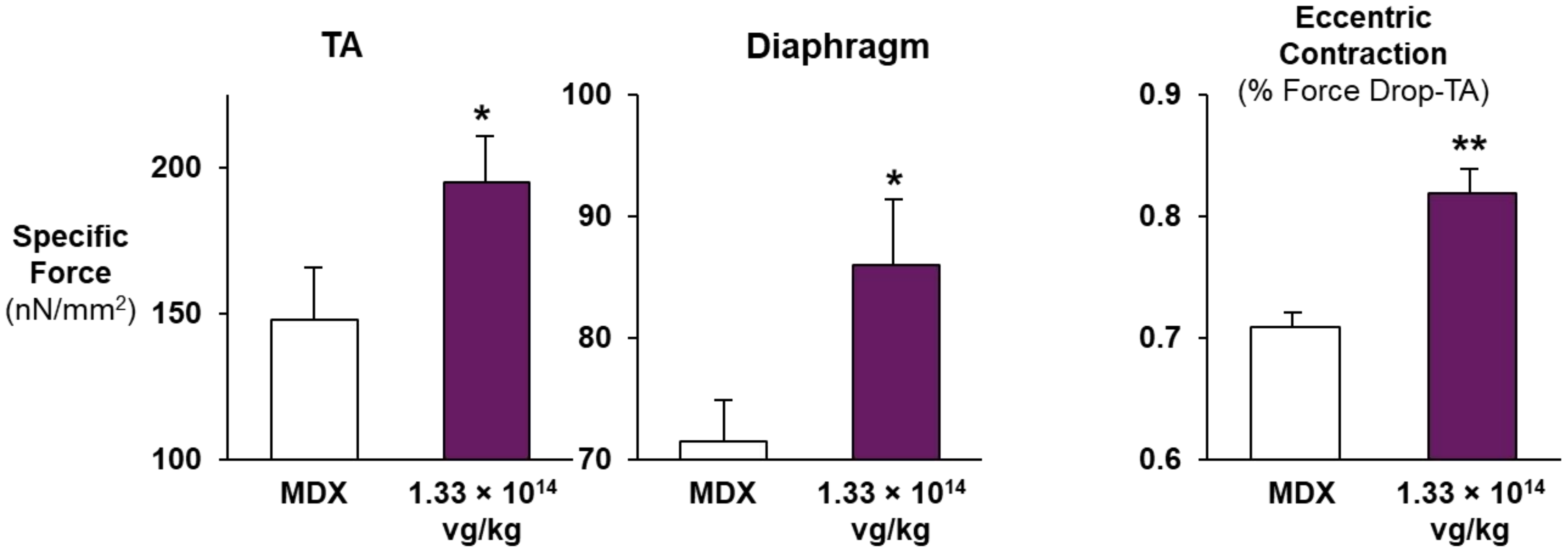


SRP-9001



Improved Function

Increased Specific Force



1.33 × 10^{14} vg/kg clinical dose is statistically significant compared to DMD^{MDX} untreated cohorts: * $p < 0.05$; ** $p < 0.0001$

TA = tibialis anterior

Empirical Evidence for Surrogacy

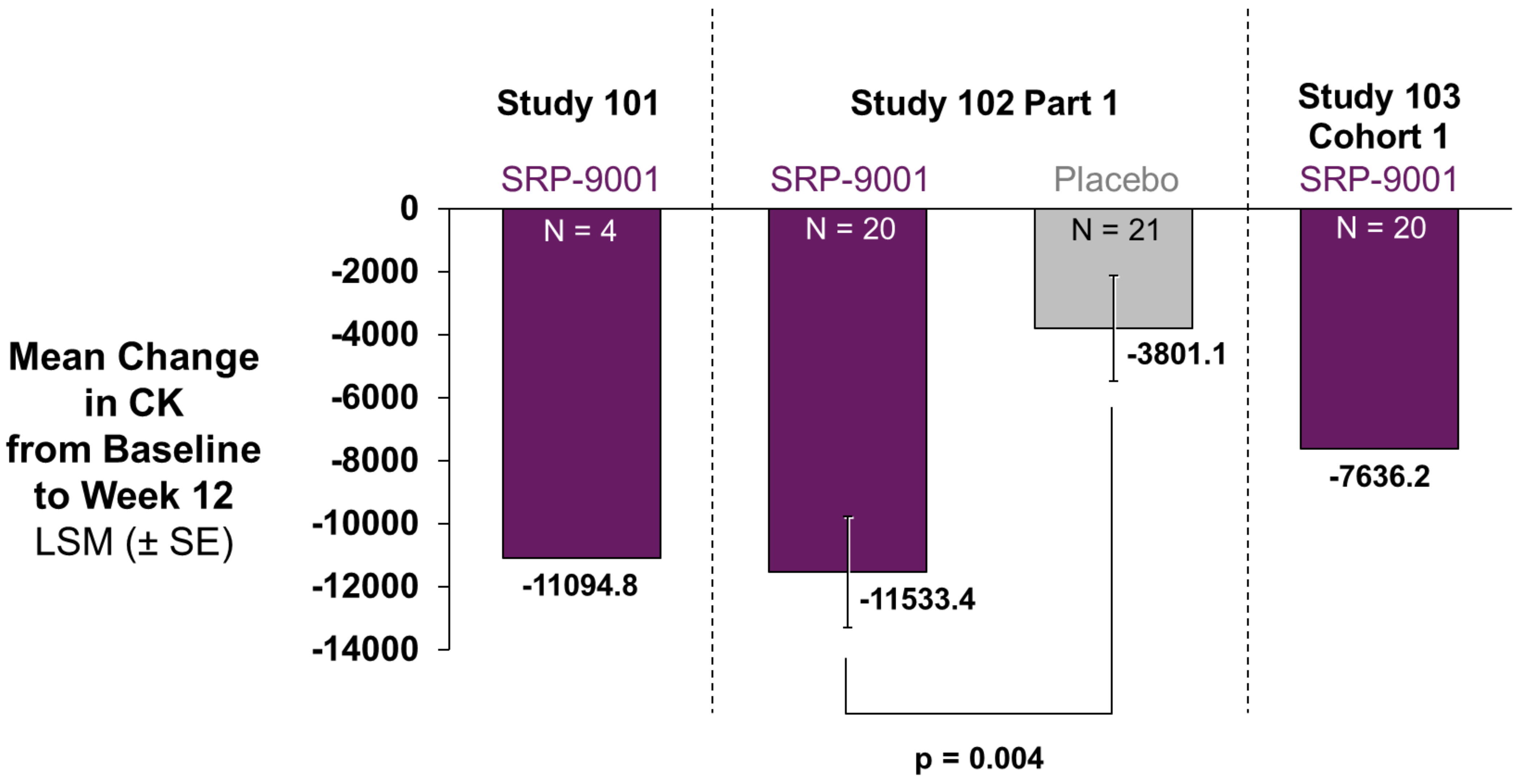
Clinical

Consistent and Robust Biological Response at 12 Weeks

Mean Change from Baseline (SD)	**Study 101** N = 4	**Study 103 Cohort 1** N = 20	**Study 102 Part 1 SRP-9001** N = 20	**Study 102 Part 1 Placebo** N = 21
Vector genome copy number	**5.7** (4.1)	**3.4** (2.4)	**1.6** (1.5)	**0** (0)
SRP-9001 dystrophin expression (western blot, % of normal)	**70.5*** (76.1)	**54.2** (42.6)	**23.8** (39.8)	**0.1** (1.2)
			p < 0.0001	
IF fiber intensity (% of control)	**93.6** (43.9)	**66.5** (64.1)	**25.8** (46.2)	**-0.5** (6.3)
PDPF (%)	**81.2** (10.2)	**48.3** (25.4)	**23.9** (25.6)	**5.1** (13.0)

***Western blot method used for Study 101 was not adjusted to muscle content**

CK Reductions Due to Muscle Membrane Stabilization



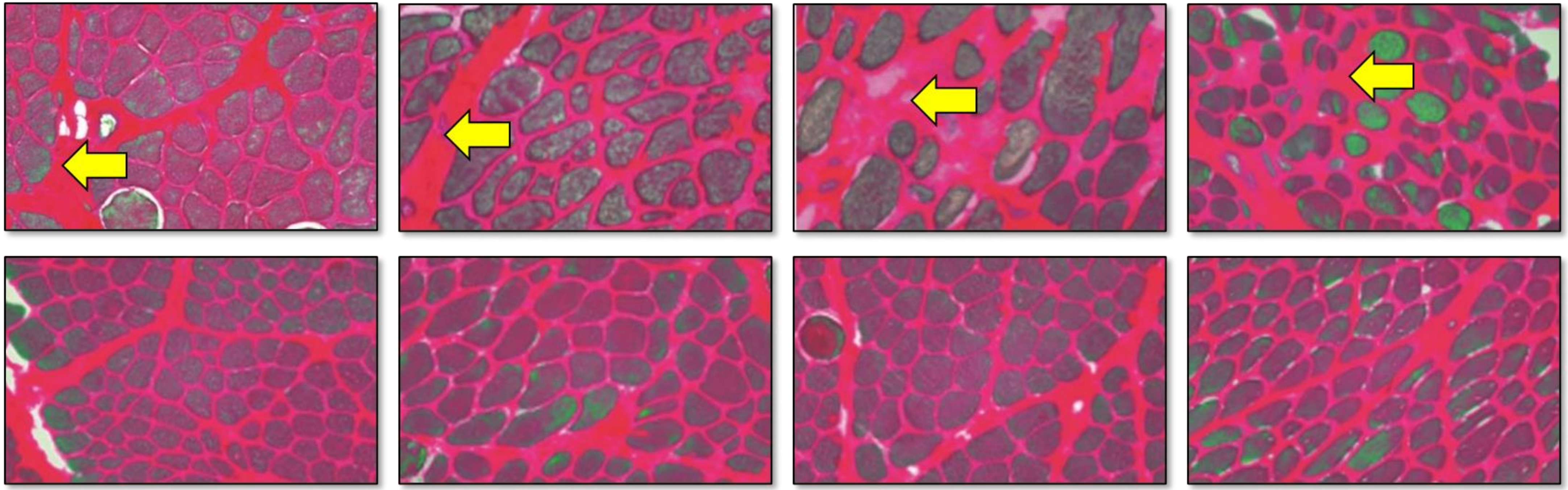
Reduced Collagen Deposition Improves Muscle Health

Picrosirius red staining of Baseline and Day 90 biopsies from Study 101

Patient 1 | Patient 2 | Patient 3 | Patient 4

Pre-Treatment

Post-Treatment



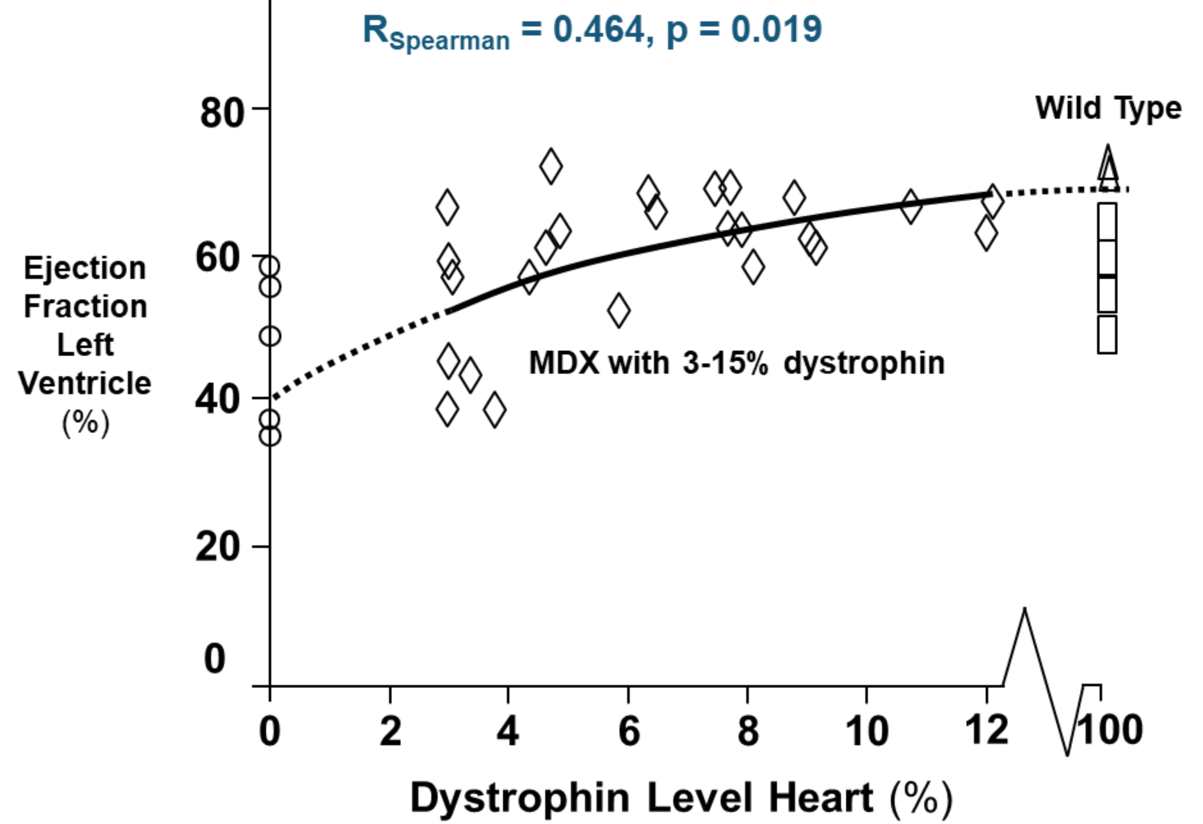
Mean decrease in collagen 26.7% after SRP-9001

Mendell et al. 2020; Images at 40X magnification

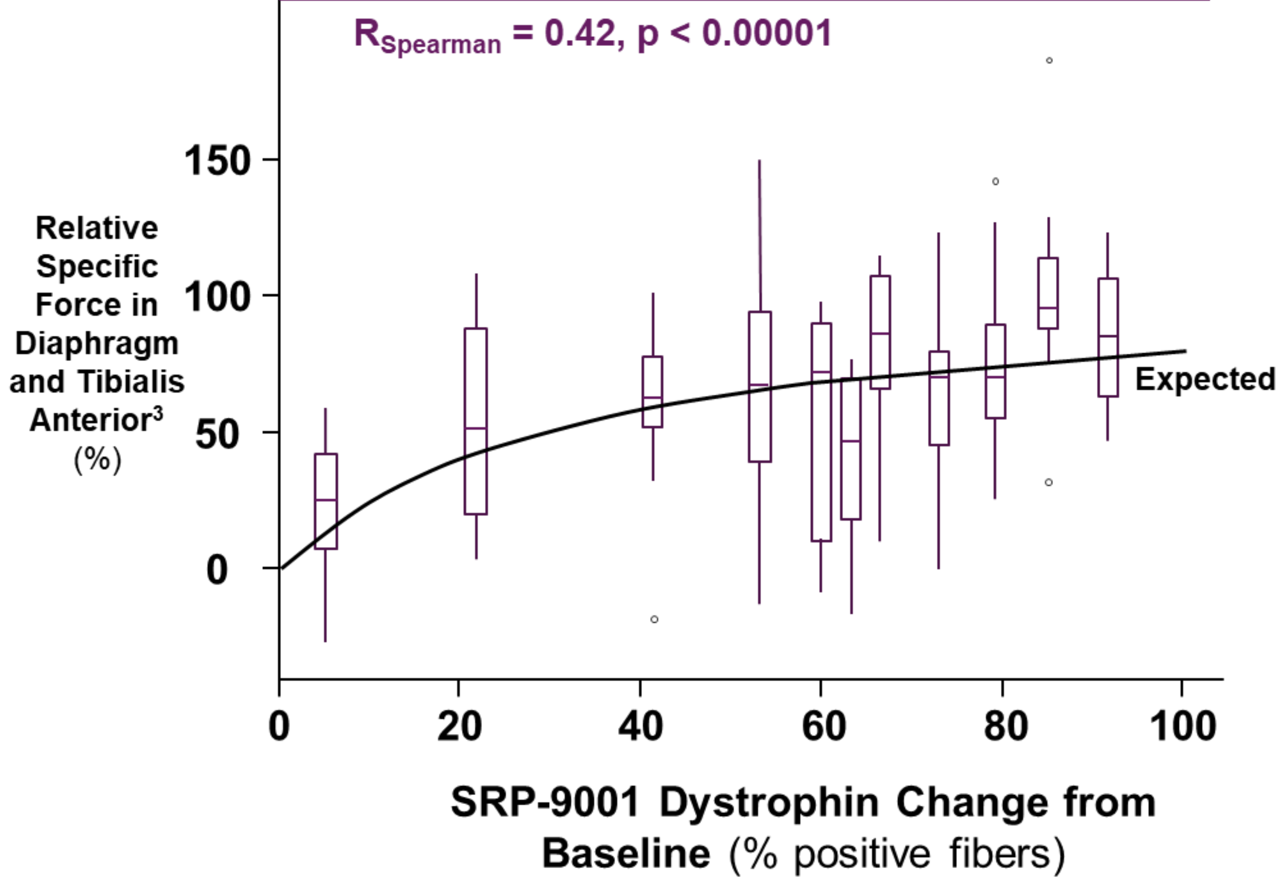
SRP-9001 Biomarker to Functional Relationship

Like Endogenous Dystrophin, SRP-9001 Dystrophin Is Correlated with Improved Function that Is Saturable

Endogenous Dystrophin & Function[1] (DMD^{MDX} Mouse Model)

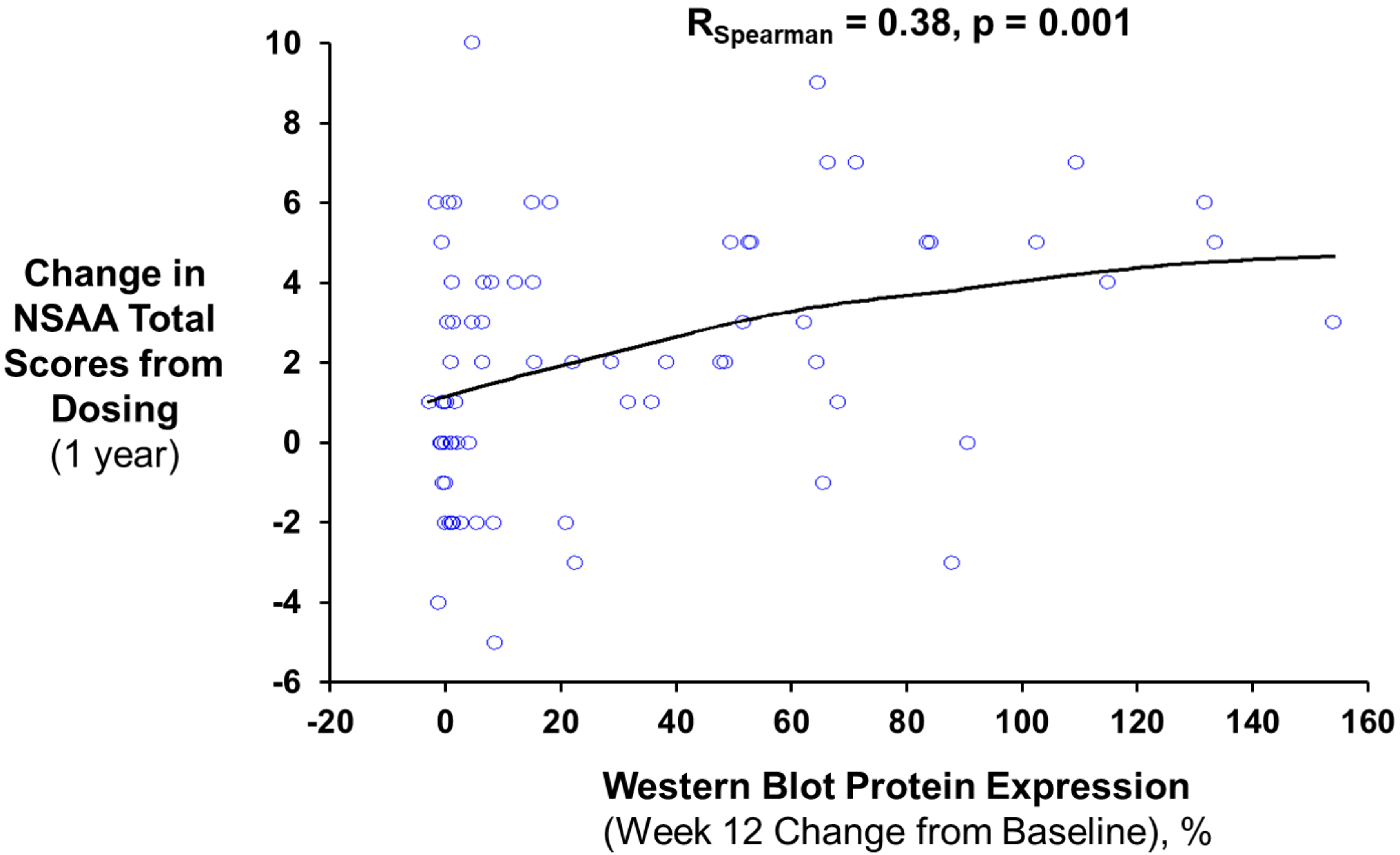


SRP-9001 Dystrophin & Function[2] (DMD^{MDX} Mouse Model)



1. Adapted from Van Putten et al. 2014
2. Box plot shows median, interquartile and range of observed data from 0.0443 to 4.01 x 10^{14} vg/kg
3. Relative specific force = muscle contraction from diaphragm and tibialis anterior

Positive and Statistically Significant Association Between SRP-9001 Dystrophin and NSAA 1-Year Change



Includes Study 102 and 103 Cohort 1 age 4 – 7 years old

Summary of Rational Design and Evidence for Surrogacy of SRP-9001

- Dystrophin is protein that acts as link between extracellular matrix and intracellular cytoskeleton in muscle cells
- Evidence of nature informed rational design of SRP-9001 to include key components needed for function
- SRP-9001 restores biological cascade that is downregulated in absence of dystrophin
  - DAPC restoration, normalization of muscle microenvironment, and decreased CK
- SRP-9001 protein expression correlated with improved function in nonclinical and clinical studies
- Evidence supports Accelerated Approval criteria that SRP-9001 is reasonably likely to predict clinical benefit

Clinical Trial Results

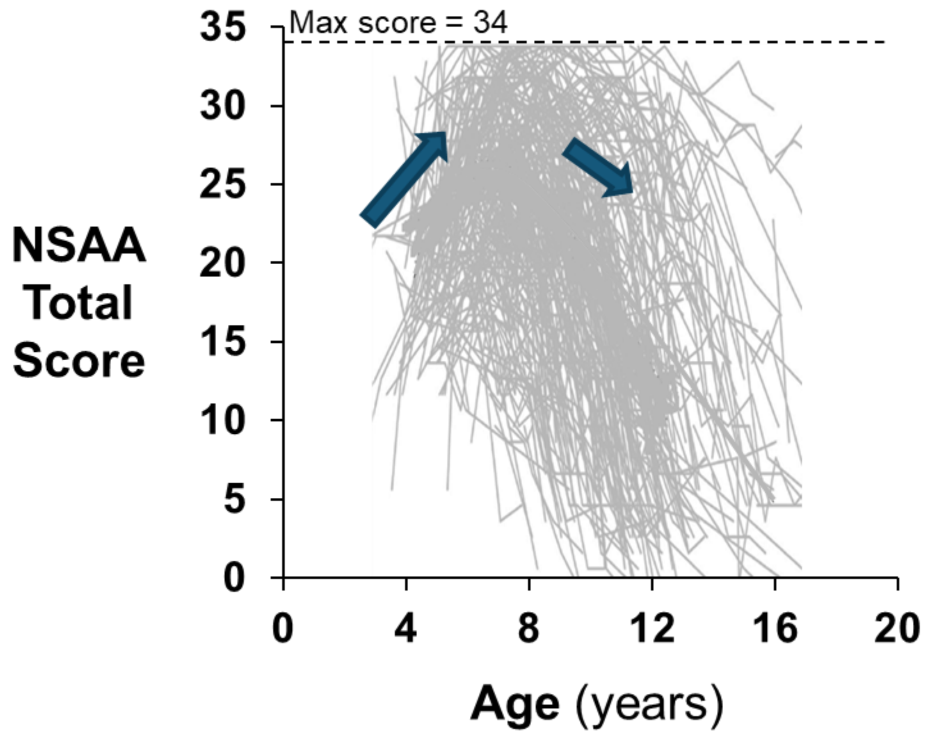
Stefanie Mason, MD

Senior Medical Director, Clinical Development

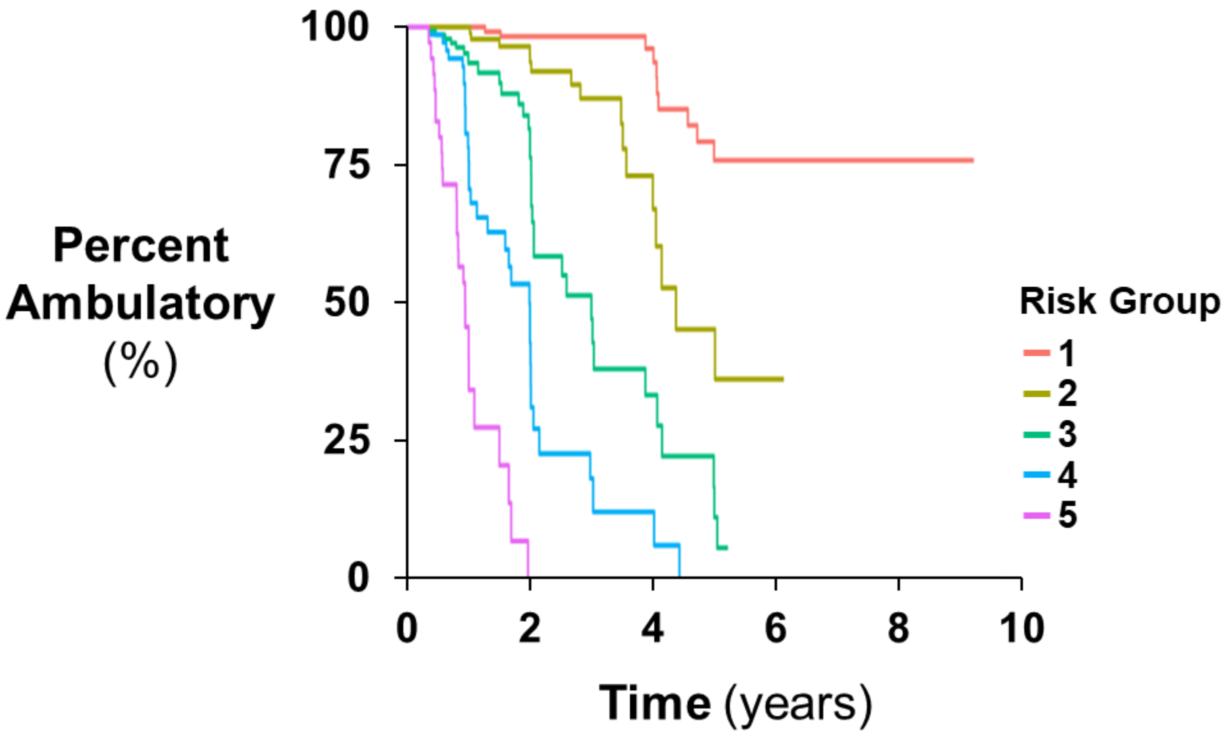
Sarepta Therapeutics

DMD Disease Progression Is Heterogenous but Predictable

Consistent Pattern Over Time



Predictable Using Baseline Function



Validated predictive model based on ***Time to Rise*** *and* ***10 meter walk/run***

Muntoni et al. 2019

McDonald et al. 2022

Disease Modification Across Ambulatory Trajectory

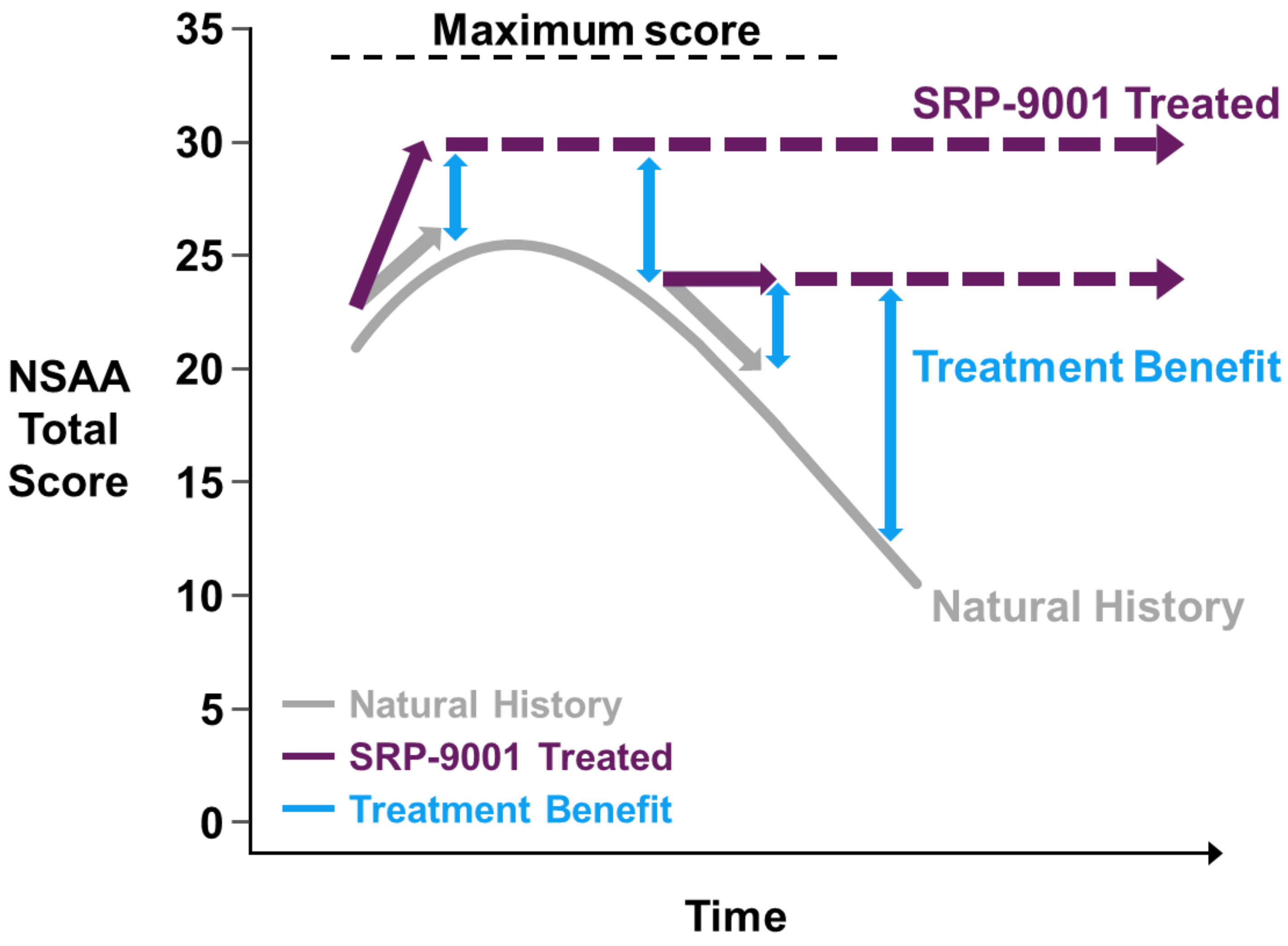


Figure adapted from Muntoni et al. 2019

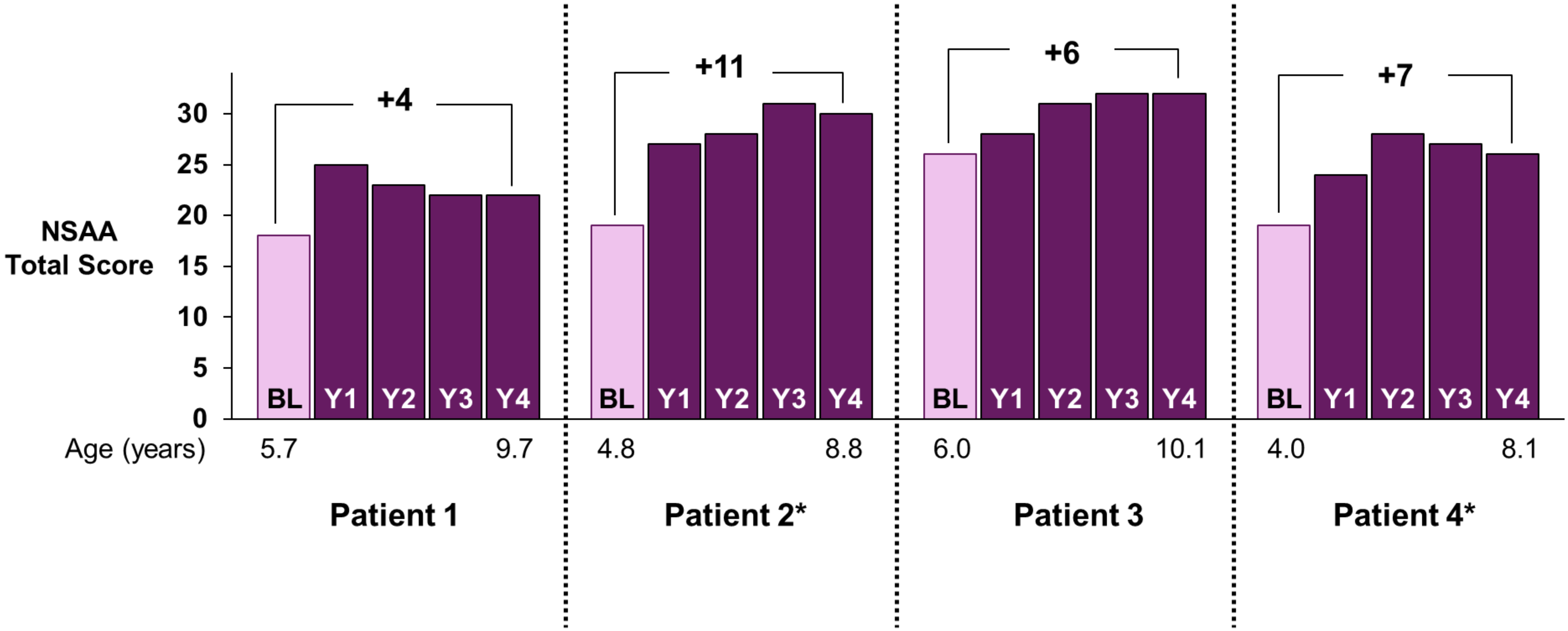
Study 101: Design

Key inclusion/exclusion criteria:

- 4 – 7 years of age
- Stable oral corticosteroids x 12 weeks
- Antibody titers ≤ 1:400

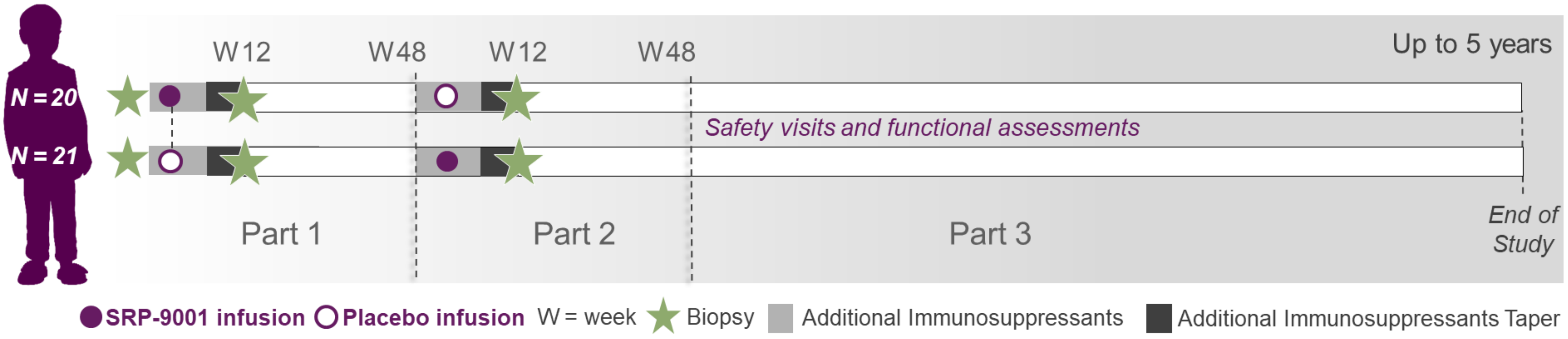
	Median (range)
Age (years)	**4.8** (4 – 6)
Weight (kg)	**18.1** (13.7 – 21.4)
Height (cm)	**107.1** (95.7 – 110.0)
BMI (kg/m^2)	**16.3** (15.0 – 17.7)

Study 101: Stable NSAA Scores 1 – 4 Years After SRP-9001 Infusion



*Patient 2: 3-year NSAA value and Patient 4: 2-year NSAA value was from a remote assessment due to COVID-19 related restrictions at the site.
Mendell et al. 2021; BL = Baseline; Y = Year

Study 102: Design



Key inclusion/exclusion criteria:

- 4 – 7 years of age
- Stable oral corticosteroids x 12 weeks
- Antibody titers ≤ 1:400

Study 102: Baseline Demographics

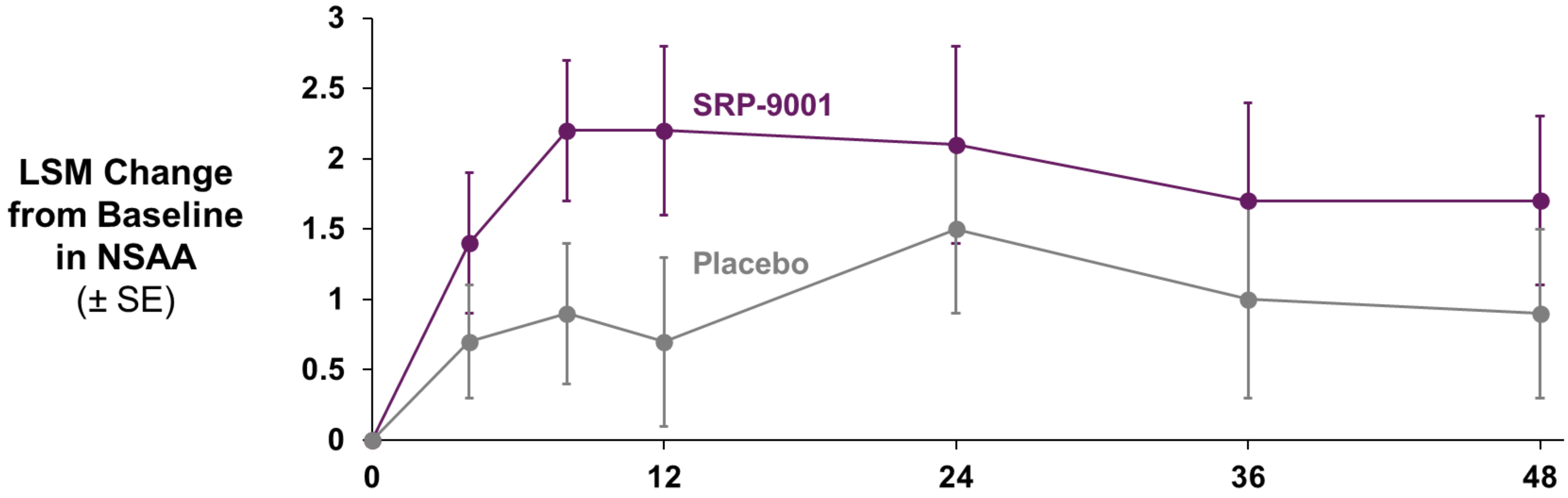
Baseline	Age 4 – 5 SRP-9001 N = 8	Age 4 – 5 Placebo N = 8	Age 6 – 7 SRP-9001 N = 12	Age 6 – 7 Placebo N = 13
Age, mean (years)	5.0	5.2	7.2	6.9
Years since corticosteroid treatment started	1.2	1.0	0.9	1.5
Corticosteroid type, deflazacort, n (%)	1 (13%)	2 (25%)	6 (50%)	5 (39%)
Dosing weight, mean (kg)	20.1	19.8	25.4	22.7
NSAA total score, mean	20.1	20.4	19.6	24.0
Time to Rise, mean (seconds)	3.6	3.8	5.9	3.4
10 m walk run, mean (seconds)	5.0	5.2	5.6	4.6

Imbalanced at Baseline $p < 0.05$

Age was only stratification factor for randomization

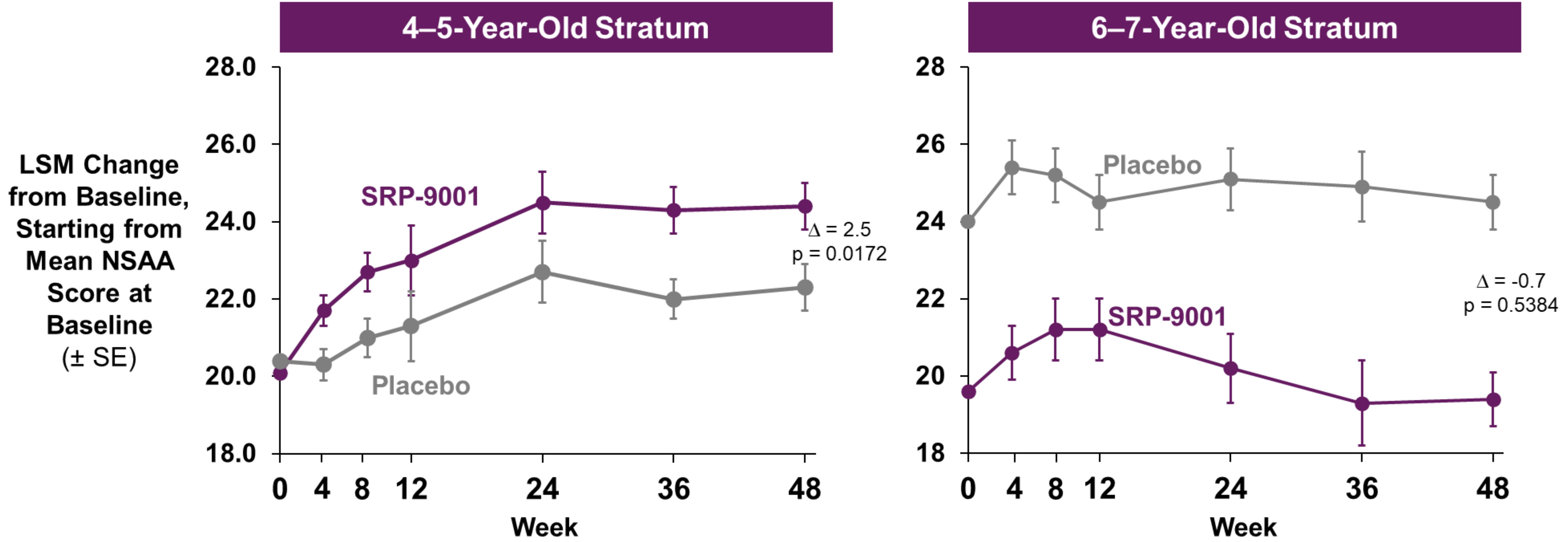
Study 102: ITT Population Primary Result

NSAA Change from Baseline = +1.7 in SRP-9001 vs +0.9 in placebo (p = 0.37)



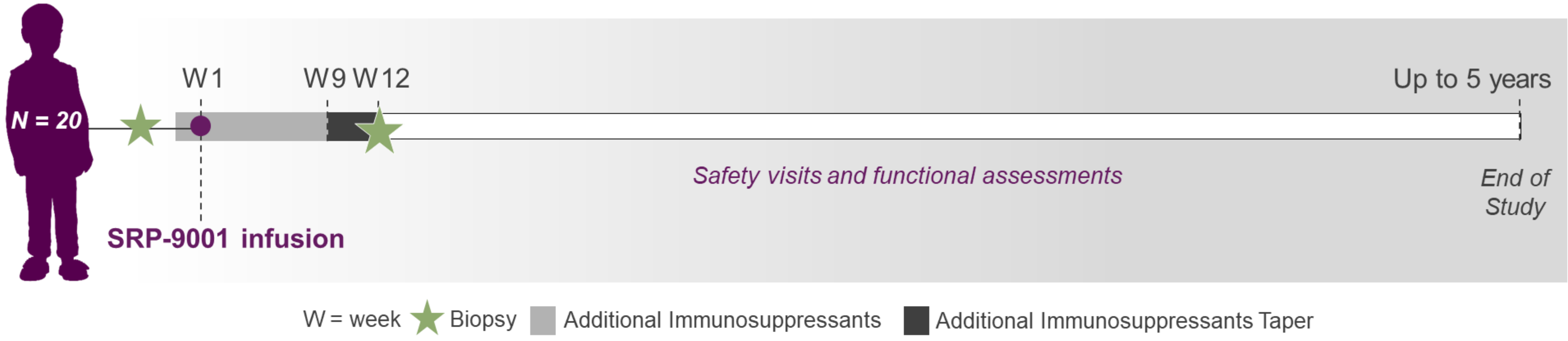
SRP-9001 (n)	20	20	18	19	15	14	19
Placebo (n)	21	21	19	20	16	19	21

Study 102: Primary Analysis by Pre-Specified Age Stratum



	0	4	8	12	24	36	48	0	4	8	12	24	36	48
SRP-9001 (n)	8	8	7	8	6	5	8	12	12	11	11	9	9	11
Placebo (n)	8	8	8	8	7	8	8	13	13	11	12	9	11	13

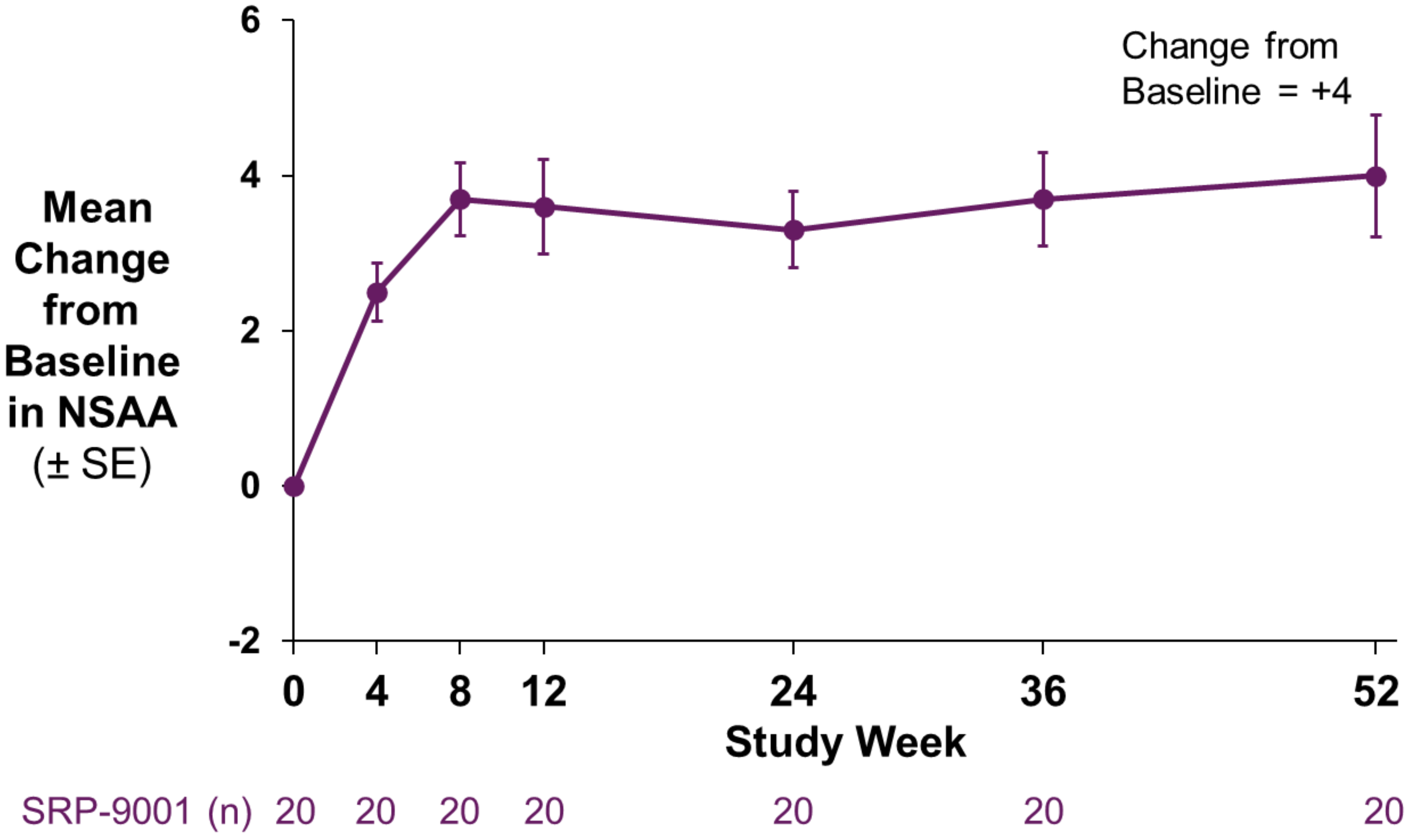
Study 103: Design



Key inclusion/exclusion criteria:

- 4 – 7 years of age
- Stable oral corticosteroids x 12 weeks
- Antibody titers ≤ 1:400
- NSAA score > 17 and ≤ 26

NSAA Improvement Over 1 Year



	Cohort 1 N = 20
Age (years)	
Mean (SD)	**5.81** (1.14)
4 to 5 years, n (%)	**11 (55.0%)**
6 to 7 years, n (%)	**9 (45.0%)**
Race, n (%)	
White	**15 (75.0%)**
Non-white	**5 (25.0%)**
Weight, kg	
Mean (SD)	**21.15** (4.23)
BMI, kg/m²	
Mean (SD)	**17.76** (2.26)

External Control Analyses

James Signorovitch, PhD

Co-Founder, Collaborative Trajectory Analysis Project (cTAP) in Duchenne

Managing Principal, Analysis Group

Pre-Specified External Control Analyses

Purpose

- Contextualize clinical outcomes of SRP-9001 in trials versus natural history
- Further test reasonably likely surrogacy of SRP-9001 expression for effects on clinical outcomes

Risks

- Potential for bias when comparing across non-randomized groups

Primary Risks Considered for External Controls

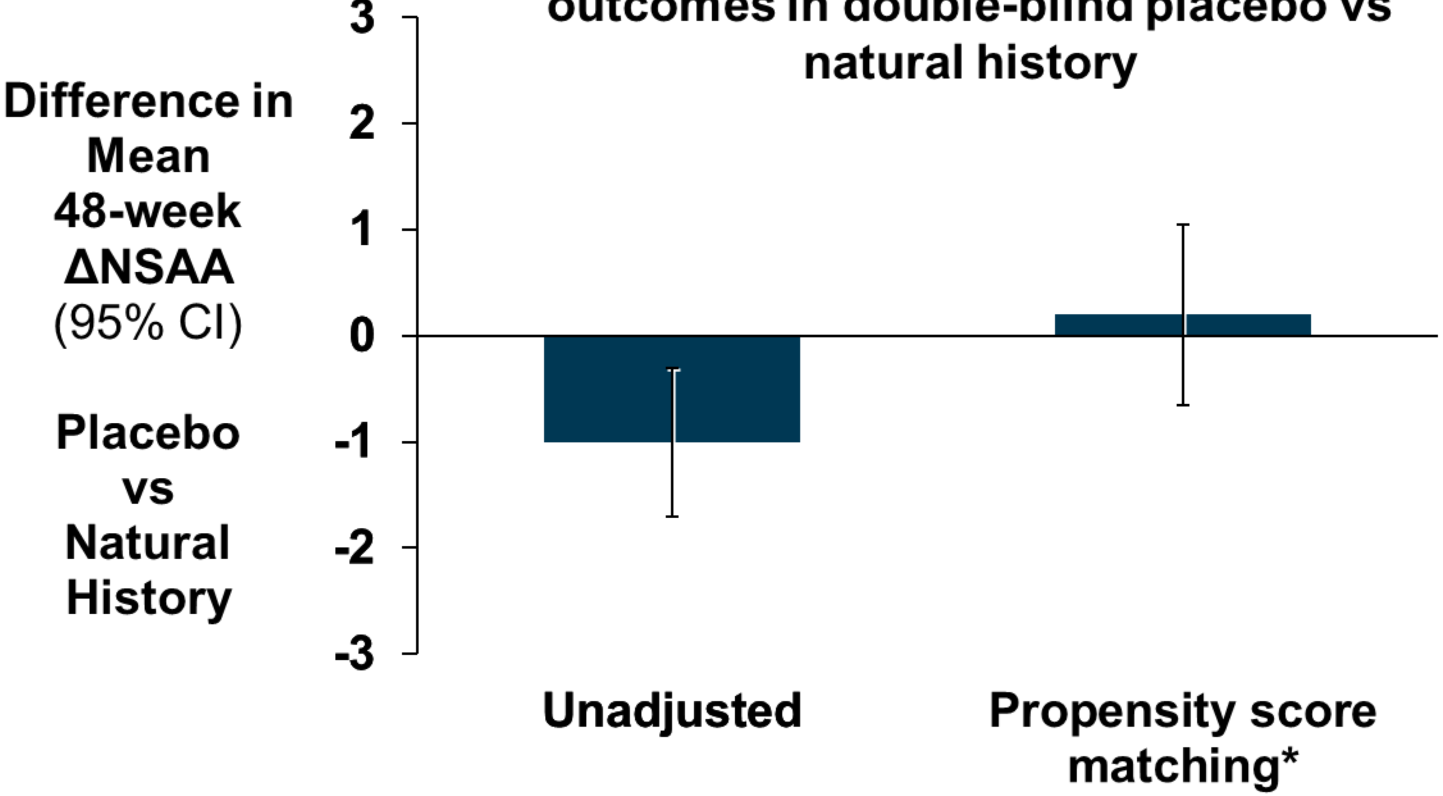
Sources of Potential Bias	Questions We Asked
Outcomes	▪ As a performance-based measure, do NSAA outcomes vary across data sources? ▪ Do differences in patient motivation or assessment processes bias outcomes measured in trials vs external controls?
Background standards of care	▪ How different are trials and external controls in terms of standards of care, geography and time periods? ▪ Do these differences impact outcomes?
Prognosis	▪ How predictable is the disease course? ▪ Are important prognostic factors balanced between trials and external controls?

Consistency of NSAA Outcomes Across Data Sources

Large collection of NSAA data from diverse sources

- N = 569 patients
- 7 data sources
- > 20 countries
- Years 2005 to 2018
- Double-blind placebo
- Natural history data

No evidence of significantly better NSAA outcomes in double-blind placebo vs natural history



*Adjusted for: age, steroid type, height, weight, BMI, and baseline function (NSAA, 10 m walk run, Time to Rise)

Muntoni et al. 2022

SRP-9001 EC Selection Driven by Assessment of Quality and Type of Data Available to Sponsor at Patient Level

From high-quality study with patients treated in line with current standard of care
Studies = 9

Rights are or can be obtained to use patient level data in a regulatory submission
Studies = 5

Moderate or better sample size with relevant endpoints
Studies = 3

- *CINRG Natural History Study*
- *Lilly Tadalafil DMD Trial*
- *FOR-DMD Trial (daily steroid arms)*

Subject-level inclusion / exclusion

- Meet steroid and age inclusion criteria for the SRP-9001 trials
- Have baseline function (NSAA, TTR, 10MWR) within baseline ranges of SRP-9001 trials
- N = 131 available as candidate external controls
- > 90% were drawn from clinical trials

CINRG = Cooperative International Neuromuscular Research Group
EC = external control; TTR = Time to Rise; 10MWR = 10 Meter Walk Run

SRP-9001 Pre-Specified Analyses for External Controls

Primary Analysis

Propensity score weighted external controls

Population	Integrated Summary of Efficacy sample
Intervention	SRP-9001 at target dose
Outcome	1-year change from baseline in NSAA
Comparator	External control sample
Methods	▪ Propensity score weighting based on age group (4 – 5, 6 – 7, 8 yrs), NSAA, 10MWR, and TTR ▪ Additional weighted regression adjustment for age group and NSAA by age group ▪ Estimate the average treatment effect among the treated (ATT)

Key Sensitivity Analysis

Predicted controls for NSAA trajectory

- Used different data sources and methods than the primary analysis
- Independently developed prediction model (cTAP)
- Based on different data sources than primary external controls
- Key predictors included in model: age, steroid type, height, weight, BMI, NSAA, 10MWR, TTR

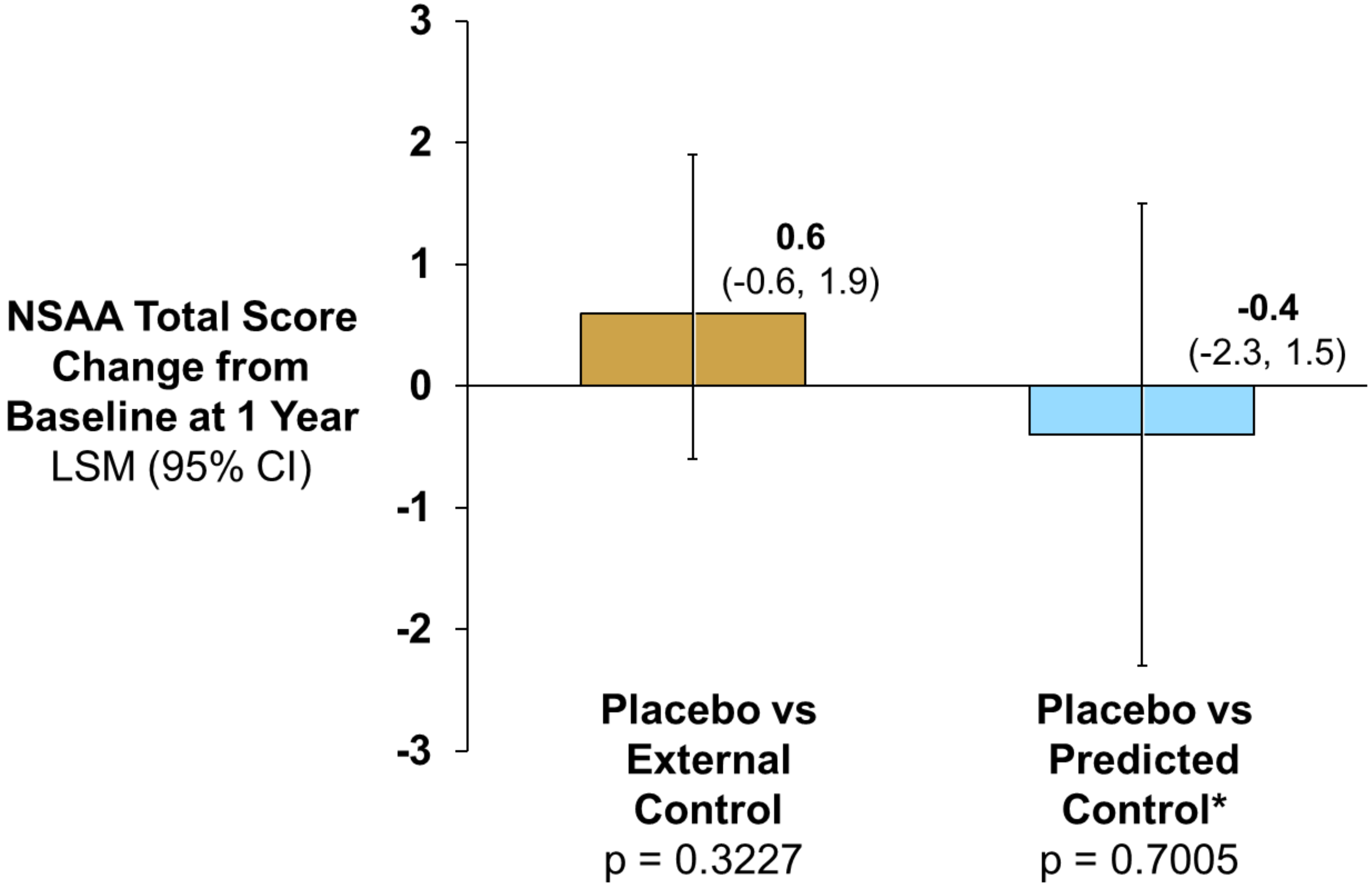
cTAP = Collaborative Trajectory Analysis Project; TTR = Time to Rise; 10MWR = 10 Meter Walk Run

Baseline Balance in Key Prognostic Factors

	SRP-9001 Treated (Pooled) N = 52	External Controls Before PS Weighting N = 131	External Controls After PS Weighting N = 105	Standardized Mean Difference After PS Weighting
Age, years	6.44 (1.32)	6.75 (1.08)	6.67 (0.68)	-0.19
Height, cm	112.08 (7.71)	113.53 (7.88)	113.33 (5.01)	-0.16
Weight, kg	22.81 (4.66)	22.52 (5.24)	22.70 (3.78)	0.02
BMI	18.03 (2.40)	17.27 (2.30)	17.46 (1.72)	0.24
NSAA	22.1 (3.8)	23.8 (4.3)	21.4 (3.1)	0.18
10 m Walk Run, sec	5.14 (1.10)	5.38 (1.06)	5.17 (0.7)	-0.03
Time to Rise, sec	4.48 (1.83)	5.02 (2.03)	4.49 (1.15)	0.00

Means (standard deviations) shown unless otherwise indicated
PS = Propensity Score

Consistency of External Controls vs Internal Controls



*Derived from fully independent EC datasets than primary analysis

Role of External Controls for SRP-9001 Clinical Data

- A well-designed, randomized, placebo-controlled trial is the gold standard, and will be provided by the fully enrolled confirmatory trial 301
- External controls require careful assessment of bias. In this case, multiple lines of evidence indicate bias is likely smaller than expected treatment effects
  - Independently published consistency in NSAA across multiple care settings and data sources
  - Demonstrated consistency between Study 102 placebo and two distinct external control analyses
- SRP-9001 pre-specified external controls pass key tests of reliability, and can add further weight to the evaluation of reasonable likelihood of predicted benefit

External Control Results

Craig M. McDonald, MD

Director, Neuromuscular Disease Clinic

University of California, Davis Children's Hospital

Study Chair, CINRG Duchenne Natural History Study

Primary Integrated External Control Analyses

Integrated Analysis
All patients who received 1.33 × 10^{14} vg/kg
N = 52

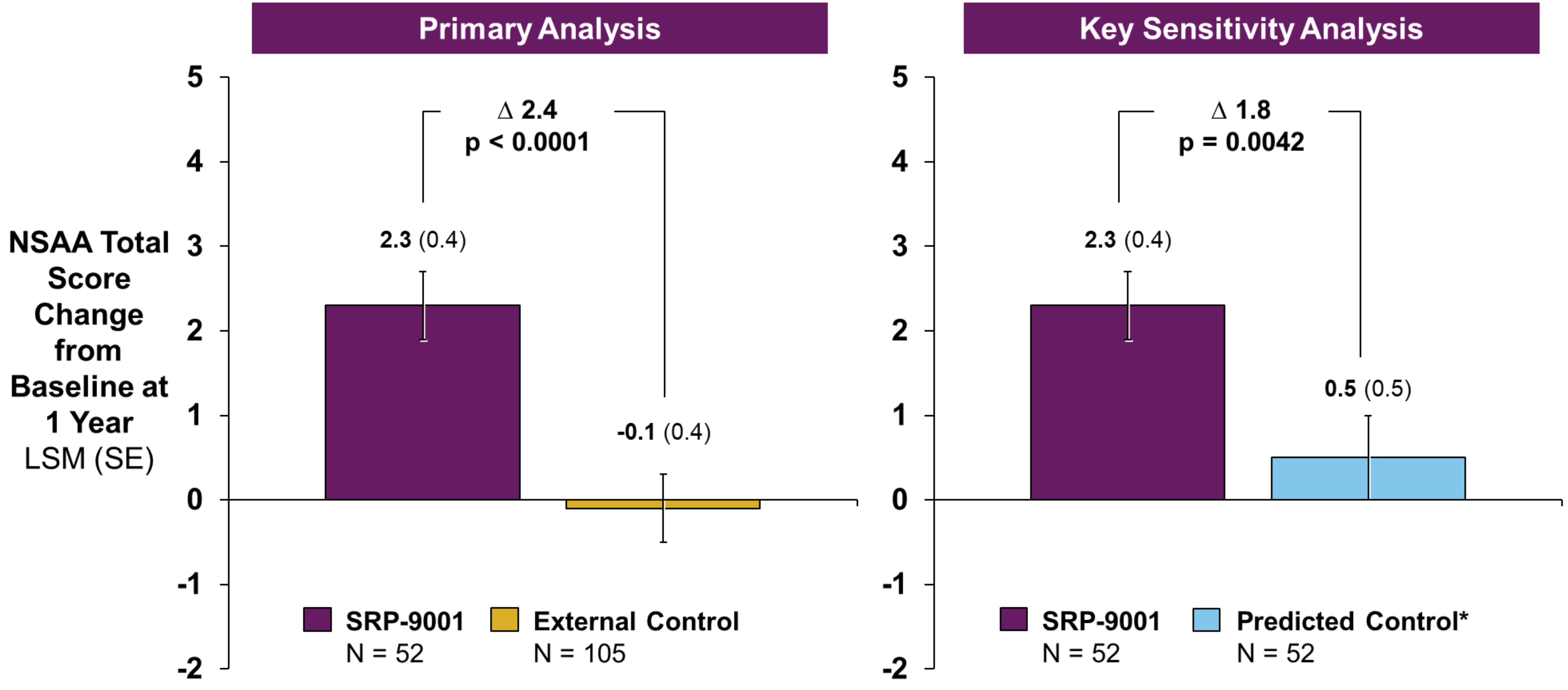
Study 103 Cohort 1
N = 20

Study 101
N = 4

Study 102
N = 28

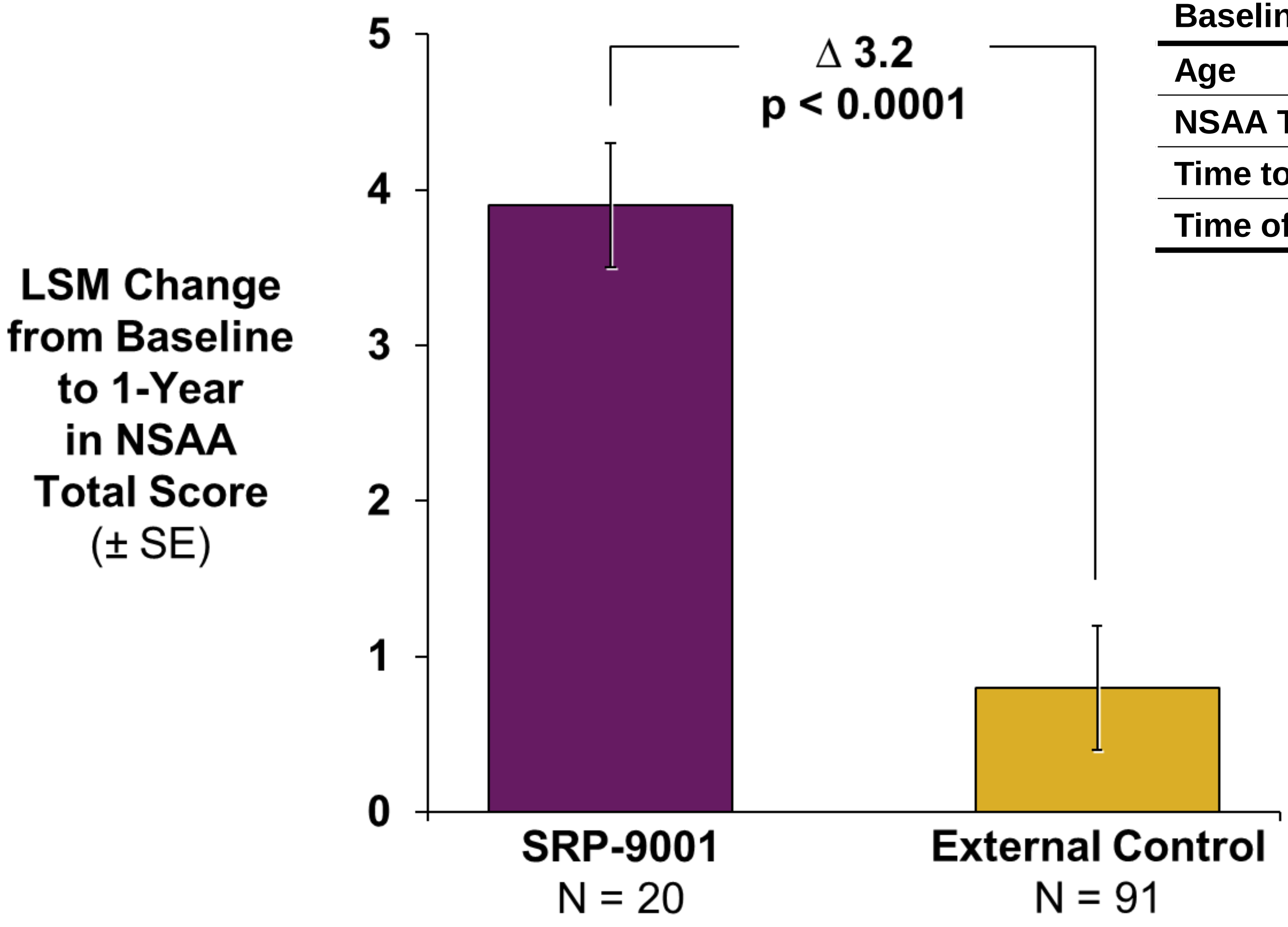
Excluded	**13**
Did not receive 1.33 × 10^{14} vg/kg based on retrospective titer methodology change	*12*
Incomplete NSAA data	*1*

Primary Integrated External Control Analysis: Treatment Effect Across Ages 4 – 8 Years



*Derived from fully independent EC datasets than primary analysis

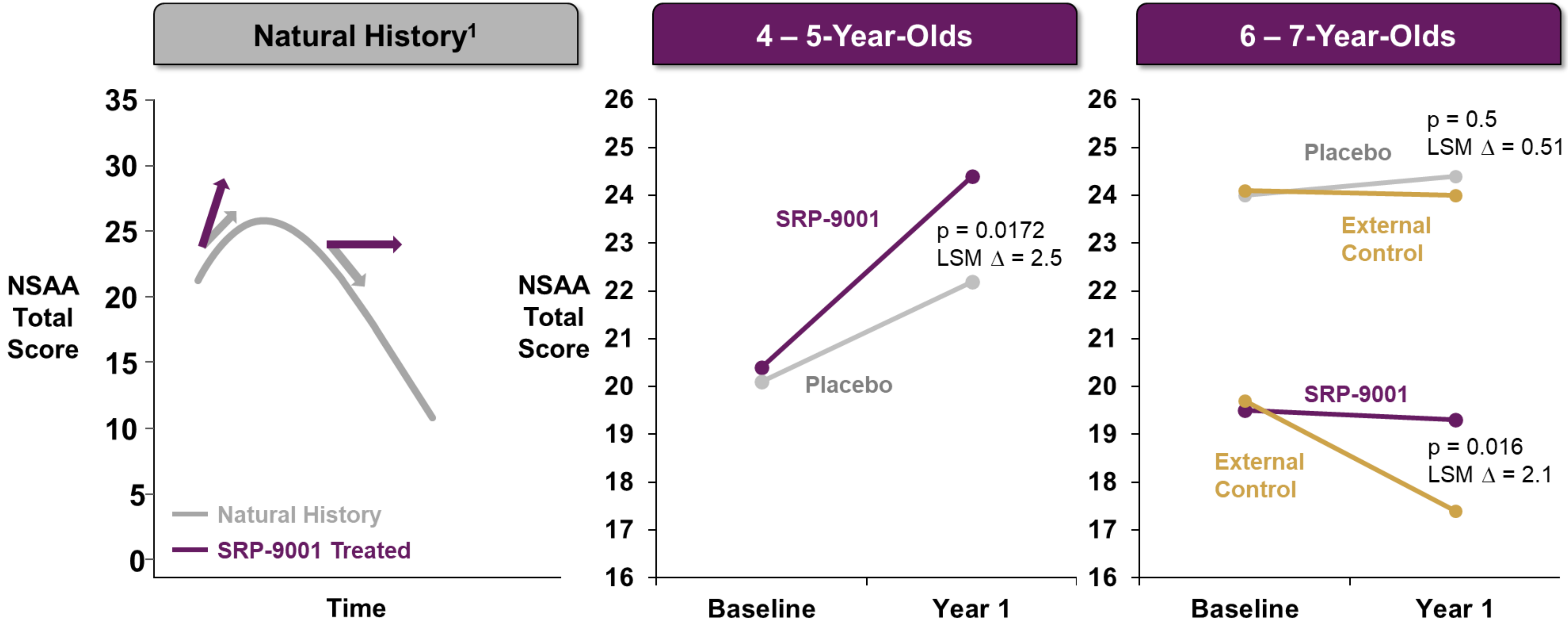
Study 103: Patients Have Greater Functional Gain vs External Controls



Baseline Mean	SRP-9001 N = 20	EC N = 91
Age	5.8	6.2
NSAA Total Score	22.1	21.9
Time to Rise	4.2	4.2
Time of 10MWR	5.1	5.1

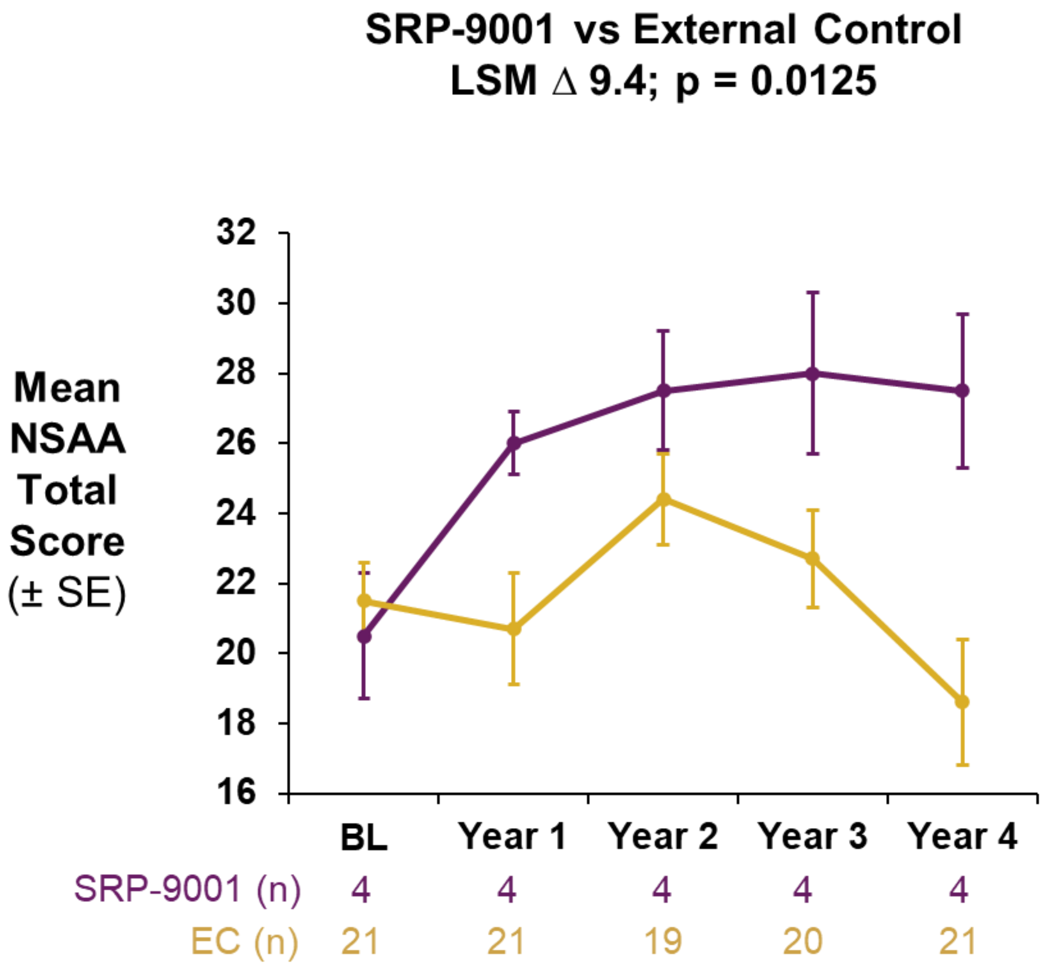
10MWR = 10 Meter Walk Run

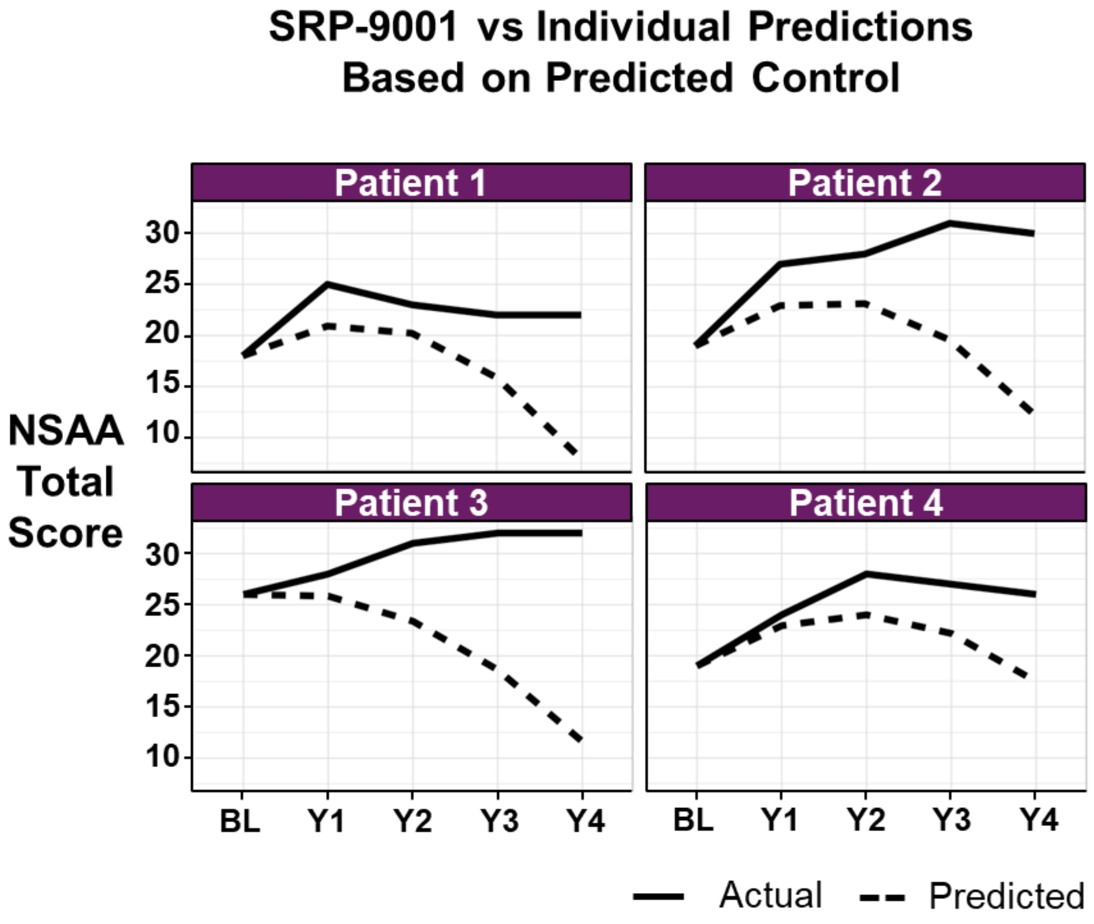
Study 102: Similar Treatment Effect Across Ages



1. Muntoni F et al. 2019

Study 101: NSAA Scores Over 4 Years vs External Controls



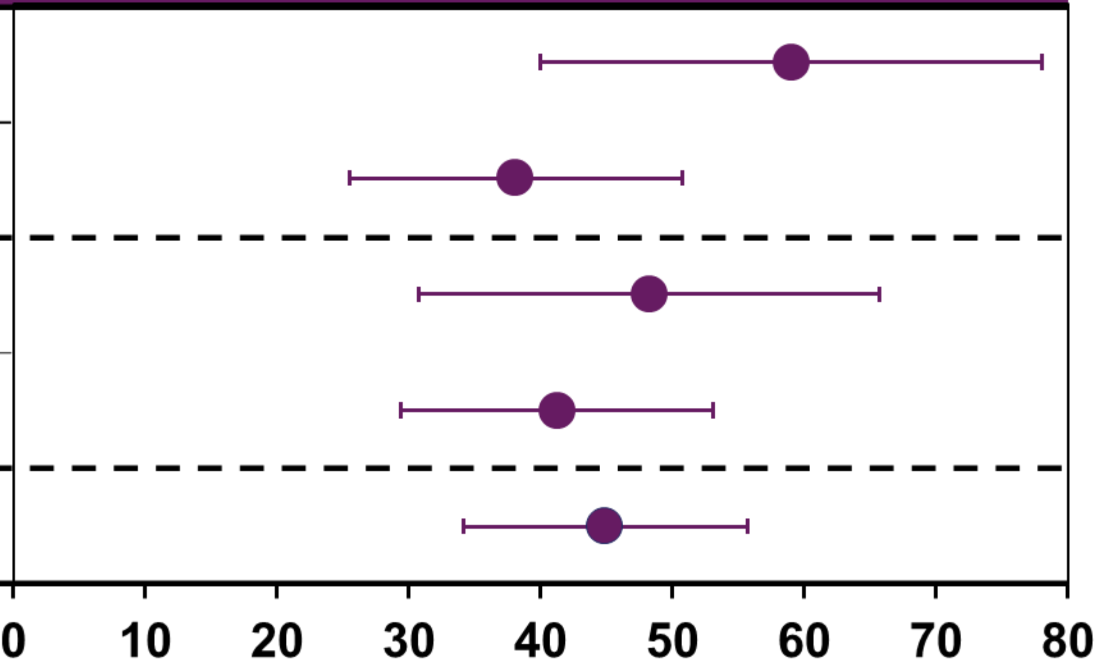


BL = Baseline; Y = Year

1. Muntoni F et al., 2019

Consistent Relationship of SRP-9001 Expression Seen Across Ambulatory DMD Patients

Subgroup, n	SRP-9001	Western Blot (Percent of Normal) Mean Change from Baseline (95% CI)
Age 4 to 5	16	
Age 6 to 8	33	
NSAA baseline ≤ 22	26	
NSAA baseline > 22	23	
1.33×10^{14} vg/kg*	49	

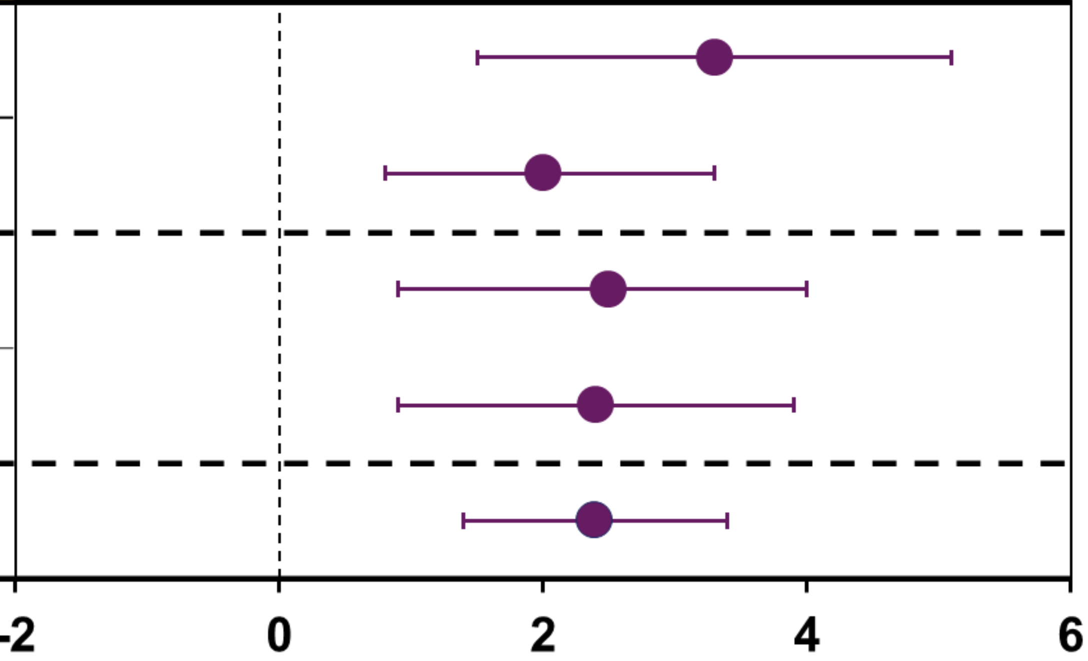


*Patients from Study 101 were not included as the western blot method differed

Data extraction date: Study 102: 31 January 2022; Study 103 and Integrated Summary: 09 February 2022

Consistent Relationship of SRP-9001 and Functional Gain Seen Across Ambulatory DMD Patients

Subgroup, n	SRP-9001	External Control	NSAA LSM Change Difference (95% CI)
Age 4 to 5	19	31	
Age 6 to 8	33	74	
NSAA baseline ≤ 22	28	47	
NSAA baseline > 22	24	58	
1.33×10^{14} vg/kg	52	105	



Consistent functional effect data further supports robust empirical evidence of surrogacy

Data extraction date: Study 102: 31 January 2022; Study 103 and Integrated Summary: 09 February 2022

Summary of Safety

Eddie Darton, MD, JD

Executive Medical Director, Safety Evaluation & Risk Management

Sarepta Therapeutics

Overview of Adverse Events (AEs)

- Safety database of 85 patients
  - 183 patient-years of exposure
  - Mean follow-up time of 2.2 years (min 0.5, max 4.8)
- 98.5% of all TEAEs were mild to moderate in severity
- 95% of patients first had TEAE within 90 days of SRP-9001 infusion
- AEs comparable across studies

	All Patients N = 85
Number of TEAEs	**1,230**
Mild, n (%)	759 (61.7%)
Moderate, n (%)	453 (36.8%)
Severe, n (%)	18 (1.5%)
Number of SAEs, n (%)	**13** (1.1%)
AEs Leading to Discontinuation	**0**
Deaths	**0**

SAE = serious adverse event; TEAE = treatment emergent adverse events
Data lock date of 17 October 2022 for Study 101, 01 April 2022 for Study 102 (Part 1 only), 03 October 2022 for Study 102 (all available data), and 19 September 2022 for Study 103

Most Frequent Adverse Reactions (Incidence ≥ 5%)

Preferred Term, n (%)	**All Patients** N = 85
Vomiting	**52** (61%)
Nausea	**34** (40%)
Liver function test increased[1]	**31** (37%)
Pyrexia	**20** (24%)
Thrombocytopenia	**10** (12%)

- Adverse reactions medically adjudicated based upon
  - Meeting frequency of ≥ 5% and ≥ 2 percentage points higher than placebo

  OR
  - Assessed as SAE and related by Investigator

1. Includes: AST increased, ALT increased, GGT increased, GLDH increased, hepatic enzyme increased, transaminases increased, blood bilirubin increased
Data lock date of 17 October 2022 for Study 101, 01 April 2022 for Study 102 (Part 1 only), 03 October 2022 for Study 102 (all available data), and 19 September 2022 for Study 103

Serious Treatment Emergent Adverse Events

	All Patients N = 85
Total SAEs	**13**
Patients with SAEs, n (%)	**11** (12.9%)
Preferred term events, n (%)	
Hypertransaminasaemia / Liver injury	**3** (3.5%)
Vomiting	**2** (2.4%)
Rhabdomyolysis	**2** (2.4%)
Immune-mediated myositis	**1** (1.2%)
Myocarditis	**1** (1.2%)
Femur fracture	**3** (3.5%)
Appendicitis	**1** (1.2%)

9 considered related to SRP-9001 by Investigator

Data lock date of 17 October 2022 for Study 101, 01 April 2022 for Study 102 (Part 1 only), 03 October 2022 for Study 102 (all available data), and 19 September 2022 for Study 103

Potential Risks Associated with AAV Gene Therapy

- Hepatotoxicity
- Immune-mediated myositis
- Myocarditis
- Complement activation
- Oncogenicity
- Antibody formation post-exposure potentially limiting future AAV dosing

Hepatotoxicity/Acute Liver Injury (ALI)

- Acute Liver Injury defined as:
  - GGT > 3 × ULN
  - GLDH > 2.5 × ULN
  - ALP > 2 × ULN
  - ALT > 3 × BL when BL is elevated

n (%)	All Patients N = 85
ALI patients	**31 (36.5%)**
GGT > 3 × ULN	15 (17.5%)
GLDH > 2.5 × ULN	22 (25.9%)
ALP > 2 × ULN	0
ALT > 3 × BL	14 (16.5%)
Total Bilirubin > 2 × ULN	3 (3.5%)

- Events observed 4 – 8 weeks post SRP-9001 infusion with no cases after 90 days
  - No acute liver failure
  - No elevation in INR
  - All recovered to baseline spontaneously or with corticosteroid treatment

- **Risk Mitigation:** Pre- and post-infusion monitoring of liver enzymes

GGT = gamma-gluatamyl transferase; GLDH = glutamate dehydrogenase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; BL = baseline; ULN = upper limit of normal; INR = international normalized ratio

Immune-Mediated Myositis

- 1 SAE in 9-year-old patient with exon 3 – 43 deletion mutation (Study 103 Cohort 2)
  - Presented with muscle weakness, dysphagia, dysphonia, difficulty sitting, and walking 4 weeks after SRP-9001 infusion
  - During hospitalization, treated with corticosteroids and plasmapheresis
    - Started on tacrolimus prior to discharge
    - Patient remains ambulatory with residual muscle weakness
    - 1-year cMRI showed normal cardiac function
- Suspected mechanism of action is an immune response to the transgene
  - Patient's mutation deletes a highly immunogenic region contained within the SRP-9001 transgene, leading to lack of self-tolerance to the transgene protein
  - Immunological investigations and clinical experience indicate patients with full deletions of exons 9 – 13 at highest risk
- **Risk Mitigation**: Proposed contraindication for patients with any deletion mutation that fully includes exons 9 – 13

cMRI = cardiac magnetic resonance imaging

Myocarditis

- 1 SAE* in 11-year-old patient, Study 103 Cohort 2
  - Patient initially hospitalized for management of vomiting during which troponin-I elevation detected
  - Transient chest pain with no ECG or echocardiogram changes
  - No acute cardiac dysfunction
  - Troponin-I returned to baseline
    - cMRI changes relative to exam one year prior to SRP-9001 infusion resulting in adjustment of pre-existing cardiac modifying therapy
- **Risk Mitigation:** Weekly troponin-I monitoring during first month following treatment

*Additional 1 in ongoing blinded Study 301

Complement Activation / Thrombocytopenia

- Clinically significant complement activation not observed during SRP-9001 development program
- Transient decreases in complement (C3 and C4)
  - Observed at Week 1 without any associated symptoms
  - No cases of thrombotic microangiopathy (TMA) or atypical hemolytic uremic syndrome (aHUS)
- Transient decreases in platelet counts
  - Within first 7 – 16 days
  - Lowest value 51,000 at Week 2 (baseline of 153,000; no clinical complication and returned to baseline without intervention)
- Both complement and platelet counts resolved spontaneously
- **Risk Mitigation:** Weekly platelet monitoring during first 2 weeks

Oncogenicity

- Theoretical risk with missing information
- No AEs observed
- **Risk Mitigation:** Long-term proposed studies with up to 10 years

SRP-9001 Safety Summary

- Well tolerated and favorable safety profile
- AEs monitorable and manageable with majority occurring within first 90 days after SRP-9001 infusion
- No deaths
- Proposed risk mitigations
  - Pre- and post-infusion monitoring of liver enzymes
  - Weekly troponin monitoring during first month following treatment
  - Weekly platelet monitoring during first 2 weeks
  - Proposed contraindication for patients with any deletion mutation that fully includes exons 9 – 13
  - Long-term follow-up to better characterize safety concerns

Clinical Perspective on Risk/Benefit Profile of SRP-9001

Craig M. McDonald, MD

Director, Neuromuscular Disease Clinic

University of California, Davis Children's Hospital

Study Chair, CINRG Duchenne Natural History Study

What Patients with DMD Need

- Effective, safe therapies which modify this devastating disease
- Treatment goal of stabilization supported by patient community[1]
- Modification of key milestones linked to quality and duration of life
- Maintain muscle function, including ambulation, and upper limb function
- Preserve respiratory function and cardiac function

1. Peay HL et al., 2019

SRP-9001 Has Favorable Safety Profile

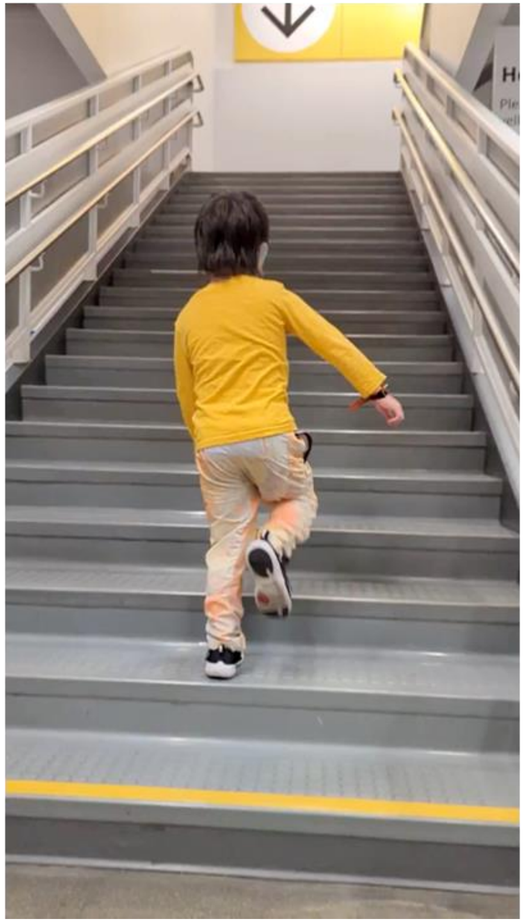
- Experienced, organized centers with sufficient infrastructure to administer SRP-9001
  - Neuromuscular disease centers based on experience with AAV gene therapy in spinal muscular atrophy
- Important risks have been identified
  - AEs monitorable and manageable
- Reassuring that no TMA or serious thrombocytopenia has occurred with SRP-9001
- Genetic inclusion criteria mitigates risk of immune-mediated myositis

TMA = Thrombotic microangiopathy

SRP-9001 Produces Clinically Meaningful Benefits to Patients with DMD and Their Families

Pre-treatment

6 months Post-Gene Transfer Therapy



Videos shown with patient consent

6 Months Post-SRP-9001 Gene Therapy in Same 6-Year-Old Boy

Videos shown with patient consent

Today Marks Important Opportunity to Advance Treatment for DMD Which Is Relentlessly Progressive

- ✓ **Surrogacy:** Sufficient evidence SRP-9001 dystrophin is surrogate endpoint reasonably likely to predict clinical benefit
- ✓ **Clinical Meaningfulness:** Totality of clinical evidence with appropriate clinical trial comparators sufficient to support accelerated approval
- ✓ **Positive Benefit-Risk:** Risks monitorable and manageable; magnitude of likely benefits outweighs risks
- ✓ **Confirmatory Study:** Fully enrolled; Part 1 report early 2024

Time is muscle

Waiting for confirmatory data guarantees irreparable loss of muscle

SRP-9001 (delandistrogene moxeparvovec) for Treatment of Duchenne Muscular Dystrophy

May 12, 2023

Cellular Tissue and Gene Therapy Advisory Committee

Sarepta Therapeutics