Patients can’t wait for the next breakthrough in medical research.

# So neither will we.

**DILLON**
Living with Duchenne muscular dystrophy

SAREPTA THERAPEUTICS

Fall 2025

# Forward-looking statements

This presentation contains "forward-looking statements." Any statements that are not statements of historical fact may be deemed to be forward-looking statements. Words such as “believe,” “anticipate,” “plan,” “expect,” “will,” “may,” “intend,” “prepare,” “look,” “potential,” “possible” and similar expressions are intended to identify forward-looking statements. These forward-looking statements include statements relating to our opportunities in the rare disease space; potential solutions and market opportunities with our technologies; financial projections and opportunities; the potential benefits of our manufacturing processes; the potential benefits of our collaborations and partnerships; the potential benefits of our technologies and scientific approaches, including those with our strategic partners and collaborations; the potential benefits of our products and product candidates; the estimated number of patients suffering from the diseases we aim to treat; current discussions with FDA related to our products and product candidates; and expected milestones and plans, including the timing of clinical data readouts for multiple of our programs in 2025 and 2026.

These forward-looking statements involve risks and uncertainties, many of which are beyond our control and are based on our current beliefs, expectations and assumptions regarding our business. Actual results and financial condition could materially differ from those stated or implied by these forward-looking statements as a result of such risks and uncertainties, and such risks and uncertainties could materially and adversely affect our business, results of operations and trading price. Potential known risk factors include, among others, the following: if there are significant delays in obtaining or we are unable to obtain or maintain required regulatory approvals, we will not be able to commercialize our product candidates in a timely manner or at all, which could impair our ability to generate sufficient revenue and have a successful business; our products or product candidates may be perceived as insufficiently effective, unsafe or may result in unforeseen adverse events; our products or product candidates have and may cause undesirable side effects that result in significant negative consequences following any marketing approval; our data for our different programs may not be sufficient for obtaining regulatory approval; we may not be able to comply with all FDA post-approval commitments and requirements with respect to our products in a timely manner or at all; our product candidates, including those with strategic partners, may not result in viable treatments suitable for commercialization due to a variety of reasons, including the results of future research may not be consistent with past positive results or may fail to meet regulatory approval requirements for the safety and efficacy of product candidates; success in preclinical testing and early clinical trials, especially if based on a small patient sample, does not ensure that later clinical trials will be successful; the expected benefits and opportunities related to our agreements with our strategic partners may not be realized or may take longer to realize than expected due to a variety of reasons, including any inability of the parties to perform their commitments and obligations under the agreements, challenges and uncertainties inherent in product research and development and manufacturing limitations; if the actual number of patients living with the diseases we aim to treat is smaller than estimated, our revenue and ability to achieve profitability may be adversely affected; our dependence on our manufacturers to fulfill our needs for our clinical trials and commercial supply, including any failure on our part to accurately anticipate product demand and timely secure manufacturing capacity to meet product demand, may impair the availability of products to successfully support various programs, including research and development and the potential commercialization of our gene therapy product candidates; we may not be able to successfully scale up manufacturing of our product candidates in sufficient quality and quantity or within sufficient timelines; current reimbursement models may not accommodate the unique factors of our gene therapy product candidates; we may not be able to execute on our business plans and goals, including meeting our expected or planned regulatory milestones and timelines, clinical development plans, and bringing our product candidates to market, for various reasons including possible limitations of our financial and other resources, manufacturing limitations that may not be anticipated or resolved for in a timely manner, regulatory, court or agency decisions, such as decisions by the United States Patent and Trademark Office; and those risks identified under the heading “Risk Factors” in Sarepta’s most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) and in its other SEC filings.

For a detailed description of risks and uncertainties Sarepta faces, you are encouraged to review Sarepta's filings with the SEC. We caution investors not to place considerable reliance on the forward-looking statements contained in this presentation. The forward-looking statements in this presentation are made as of the date of this presentation only and, other than as required under applicable law, Sarepta does not undertake any obligation to publicly update its forward-looking statements.

**~10,000** rare diseases

**80%+** are single gene mutations

And only a few hundred rare diseases currently have treatments

https://ncats.nih.gov/trnd/projects/gene-therapy Accessed June 2023.

**Sarepta Therapeutics, Inc.** (Nasdaq: SRPT) is a biopharmaceutical company that discovers, develops and commercializes medicines intended to treat ***rare, genetic-based diseases.***

**DARREN**
Living with Duchenne muscular dystrophy

# Company profile

**3** technology platforms

- siRNA
- RNA
- Gene Therapy

**3** RNA-based therapies on market[1]

for certain patients with Duchenne

EXONDYS 51 (eteplirsen) Injection

VYONDYS 53 (golodirsen) Injection

AMONDYS 45 (casimersen) Injection

**1st** gene therapy FDA approved to treat Duchenne[2]

Elevidys delandistrogene moxeparvovec-rokl suspension for intravenous infusion

## Advancing Pipeline

### siRNA

- Facioscapulohumerol muscular dystrophy (FSHD)
- Myotonic Dystrophy Type 1 (DM1)
- Spinocerebellar Ataxia Type 2 (SCA2)
- Huntington's Disease
- Spinocerebellar Ataxia Type 1 (SCA1)
- Spinocerebellar Ataxia Type 3 (SCA3)
- Idiopathic pulmonary fibrosis (IPF)

up to **6** DISCOVERY TARGETS[3]

### GENE THERAPY

- LGMD Type 2E

**MAIN OFFICES:**

**Company Headquarters:** Cambridge, MA

**Research & Manufacturing:** Andover, MA; Bedford, MA

**Genetic Therapies Center of Excellence (GTCOE):** Columbus, OH

1 Candidates received accelerated approval in the U.S., confirmatory studies required.
2 Approved to treat individuals with Duchenne muscular dystrophy with a confirmed mutation in the DMD gene who are at least 4 years of age via FDA's traditional approval pathway for ambulatory patients; accelerated approval granted by FDA for non-ambulatory patients. Continued approval for non-ambulatory Duchenne patients may be contingent upon verification of clinical benefit in a confirmatory trial. ELEVIDYS is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the DMD gene.
3 In accordance with Sarepta's agreement with Arrowhead Pharmaceuticals announced November 2024.

**LOUISE RODINO-KLAPAC, Ph.D.**
*President, R&D and Technical Operations*

**GARY CHARBONNEAU**
*Chief Quality Officer*
*and Enterprise Services*

# GENETIC THERAPIES CENTER OF EXCELLENCE (GTCOE)

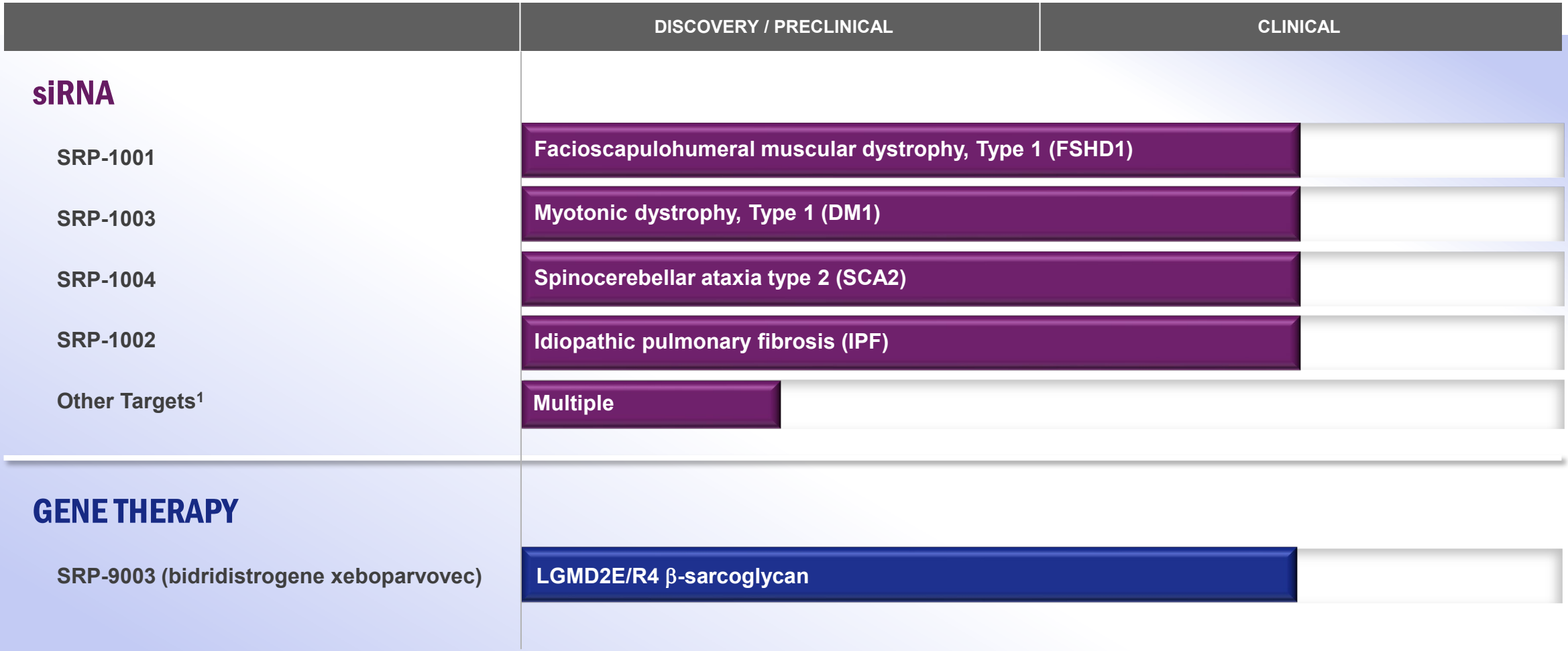
## COLUMBUS, OH

### Discovery, Preclinical Pharmacology and Safety Research
Identify target diseases/genes, and assess viability for clinical development

### Translational & Clinical Development
Develop and run critical clinical assays for immunogenicity, efficacy, safety

### Process & Analytical Development
Optimize and produce preclinical test article material and drive early-stage analytical development activities

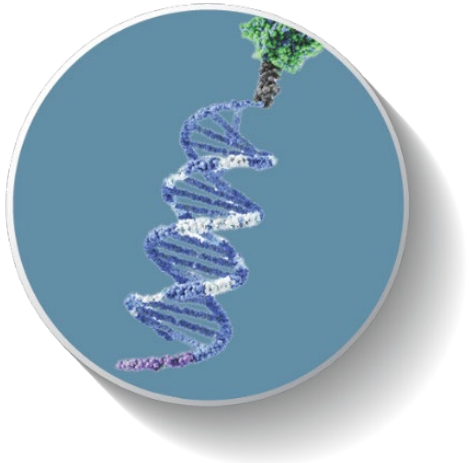
# Advancing pipeline




1. Other siRNA indications include Huntington's Disease, SCA1 and SCA3.

Updated August 2025

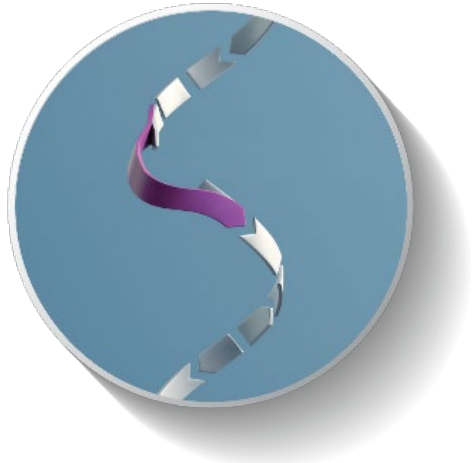
# Three distinct, proprietary scientific platforms



## siRNA

**Knockdown**

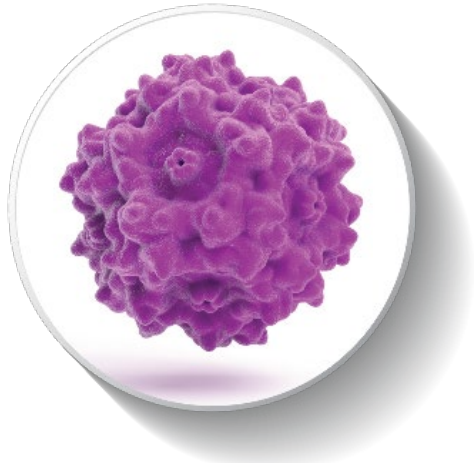
Suppresses overexpression of mutations



## RNA

**Skipping**

Bypasses an error in the RNA, allowing the body to skip the mutation



## GENE THERAPY

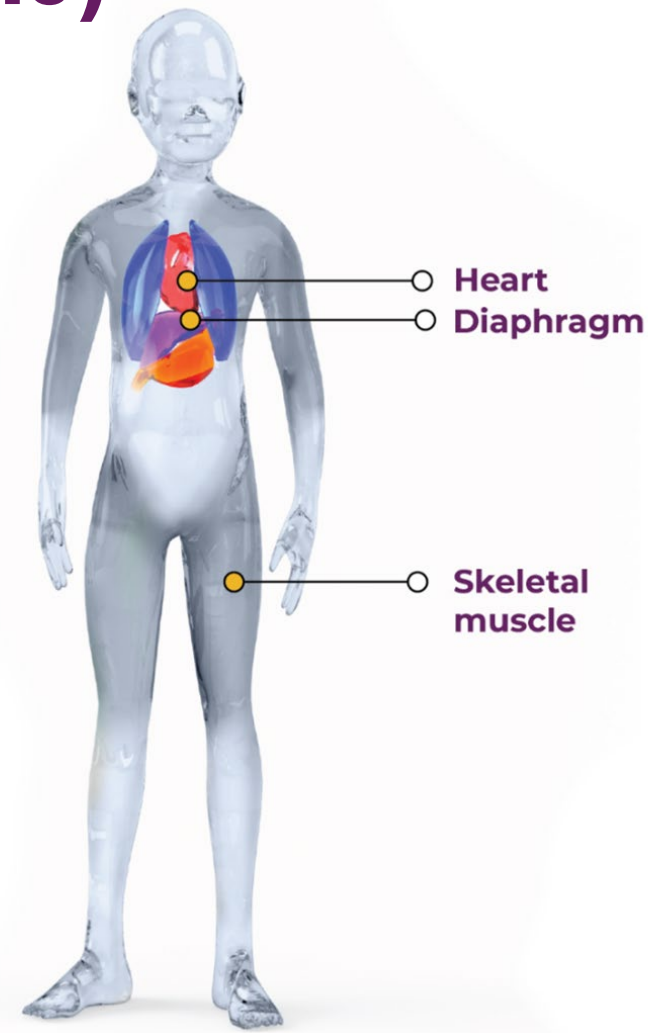
**Replacement**

Adds a functional copy (a transgene) of a missing or malfunctioning gene

# Duchenne muscular dystrophy (Duchenne)

## Duchenne affects approximately 1 in 3,500 - 5,000 newborn males worldwide[1]

- Duchenne is a rare, fatal neuromuscular genetic disease inherited in an X-linked recessive pattern[2]
- Muscle weakness becomes increasingly noticeable by 3 to 5 years of age, and most patients use a wheelchair by the time they are 10 to 14 years old[2]
- During adolescence, cardiac and respiratory muscle deterioration lead to serious, life-threatening complications[3]





1. National Institutes of Health. Genetics Home Reference. Duchenne and Becker muscular dystrophy; https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular- dystrophy. Accessed Jan 2020.
2. McDonald CM, Abresch RT, Duong T, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet*. 2018;3(391):451-461.
3. Passamano L, Taglia A, et al. Improvement of survival in Duchenne Muscular Dystrophy: retrospective analysis of 835 patients. *Acta Myologica*. 2012;31(1): 121-125.

# Disease progression in Duchenne[1-3]

## 5 TO 7 YEARS

- Motor delay
- Enlarged calves
- Toe walking
- Standing from supine, climbing stairs more difficult

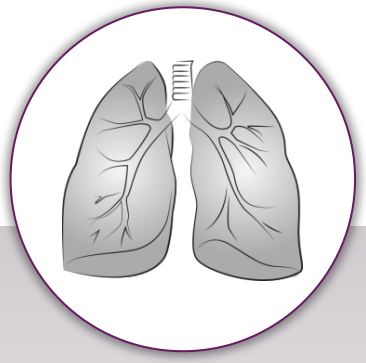
## 8 TO 11 YEARS

- Increasing loss of walking ability
- Part-time wheelchair use

## EARLY TEENS

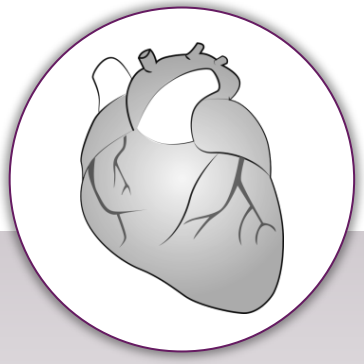
- Loss of ambulation
- Full-time wheelchair use
- Increasing loss of upper limb function

## TEENS



- Increasing respiratory impairment
- Ventilatory support often required
- Unable to perform activities of daily living

## TEENS TO TWENTIES



- Increasing cardiac dysfunction
- Heart failure
- Death

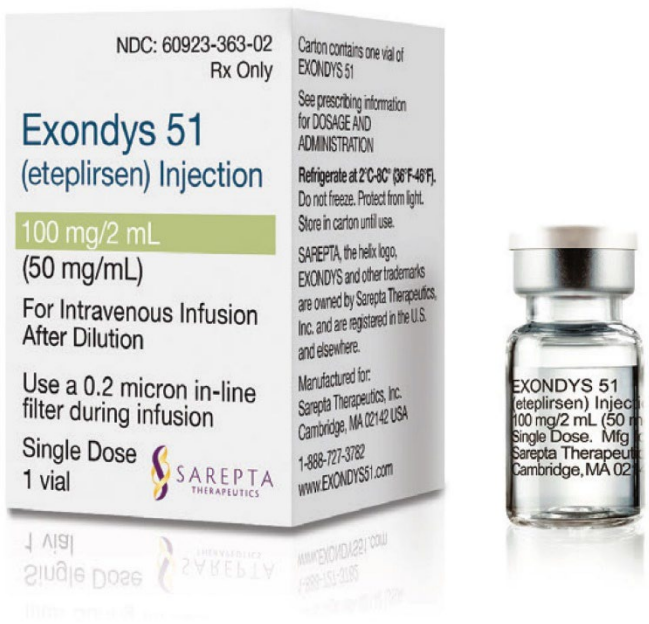
EARLY AMBULATORY | LATE AMBULATORY | EARLY NON-AMBULATORY | LATE NON-AMBULATORY


1. Bushby K, Finkel R, Birnkrant DJ, et al. *Lancet Neurol.* 2010;9:77-93.
2. Emery AEH. *Lancet*. 2002;359:687-695.
3. Landfeldt E, Lindgren P, Bell CF, et al. *Neurology*. 2014;83(6):529-536.


**PATIENTS LIVING WITH DUCHENNE TODAY*: 250,000 – 300,000 globally**

* Estimated global prevalence.

# Serving approximately 30% of the Duchenne community with RNA-based therapies

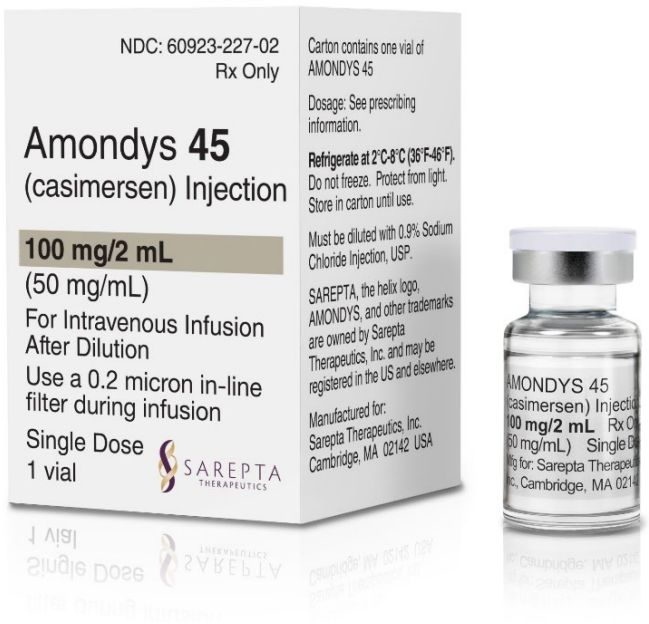



## September 2016

Approved to treat patients with a confirmed genetic mutation that is amenable to exon 51 skipping (13% of Duchenne population)*


## December 2019

Approved to treat patients with a confirmed genetic mutation that is amenable to exon 53 skipping (8% of Duchenne population)*




## February 2021

Approved to treat patients with a confirmed genetic mutation that is amenable to exon 45 skipping (8% of Duchenne population)*

*Candidate received accelerated approval in the U.S., confirmatory studies required.

# First and only gene therapy FDA approved to treat Duchenne*

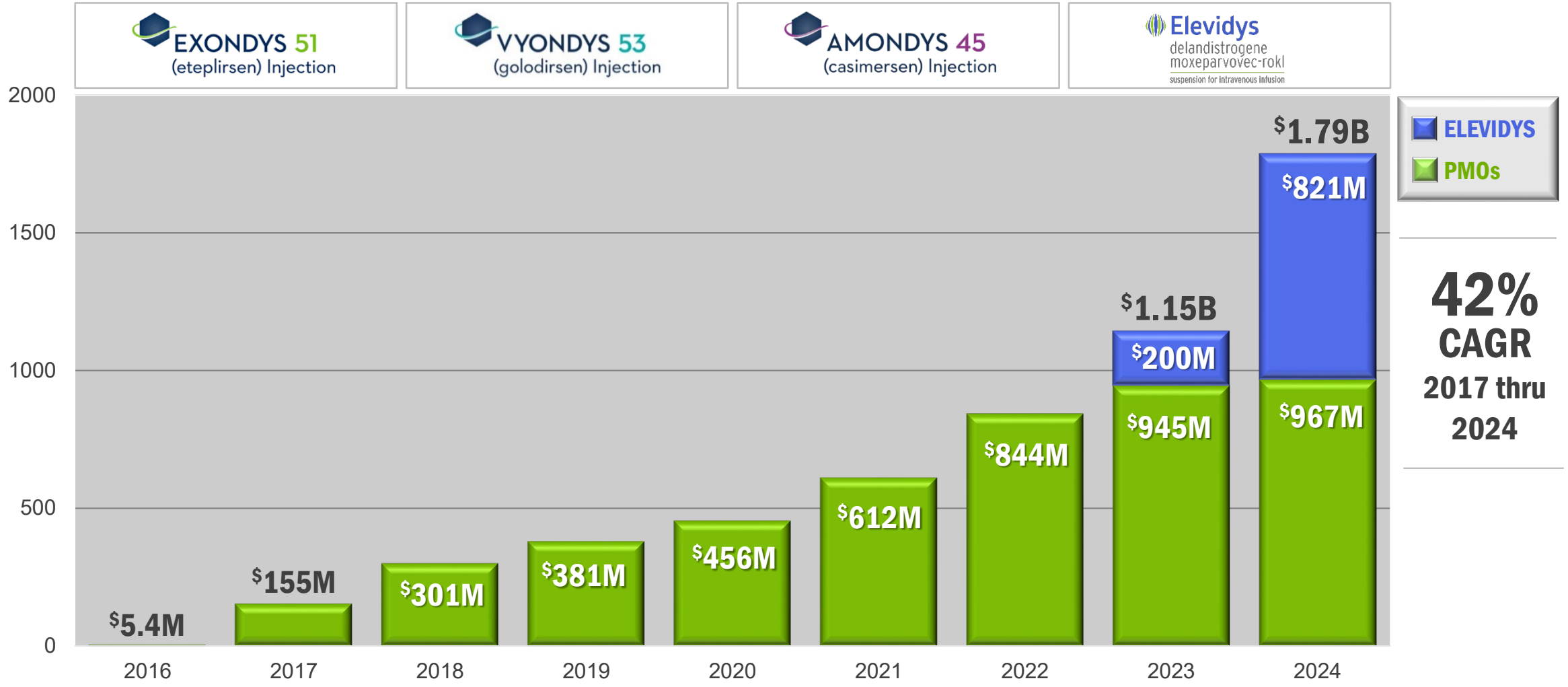
Elevidys

delandistrogene moxeparvovec-rokl

suspension for intravenous infusion


*Approved to treat individuals with Duchenne muscular dystrophy with a confirmed mutation in the *DMD* gene who are at least 4 years of age via FDA's traditional approval pathway for ambulatory patients; accelerated approval granted by FDA for non-ambulatory patients. Continued approval for non-ambulatory Duchenne patients may be contingent upon verification of clinical benefit in a confirmatory trial. ELEVIDYS is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.

# Through strong commercial execution we have delivered net product revenue at 42% CAGR since 2017



SAREPTA THERAPEUTICS

# EMBARK

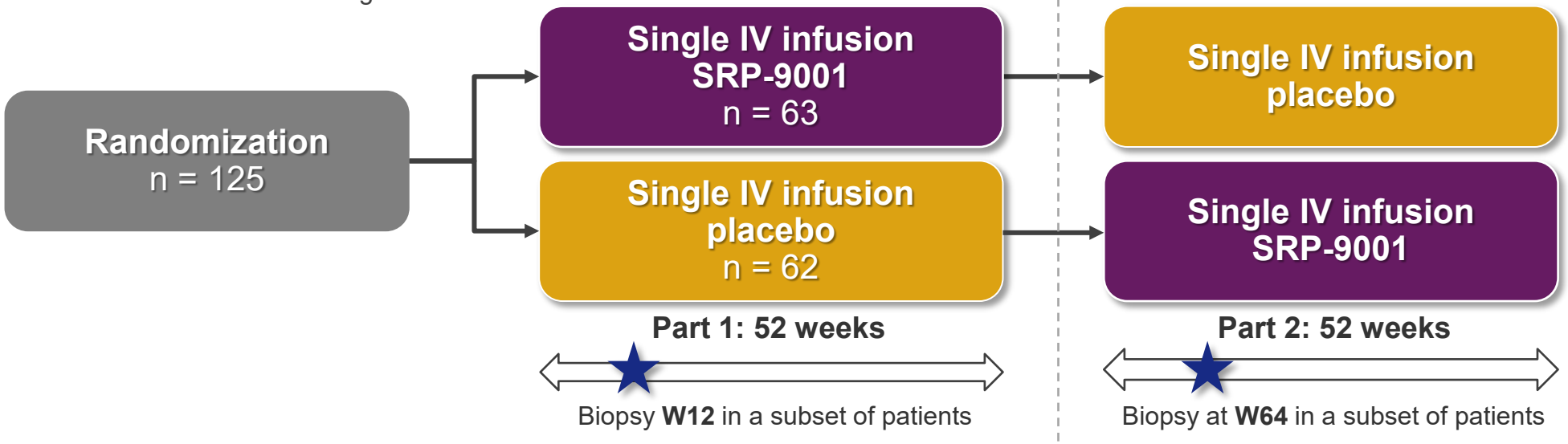
## SRP-9001-301 Part 2 Results

# EMBARK (Study SRP-9001-301) study design

Phase 3, multinational, double-blind, randomized, placebo-controlled study evaluating the safety and efficacy of ELEVIDYS (delandistrogene moxeparvovec), in boys with DMD aged 4–7 years old

**Key functional inclusion criteria**:

- NSAA score 17-28 (inclusive) at Screening
- Time to Rise < 5 sec at Screening




**Primary endpoint**:

- Change in North Star Ambulatory Assessment (NSAA) total score from Baseline to Week 52

**Key Secondary endpoints**:

- Quantity of SRP-9001 dystrophin protein expression, as measured by WB, at Week 12
- Change in time to rise (TTR) from floor from Baseline to Week 52
- Change in 10-meter timed test (10MTT) from Baseline to Week 52

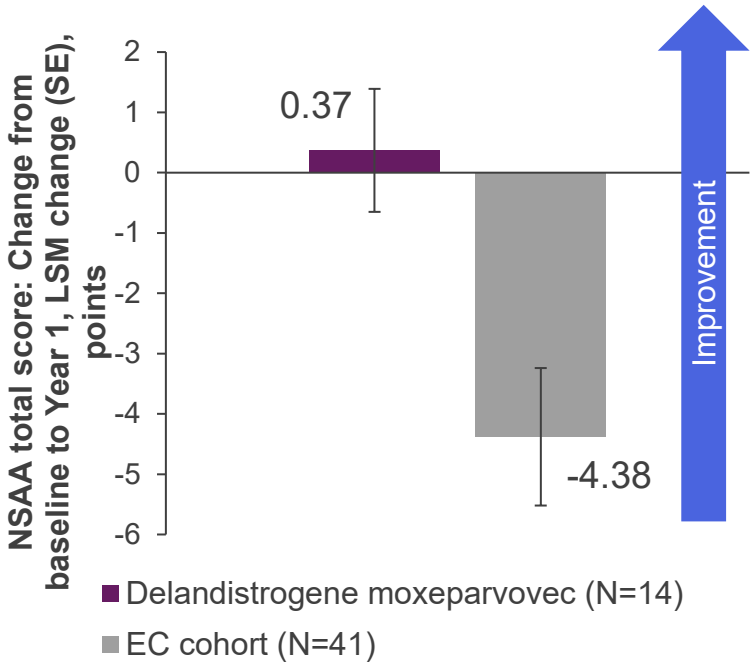
**Other timed secondary endpoints:**

- Stride Velocity 95th Centile (SV95C)
- 100-meter walk/run
- Ascend 4 Steps

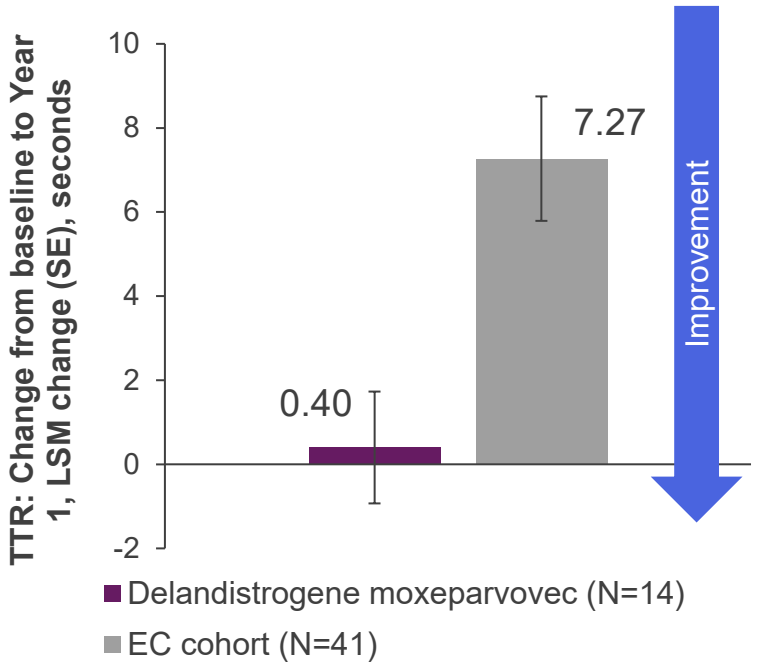
# One-year Follow-up: Functional outcomes of patients treated at ≥8 years of age

At one-year post-gene therapy, patients treated at ≥8 years of age demonstrated **statistically significant and clinically meaningful functional benefit** versus a propensity-score-weighted EC cohort

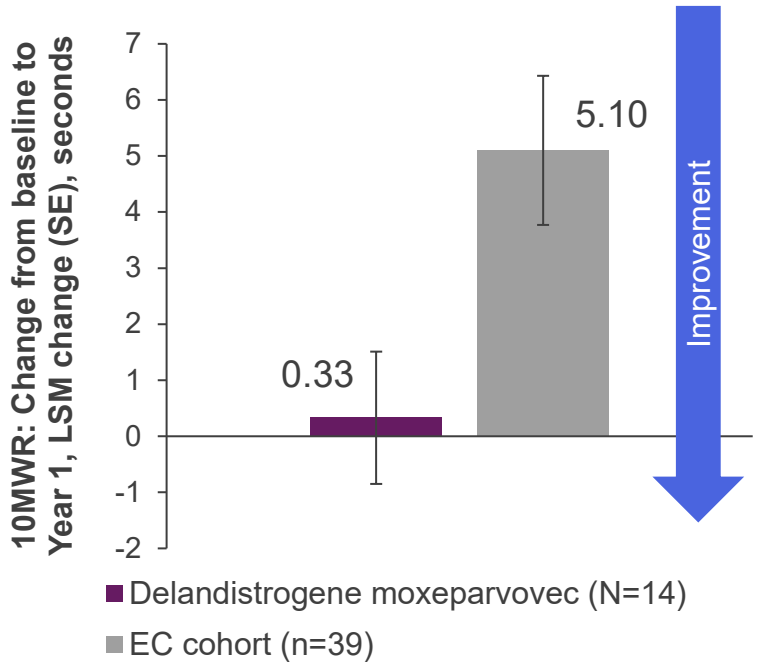
**NSAA Δ 4.75 points; *P*=0.0026**




**TTR Δ –6.87 s; *P*=0.0010**

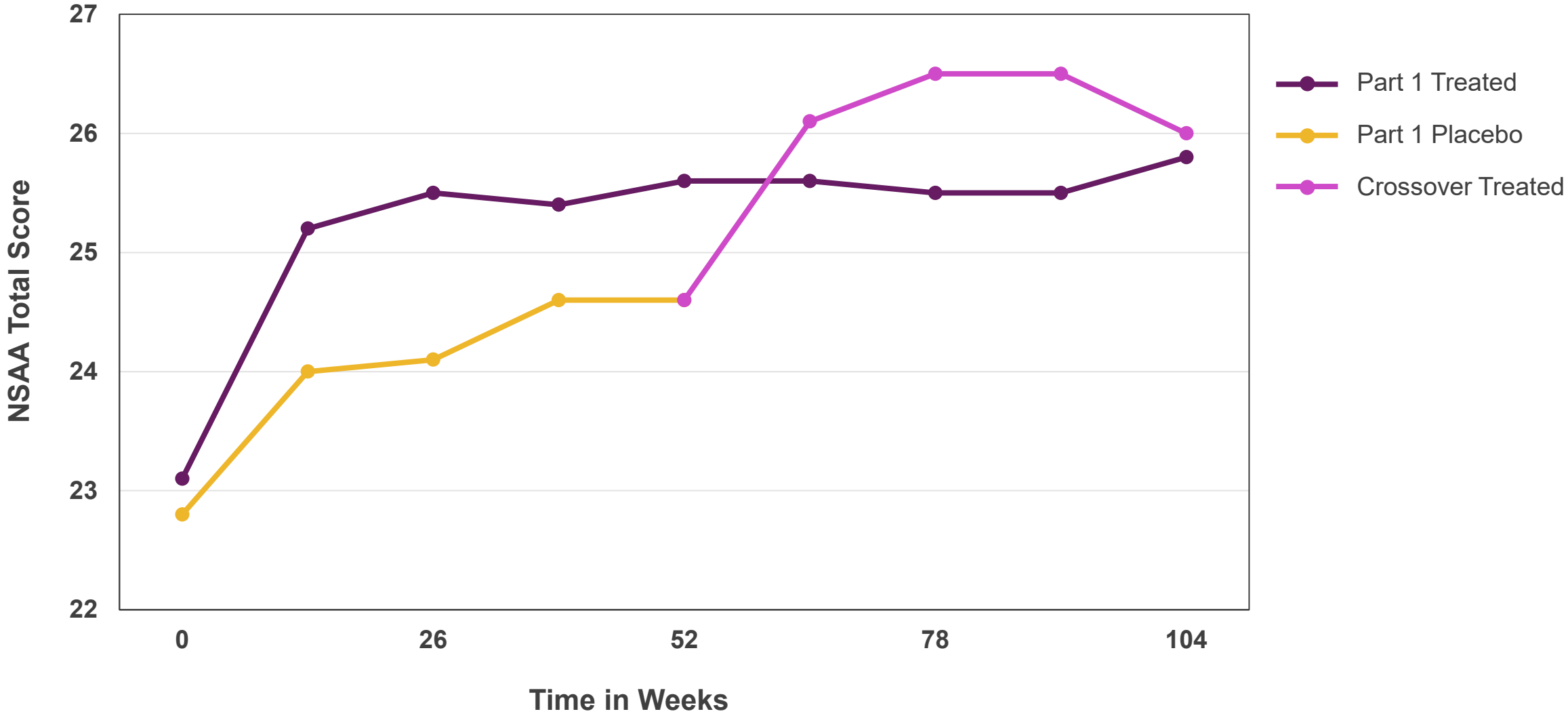



**10MWR Δ –4.76 s; *P*=0.0097**



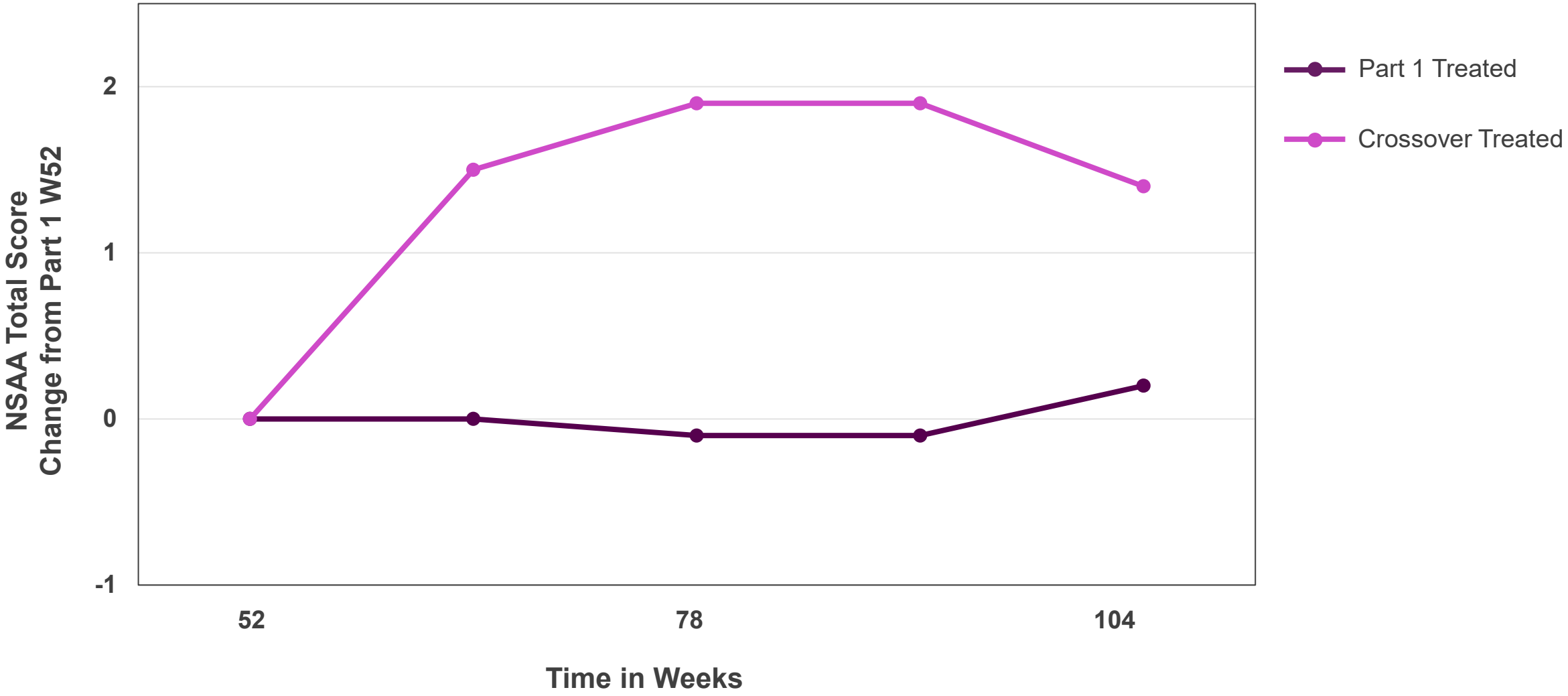

All *P*-values reported are nominal and have not been adjusted for multiple comparisons.
10MWR, 10-meter Walk/Run; EC, external control; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error; TTR, Time to Rise.

# EMBARK NSAA* Total Score: Baseline to Year 2, blinded study results

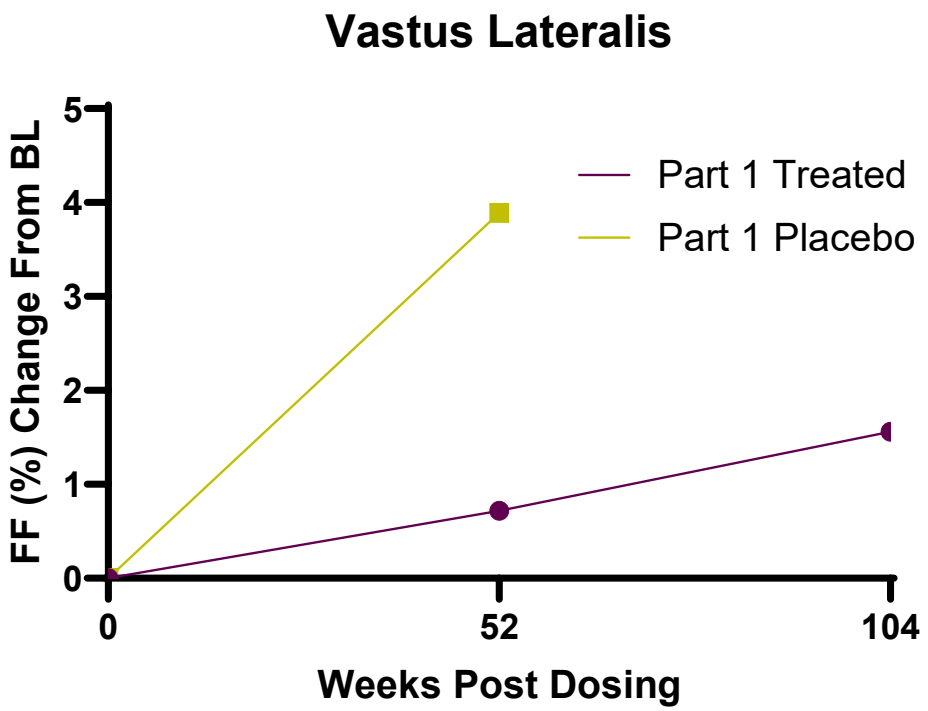


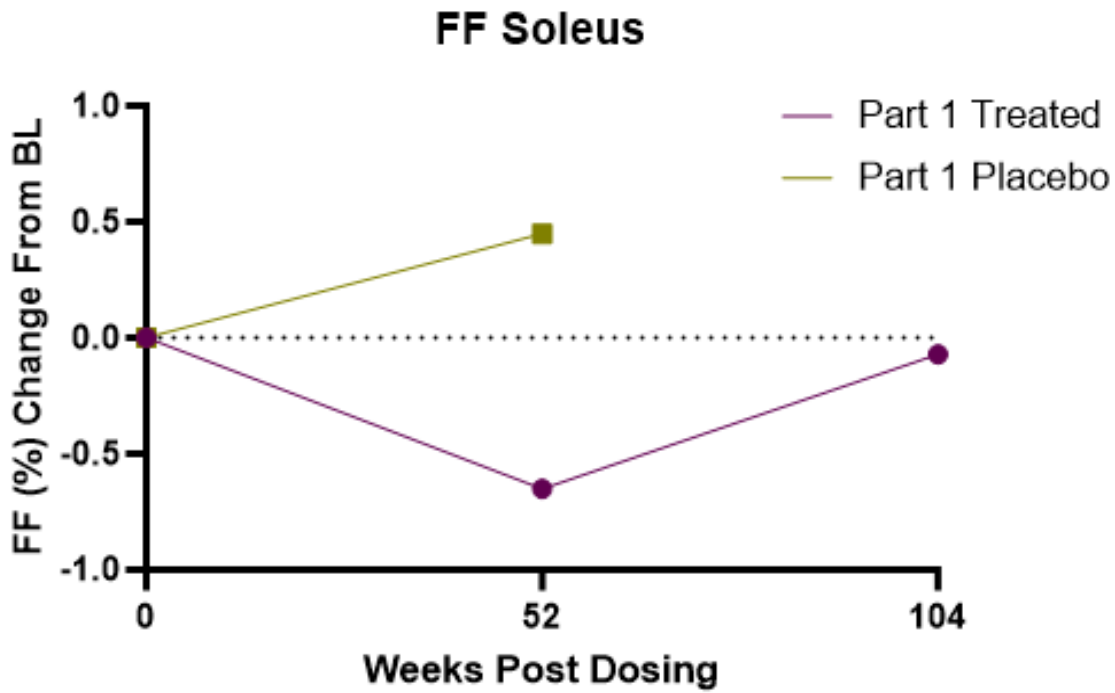

*North Star Ambulatory Assessment

# NSAA increases in crossover treated patients following ELEVIDYS dosing



# 2 Year Results: Musculoskelatal MRI - Fat Fraction



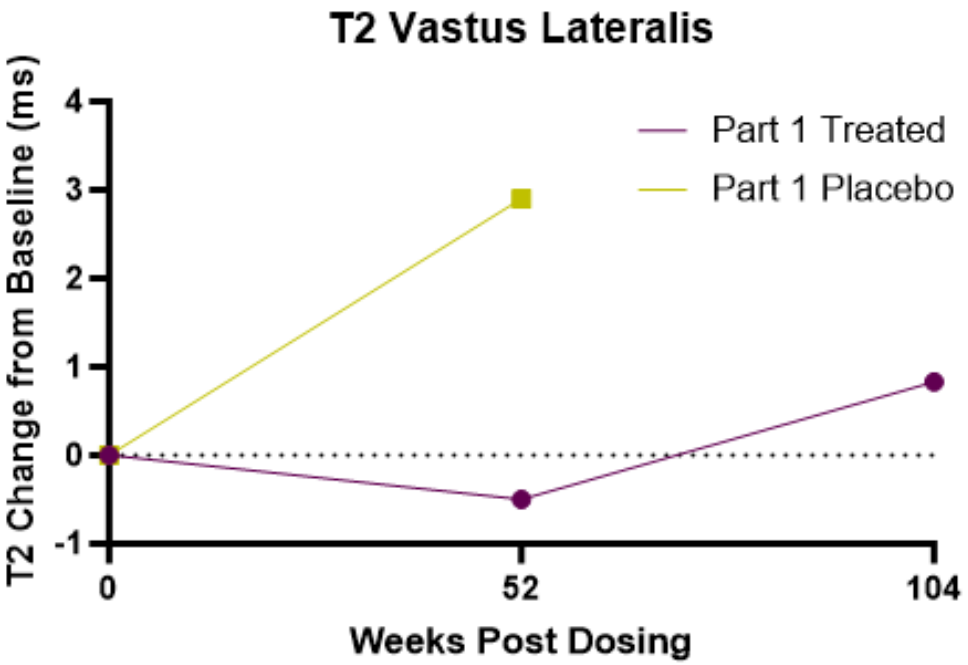

| | | | |
|---|---|---|---|
| Placebo | N=16 | N=14 | |
| Treated | N=15 | N=14 | N=14 |

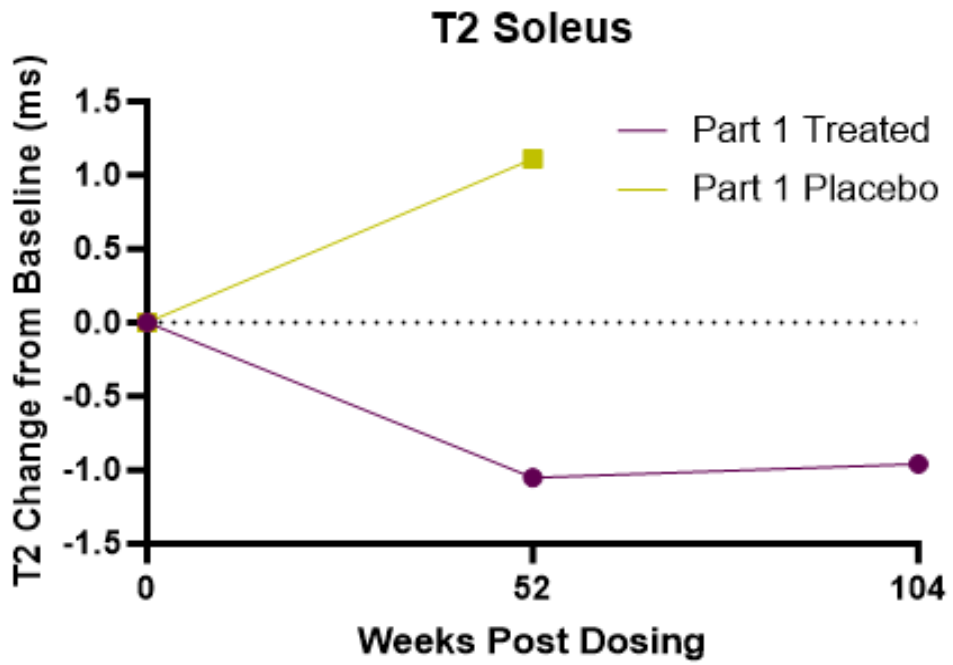
| | | |
|---|---|---|
| N=17 | N=15 | |
| N=16 | N=16 | N=15 |

**Stabilization in MRI muscle FF in 9001 treatment group with two years values below those seen in part 1 placebo group**


1. Naarding KJ, Reyngoudt H, van Zwet EW, etal. MRI vastus lateralis fat fraction predicts loss of ambulation in Duchenne muscular dystrophy. Neurology. 2020 Mar 31;94(13):e1386-e1394.
2. Barnard AM, Willcocks RJ, Triplett WT, etal. MR biomarkers predict clinical function in Duchenne muscular dystrophy. Neurology. 2020 Mar 3;94(9):e897-e909.
3. Willcocks RJ, Rooney WD, Triplett WT, etal. Multicenter prospective longitudinal study of magnetic resonance biomarkers in a large duchenne muscular dystrophy cohort. Ann Neurol. 2016 Apr;79(4):535-47. doi: 10.1002/ana.24599. Epub 2016 Feb 19. PMID: 26891991; PMCID: PMC4955760.

# 2 Year Results: Musculoskeletal MRI - T2




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | N=18 | | N=15 | | N=17 | N=15 | |
| Treated | N=13 | | N=12 | N=12 | N=15 | N=15 | N=14 |

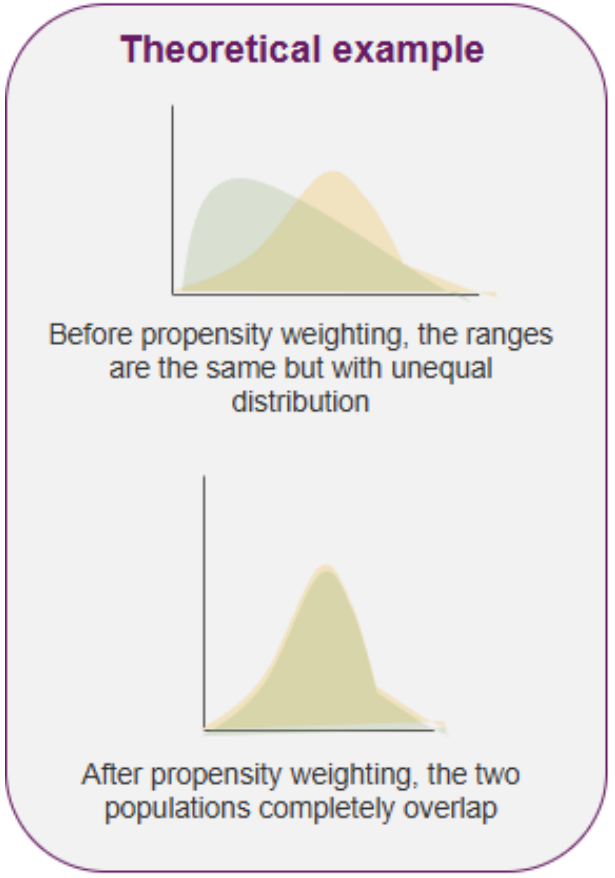
**Stable muscle T2 in most muscle groups over 2 years with lower T2 2 years after Elevidys treatment than at 1 year in placebo cohort**


1. Naarding KJ, Reyngoudt H, van Zwet EW, etal. MRI vastus lateralis fat fraction predicts loss of ambulation in Duchenne muscular dystrophy. Neurology. 2020 Mar 31;94(13):e1386-e1394.
2. Barnard AM, Willcocks RJ, Triplett WT, etal. MR biomarkers predict clinical function in Duchenne muscular dystrophy. Neurology. 2020 Mar 3;94(9):e897-e909.
3. Willcocks RJ, Rooney WD, Triplett WT, etal. Multicenter prospective longitudinal study of magnetic resonance biomarkers in a large duchenne muscular dystrophy cohort. Ann Neurol. 2016 Apr;79(4):535-47. doi: 10.1002/ana.24599. Epub 2016 Feb 19. PMID: 26891991; PMCID: PMC4955760.

# EMBARK Part 2 Results: Crossover-treated patients compared to external control, 1 year data

# EMBARK statistical analysis plan and external control

- In the absence of a placebo arm after Part 1, the EMBARK study protocol and statistical analysis plan (SAP) are used to create a pre-specified, propensity-weighted external control to contextualize study level results
- External control cohorts chosen through pre-specified selection criteria and pre-specified data sources:
  - Eli Lilly Tadalafil placebo
  - DEMAND-III placebo arm
  - PRO-DMD
  - CINRG DNHS
  - FOR-DMD
- Propensity score weighting is used to decrease bias
- Protocols agreed to by regulatory authorities prior to the start of the study



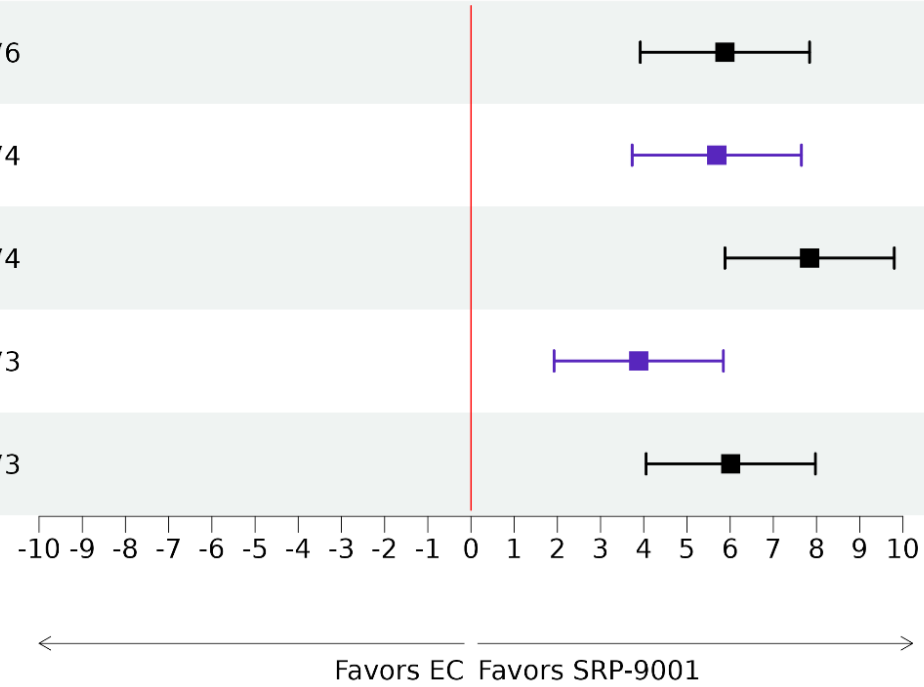
# Balanced baseline characteristics for crossover-treated patients and external control (EC)

**Baseline Characteristics (Weighted)**
**Full Analysis Set**

| Baseline | SRP-9001 (n=59)<br>Mean (Min, Max) | External Control (n=276)<br>Mean (Min, Max) |
|---|---|---|
| **Age** | 7.11 (5.07, 9.07) | 7.07 (5.05, 9.98) |
| **NSAA** | 25.0 (12, 34) | 25.0 (12, 34) |
| **Time to Rise from Floor** | 4.01 (2.00, 11.75) | 3.94 (1.60, 10.60) |
| **10M Walk/Run Time** | 5.01 (3.30, 10.90) | 4.99 (2.70, 10.20) |
| **Weight** | 25.52 (14.9, 49.9) | 24.45 (14.7, 42.4) |
| **Height** | 114.36 (97.7, 131.0) | 113.85 (94.9, 142.0) |
| **BMI** | 19.17 (13.98, 35.54) | 18.61 (13.74, 25.88) |

# Statistically significant and clinically meaningful improvements in functional outcomes one year after treatment compared to EC

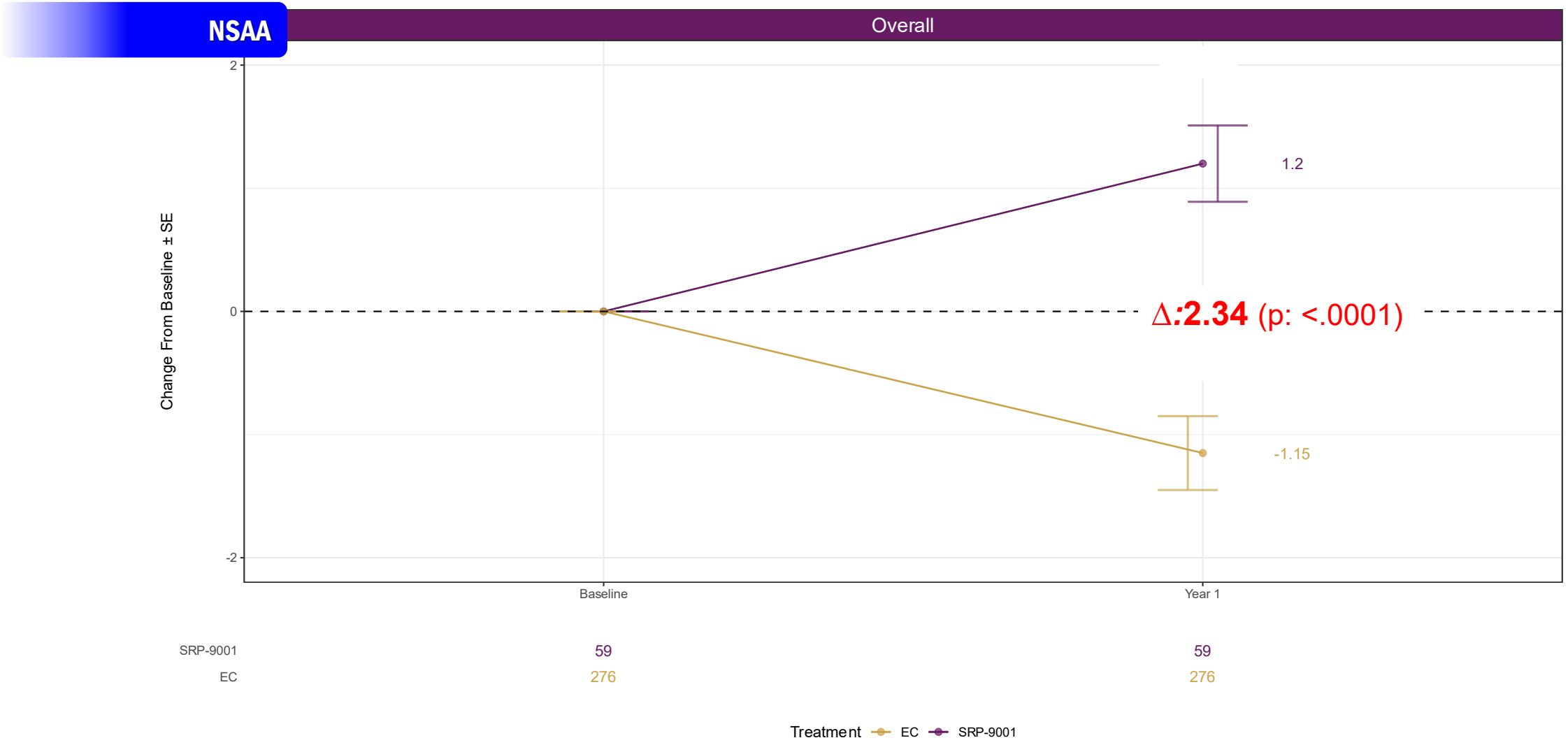
| Endpoint | SRP-9001 | EC | LSMean Diff (95% CI) | P-value |
|---|---|---|---|---|
| NSAA | 59 | 276 | 2.34 (1.56, 3.12) | <.0001 |
| TTR* | 59 | 274 | -2.7 (-3.63, -1.77) | <.0001 |
| TTR velocity | 59 | 274 | 0.068 (0.051, 0.085) | <.0001 |
| 10MWR time* | 59 | 273 | -1.07 (-1.61, -0.53) | 0.0001 |
| 10MWR velocity | 59 | 273 | 0.224 (0.151, 0.297) | <.0001 |



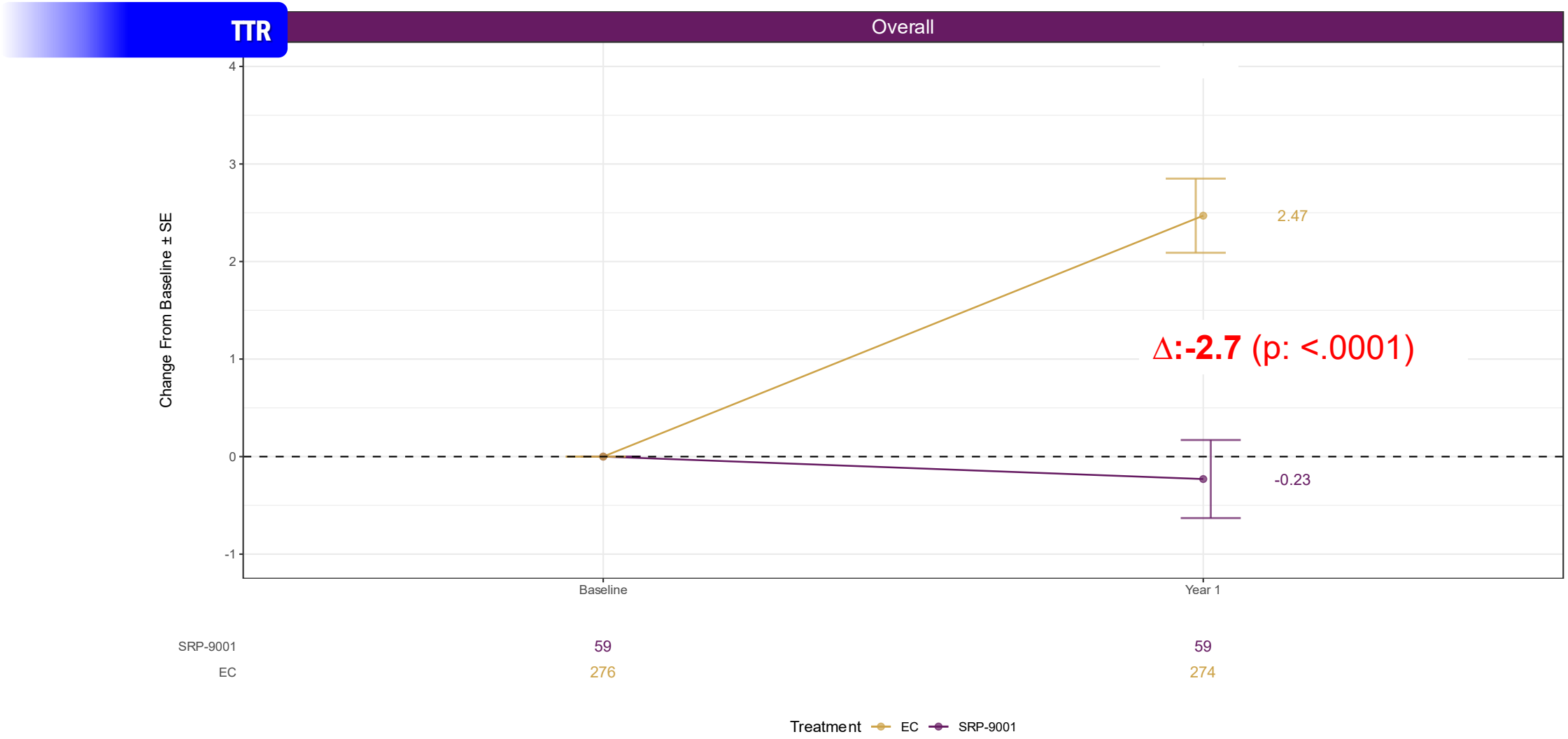

** Sign reversed to align favorable directions among effect endpoints*

Diff in Means (of change from baseline) and confidence intervals are standardized by dividing by the standard error (SE). The half width of the forest plot bars will be 1.96. Numerical results of the Diff in Means are on original scale (without SE adjustment) along with P-values (unadjusted nominal). RFFT and TMWRT signs are reversed in forest plot to align favorable directions among endpoints. Numerical results of Diff in Mean kept original sign.

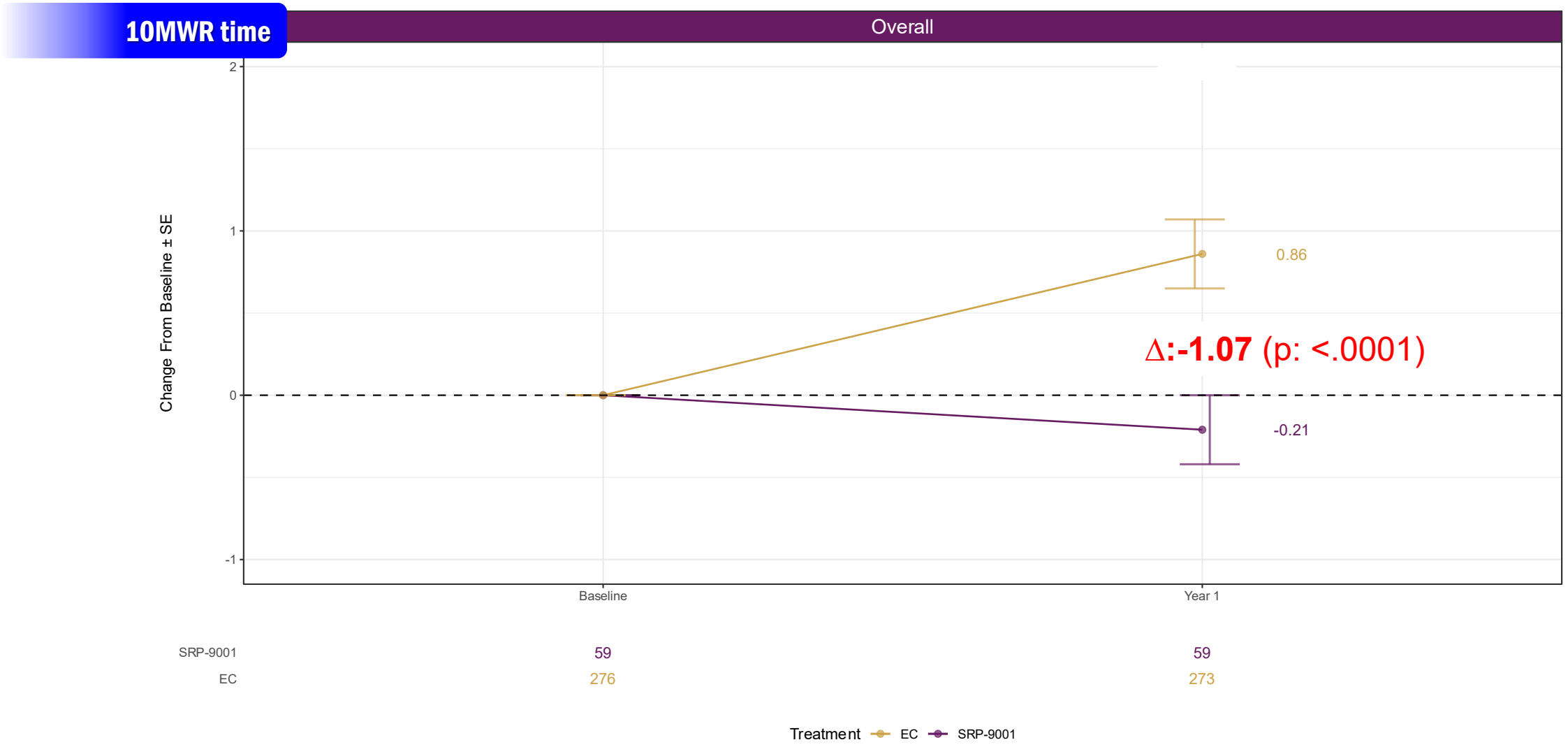
# Statistically significant increase in NSAA one year after treatment compared to EC



# Statistically significant improvements in time-to-rise from floor one year after treatment compared to EC



# Statistically significant improvement in 10m walk/run times one year after treatment compared to EC



# EMBARK Part 2 Results: Year 2 expression and functional outcomes in Part-1 treated patients

# Expression is consistent and sustained from week 12 to week 64

| Western Blot | Part 1 SRP-treated | |
|---|---|---|
| | **Week-12**<br>n = 17 | **Week-64**<br>n = 16 |
| Mean (SD) | **34.29 (41.04)** | **45.68 (39.75)** |

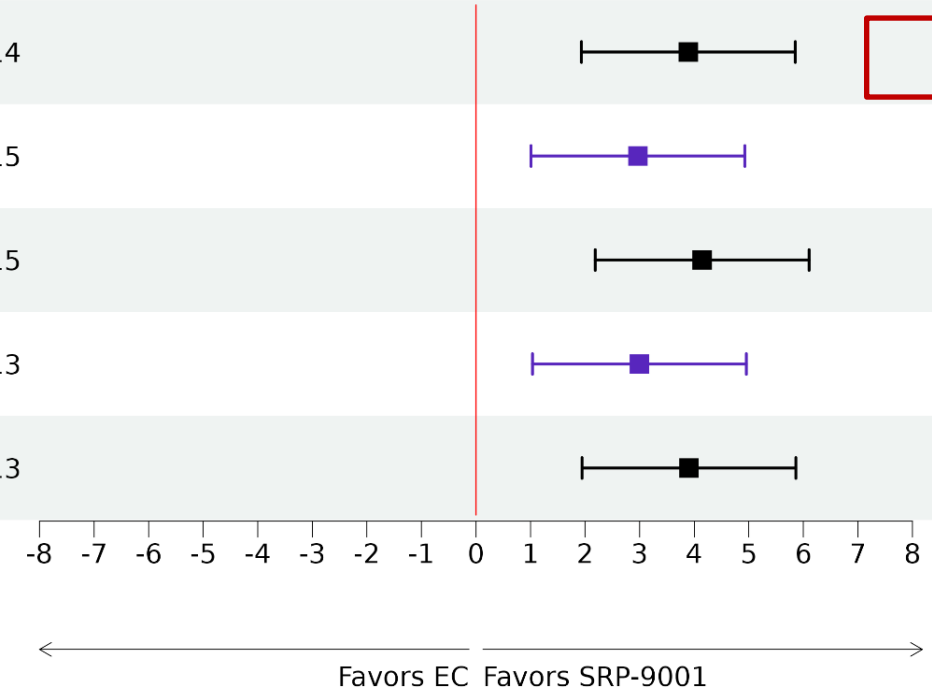
# Balanced baseline characteristics for Part 1 treated and EC

**Baseline Characteristics (Weighted)**
**Full Analysis Set**

| Baseline | SRP-9001 (n=64)<br>Mean (Min, Max) | External Control (n=143)<br>Mean (Min, Max) |
|---|---|---|
| **Age** | 5.98 (4.07, 7.87) | 6.24 (4.24, 7.99) |
| **NSAA** | 23.3 (14, 32) | 23.5 (15, 32) |
| **Time to Rise from Floor** | 3.51 (1.85, 5.75) | 3.52 (1.90, 5.70) |
| **10M Walk/Run Time** | 4.80 (3.20, 6.85) | 4.78 (3.00, 6.70) |
| **Weight** | 21.20 (13.5, 37.4) | 22.18 (14.0, 36.0) |
| **Height** | 108.65 (93.5, 127.0) | 110.60 (94.9, 131.1) |
| **BMI** | 17.80 (13.69, 24.92) | 17.90 (13.74, 23.64) |

# Statistically significant and clinically meaningful differences after treatment at Year 2 compared to EC

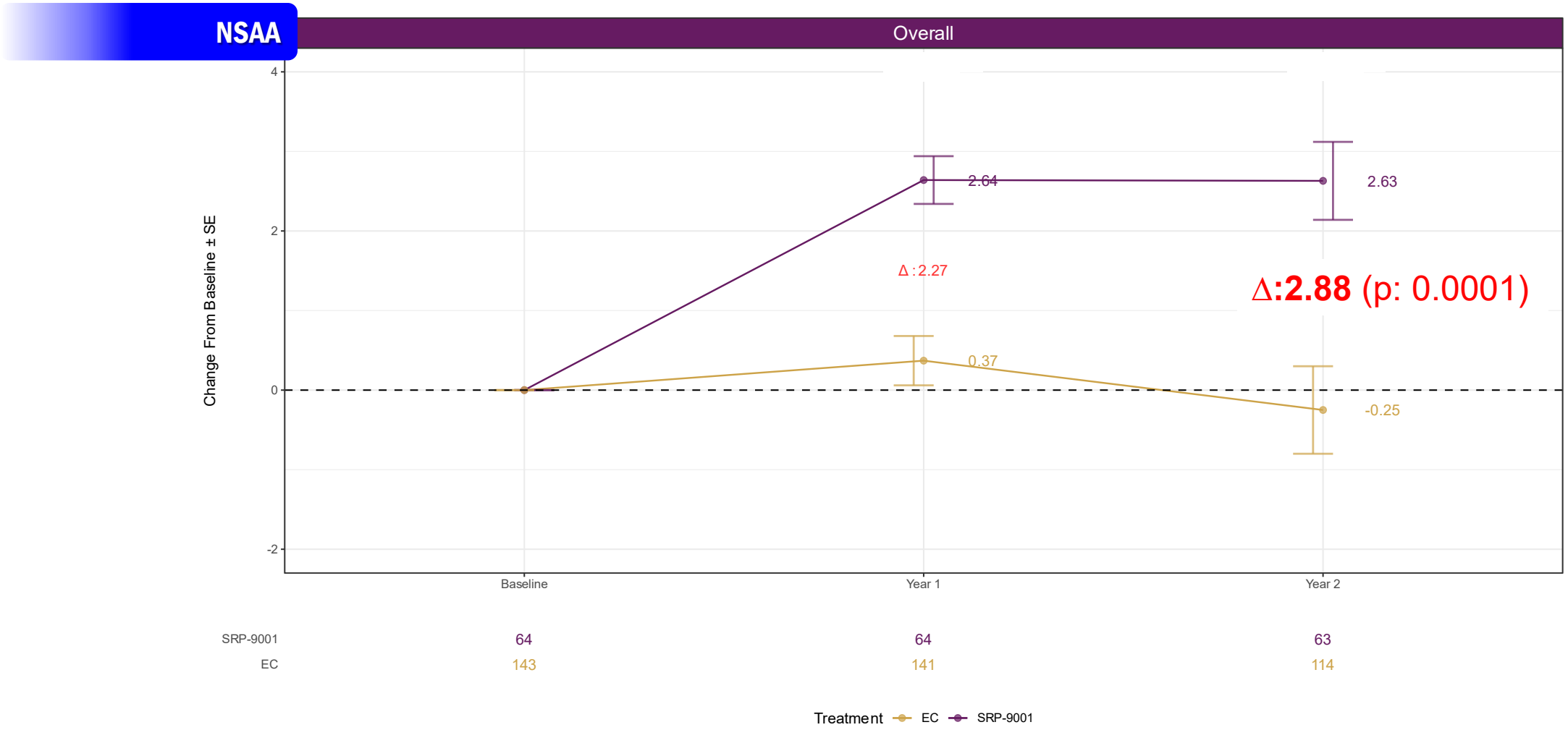
| Endpoint | SRP-9001 | EC | LSMean Diff (95% CI) | P-value |
|---|---|---|---|---|
| NSAA | 63 | 114 | 2.88 (1.43, 4.33) | 0.0001 |
| TTR* | 63 | 115 | -2.06 (-3.43, -0.7) | 0.0033 |
| TTR velocity | 63 | 115 | 0.055 (0.03, 0.081) | <.0001 |
| 10MWR time* | 63 | 113 | -1.36 (-2.24, -0.47) | 0.0028 |
| 10MWR velocity | 63 | 113 | 0.239 (0.118, 0.359) | 0.0001 |



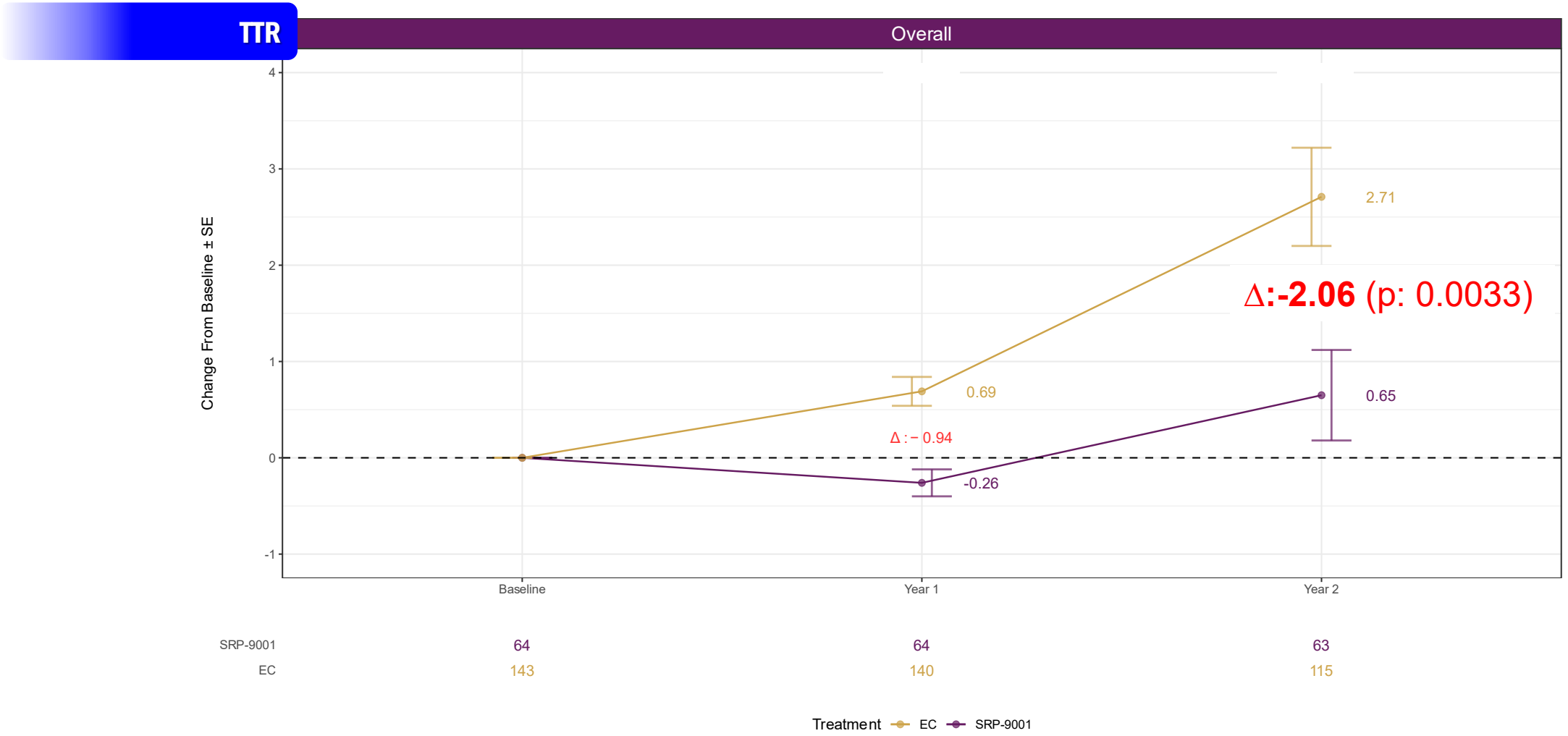

** Sign reversed to align favorable directions among effect endpoints*

Diff in Means (of change from baseline) and confidence intervals are standardized by dividing by the standard error (SE). The half width of the forest plot bars will be 1.96. Numerical results of the Diff in Means are on original scale (without SE adjustment) along with P-values (unadjusted nominal). RFFT and TMWRT signs are reversed in forest plot to align favorable directions among endpoints. Numerical results of Diff in Mean kept original sign.

# NSAA improvements were sustained two years after treatment, showing a widening divergence from natural history

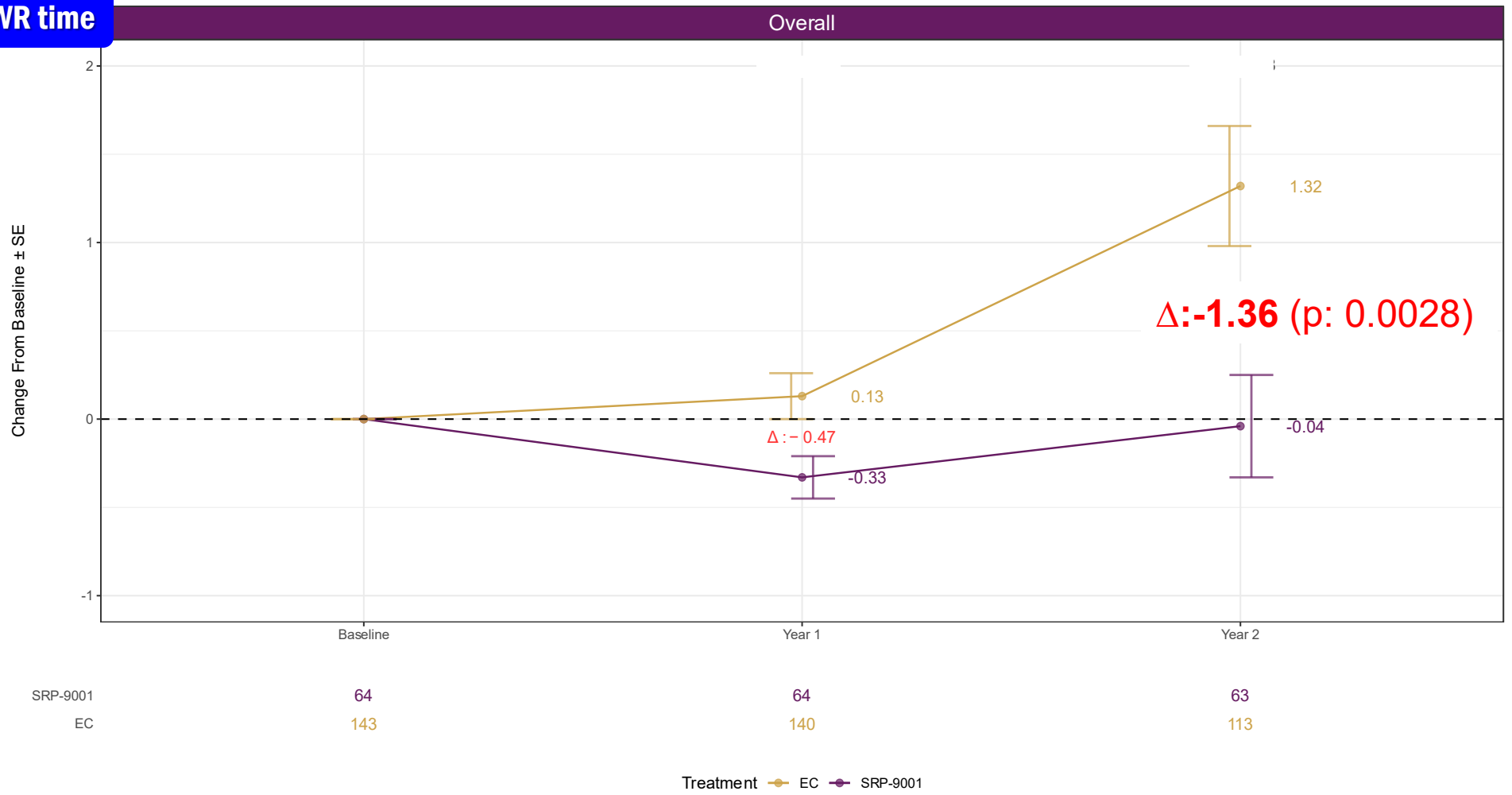


# Time-to-rise over two years also demonstrates a widening divergence over time



# 10MWR remains stable two years after treatment, with a widening divergence from natural history over time

**10MWR time**



SAREPTA THERAPEUTICS

# ENDEAVOR

## SRP-9001-103 Results

# ENDEAVOR (Study 9001-103): Protein expression and safety results in 2-year old participants at time of treatment

- **Clinical Results (cohort 6; n=6)**
  - 93.87% mean expression as measured by western blot
  - 79.9% dystrophin positive fibers (PDPF) as measured by immunofluorescence

- **Safety**
  - Safety in cohort 6 was consistent with clinical and real-world experience with ELEVIDYS
  - The most common adverse events were nausea and vomiting; elevated liver enzymes were seen in two patients and resolved with steroid administration

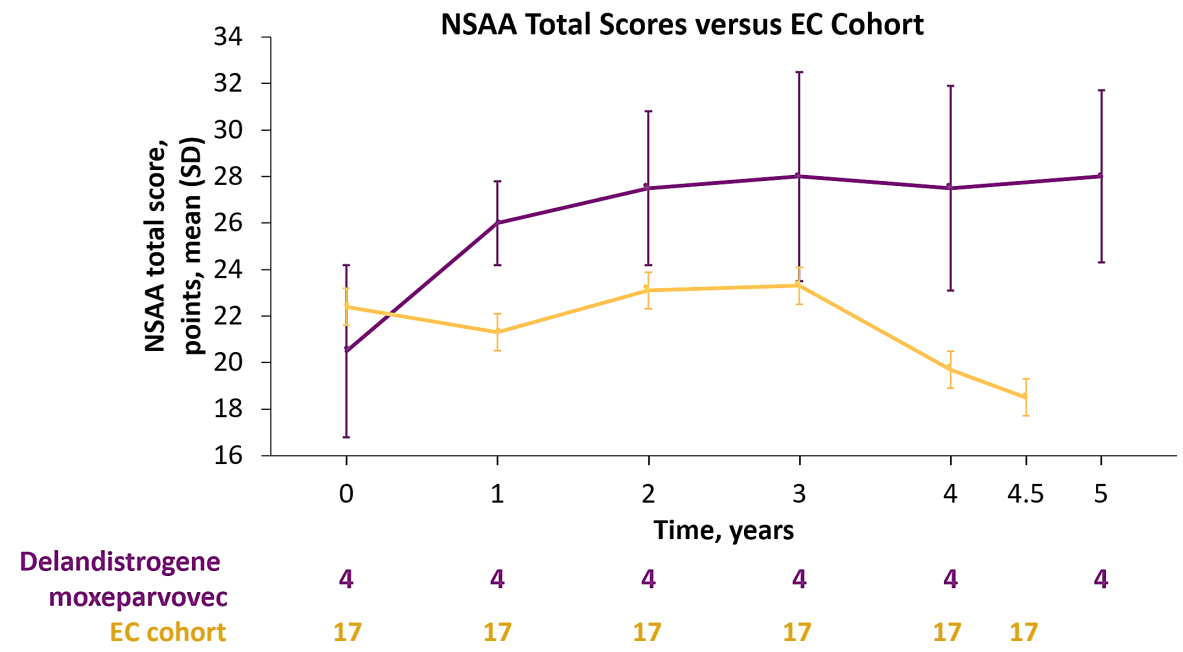
- **Study Design**
  - Open-label, Phase 1b study assessing the expression and safety of ELEVIDYS in multiple cohorts of male patients with Duchenne
  - 55 participants enrolled across 7 cohorts, and dosed participants aged 4-7 at time of treatment, older ambulant and non-ambulant individuals, and individuals younger than age 4

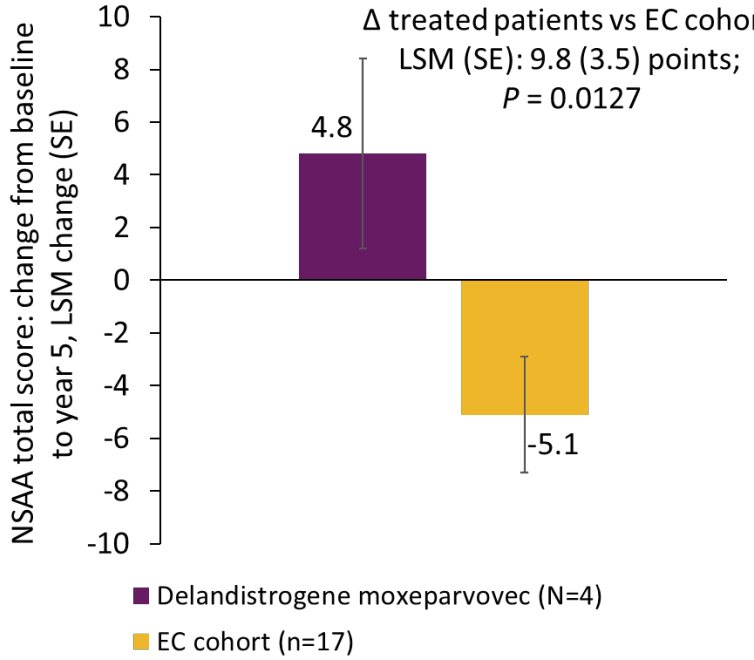
- **Endpoints**
  - **Primary endpoint:** Change from baseline in the quantity of ELEVIDYS micro-dystrophin protein expression measured by western blot at 12 weeks
  - **Key secondary outcome measures:** Change from baseline in micro-dystrophin expression measured by percent dystrophin positive fibers at 12 weeks
  - **Exploratory endpoints:** Change in vector genome copies per nucleus, NSAA and certain timed functional tests
  - Including the initial 12-week period, patients are followed for a total of five years

# SRP-9001-101
# Year 5 Results

# Study 9001-101 Year 5 results demonstrate durable response

***9.8-point difference on mean NSAA in patients receiving SRP-9001 compared to external control group***




**SRP-9001 treated patients showed a sustained increase in NSAA total score over 5 years, with a statistically significant and clinically meaningful difference at year 5 compared with the EC cohort.**

**At 5 years post-infusion, the mean (range) age of patients was 10.14 (9.02–11.02) years**

1. Balancing for age was limited by a reduced number of suitable patients in the external control database with 5-year functional data. Groups are well balanced for functional assessments predictive of disease progression.*NSAA change from baseline over 5 years SRP-9001 vs External Control calculated using unadjusted means.
BL, baseline; EC, external control; LSM, least square mean; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SE, standard error.

# ELEVIDYS Safety Data

# Safety profile in EMBARK is consistent with previous studies

| | Part 1 Treated, Year 1 post-treatment N=63 n (%) | Part 1 Treated, Year 2 post-treatment** N=63 n (%) | Crossover Treated, Year 1 post-treatment N=60 n (%) | Total SRP-9001 Treated* N=123 n (%) |
|---|---|---|---|---|
| TEAE | 62 ( 98.4) | 0 | 56 ( 93.3) | 118 ( 95.9) |
| SAEs | 14 ( 22.2) | 1 (1.6) | 8 ( 13.3) | 23 ( 18.7) |
| Treatment-related TEAE | 48 ( 76.2) | 4 ( 6.3) | 50 ( 83.3) | 102 ( 82.9) |
| Treatment-related SAEs | 7 ( 11.1) | 0 | 7 ( 11.7) | 14 ( 11.4) |
| AEs leading to study discontinuation | 0 | 0 | 0 | 0 |
| Deaths | 0 | 0 | 0 | 0 |

*Total of 123 patients received SRP-9001 in EMBARK Part 1 and 2.
**Patients who had not experienced corresponding event in part-1 but had in part-2.

# No safety concerns on cardiac MRI over 2 years of follow-up

- Values within normal range
- No statistical or clinical differences in these groups

| | Part 1 Treated: Baseline | Year 1 post-treatment | Year 2 post-treatment | Crossover Treated: Baseline | Year 1 post-placebo | Year 1 post-treatment |
|---|---|---|---|---|---|---|
| Subjects (N) | 16 | 16 | 14 | 19 | 16 | 18 |
| Left Ventricular Ejection Fraction, mean (range) | 64.69% (54-72) | 65.25% (55-74) | 61.73% (52-72) | 64.58% (47-74) | 66.38% (52-74) | 63.37% (58-75) |
| Global Circumferential Strain, mean (range) | -18.37% (-22.15 to -12.96) | -18.82% (-21.17 to -15.6) | -18.21% (-20.62 to -12.90) | -18.59% (-23.53 to -13.00) | -19.11% (-23.97 to -12.94) | -19.26% (-23 to -11.90) |

# Key siRNA Programs:

- Facioscapulohumeral muscular dystrophy type 1 (FSHD1)
- Myotonic dystrophy type 1 (DM1)
- Spinocerebellar ataxia type 2 (SCA2)
- Huntington’s Disease (HD)

# Facioscapulohumeral muscular dystrophy (FSHD)

**A rare genetic disease that causes weakness in the skeletal muscles.**
Progressively spreads from the face into other areas, including scapular girdle, upper limb, pelvic girdle, abdominal and leg muscles.[1]

- 95% of FSHD cases are linked to deletions of D4Z4 units on chromosome 4.[1]
- The average age of diagnosis is age 20.[1]
- There is currently no cure and there are no disease-modifying treatments.

**~13,000**
Diagnosed patients in the U.S.[2]

**70%**
patients experience debilitating pain and fatigue[2]

**PROGRAM:**
**SRP-1001** is an RNA interference (RNAi) conjugate designed to specifically target the gene that encodes human double homeobox 4 (DUX4) protein.

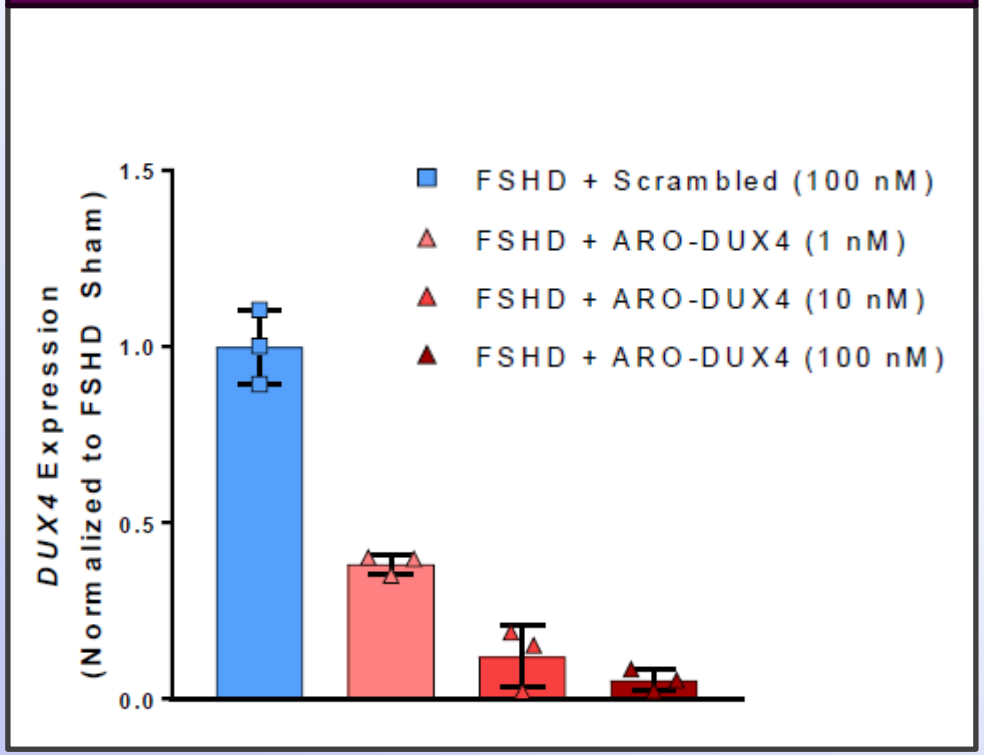
**STAGE:**
**Phase 1/2**

1. Muscular Dystrophy Association
2. FSHD Society

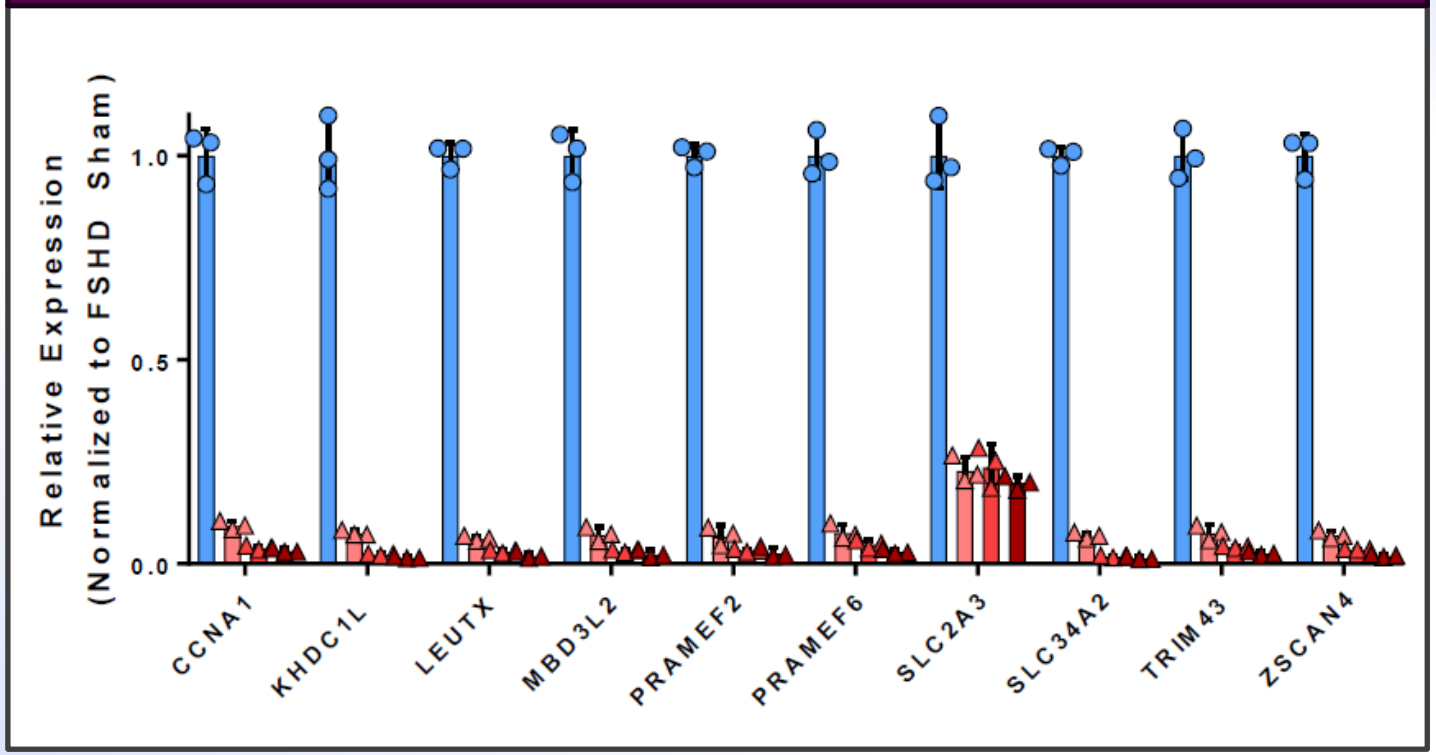
# SRP-1001 reduces DUX4 mRNA in FSHD patient cells

FSHD patient muscle cells express DUX4 in culture and is reduced with investigational SRP-1001 treatment

## SRP-1001 reduces DUX4 in FSHD myotubes



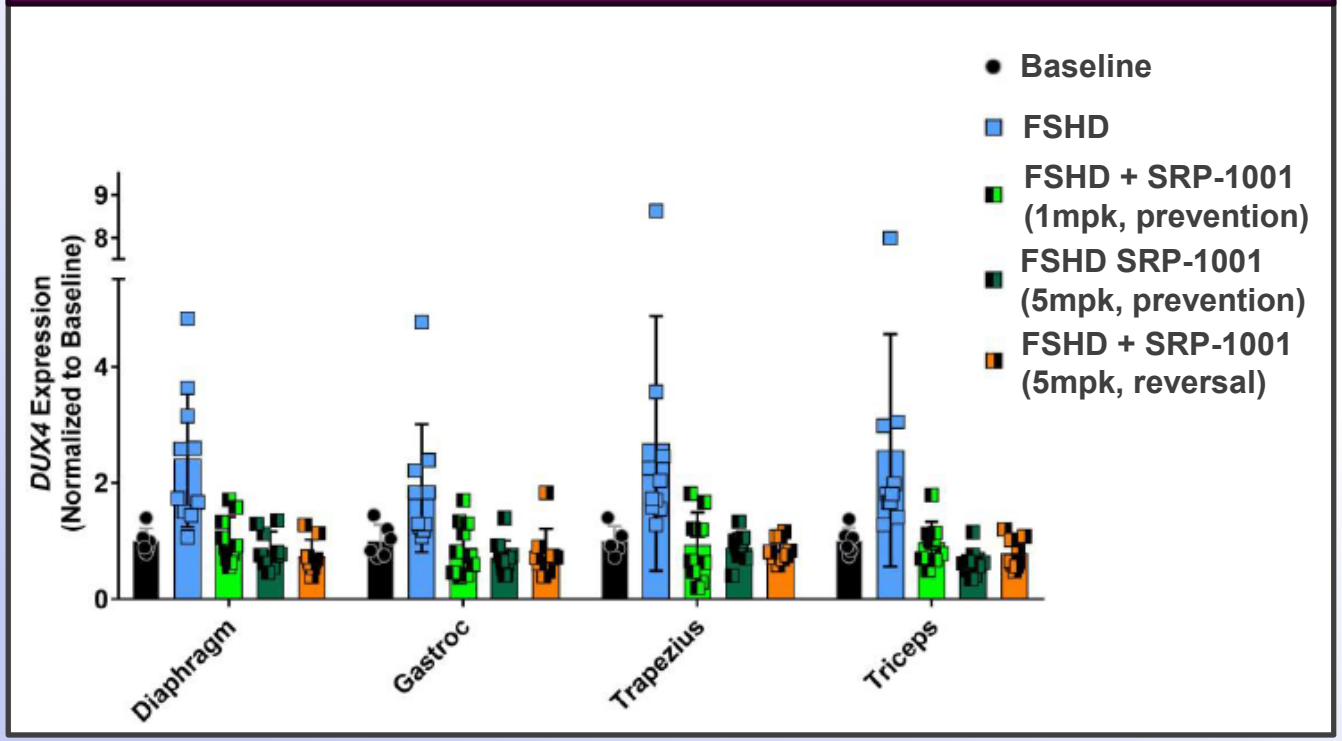

## SRP-1001 prevents DUX4-dependent gene activation



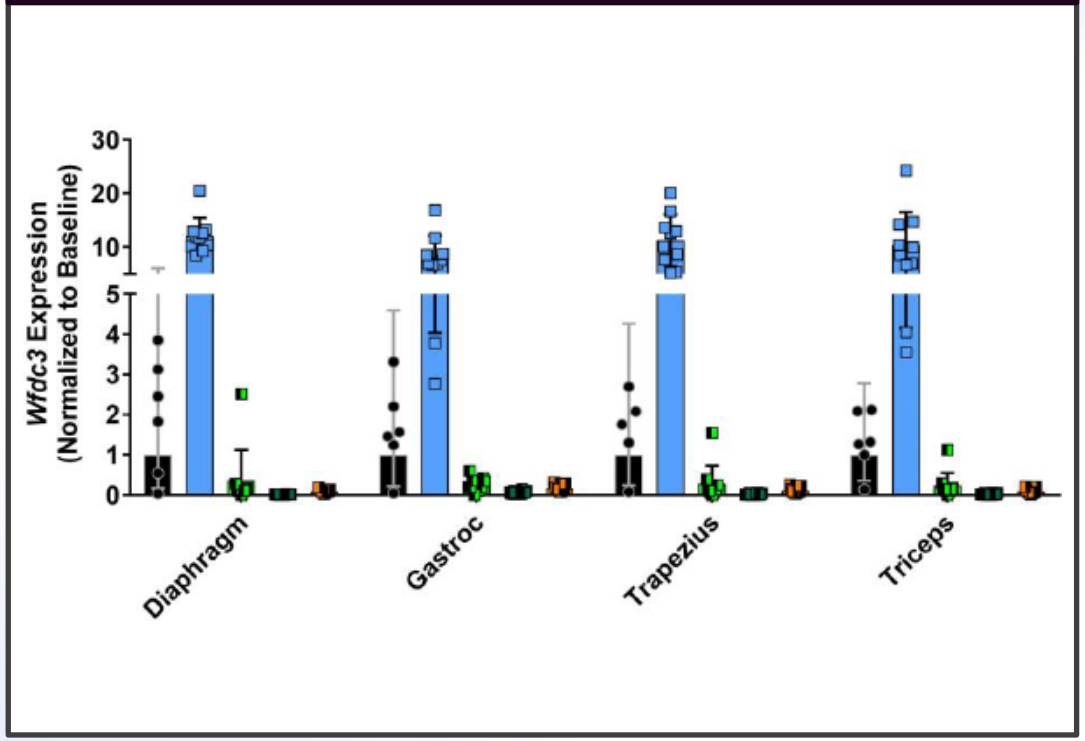
# SRP-1001 reduces DUX4 in a FSHD mouse

FSHD mouse model engineered to induce expression of human DUX4 in skeletal muscle

## SRP-1001 both prevents and reverses DUX4 mRNA in skeletal muscle from an FSHD mouse



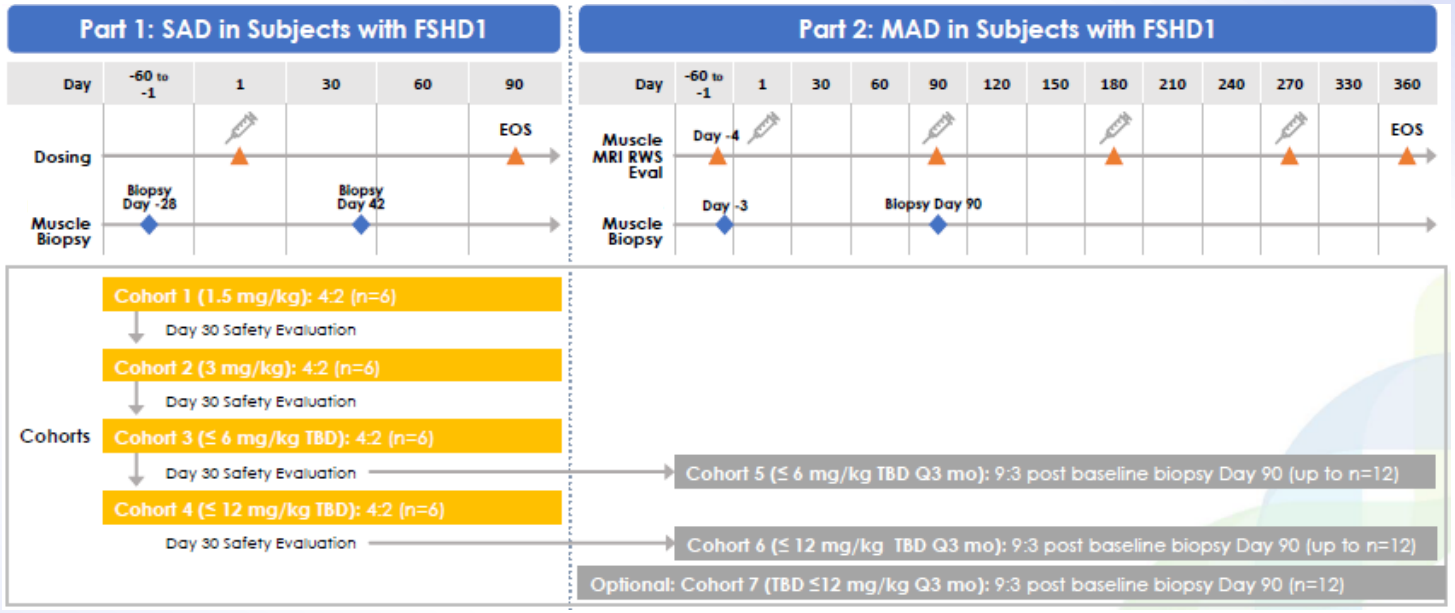

## SRP-1001 prevents and reverses DUX4-dependent gene activation in skeletal muscle



# SRP-1001: Facioscapulohumeral muscular dystrophy (FSHD)

## Proof-of-concept (POC) of DUX4 knockdown and confirmation of registrational dose

- **Development Status:** Phase 1/2
- **Design:** Placebo-controlled single ascending dose (Part 1) with placebo-controlled multiple ascending dose (Part 2) in FSHD1
- **Participants:** Cohorts 1-3 fully enrolled
- **Primary endpoint:** Safety
- **Select key secondary:**
  - *DUX4* mRNA knockdown
  - *DUX4*-regulated gene expression
  - Assessments of physical function
- **Near-term Milestone(s):**
  - First Participant In Cohorts 4 & 5 – Q3 2025
  - Preliminary data – 2H 2025




| Total Participants | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 | Cohort 5 | Cohort 6 |
|---|---|---|---|---|---|---|
| | SAD Cohorts | | | | MAD Cohorts | |
| Randomized | 6/6 | 6/6 | 6/6 | 0/6 | 0/6 | 0/6 |

# Myotonic dystrophy type 1 (DM1)

**A form of muscular dystrophy that affects muscles and many other organs in the body.**[1]

- Myotonic dystrophy (DM) is the most common form of muscular dystrophy.[2]
- There are two types of DM: DM1 is caused by mutations in the DMPK gene and is generally more severe than DM2.[1]
- DM1 impacts the respiratory muscle and significant breathing problems can result.[3] As DM1 progresses, the heart can develop an abnormal rhythm and weaken.[1]
- Life expectancy is shortened.[4]
- There is currently no cure and there are no disease-modifying treatments for DM1.

**~40,000**

Diagnosed patients in the U.S.[5]

**58 years**

Mean age at death[6]

**PROGRAM:**

**SRP-1003** is an RNAi conjugate designed to specifically silence DMPK mRNA in skeletal muscle.

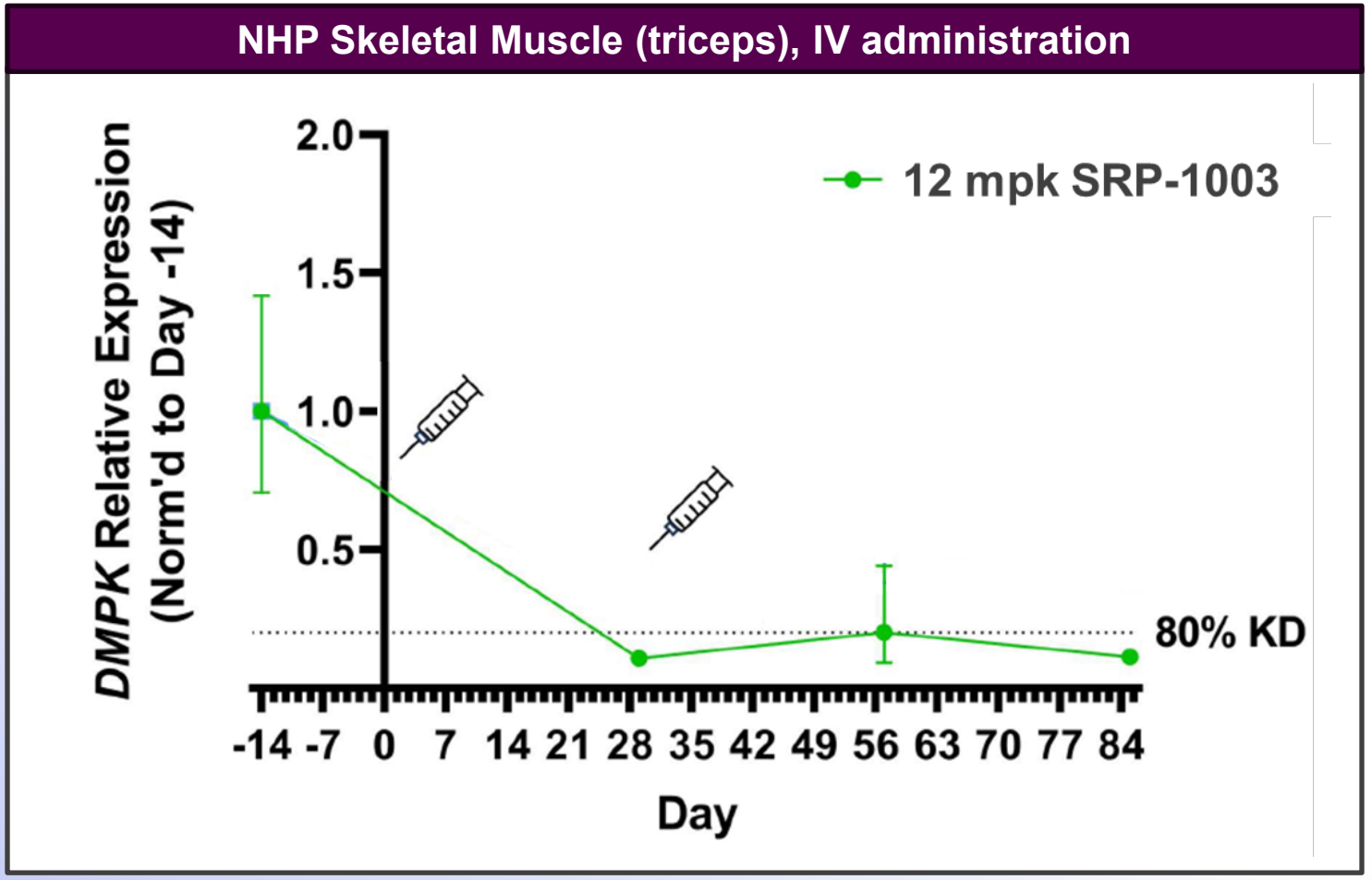
**STAGE:**

**Phase 1/2**


1. Muscular Dystrophy Association
2. National Institute of Child Health and Human Development
3. Myotonic Dystrophy Foundation
4. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2024 Nov 14]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
5. Pascual-Gilabert M, López-Castel A, Artero R. Myotonic dystrophy type 1 drug development: a pipeline toward the market. Drug Discovery Today. 2021;26(7):1765-72. doi: 10.1016/j.drudis.2021.03.024
6. Bassez et al, Neuromuscular Disorders 2024

# SRP-1003 reduces DMPK in non-human primates (NHP)

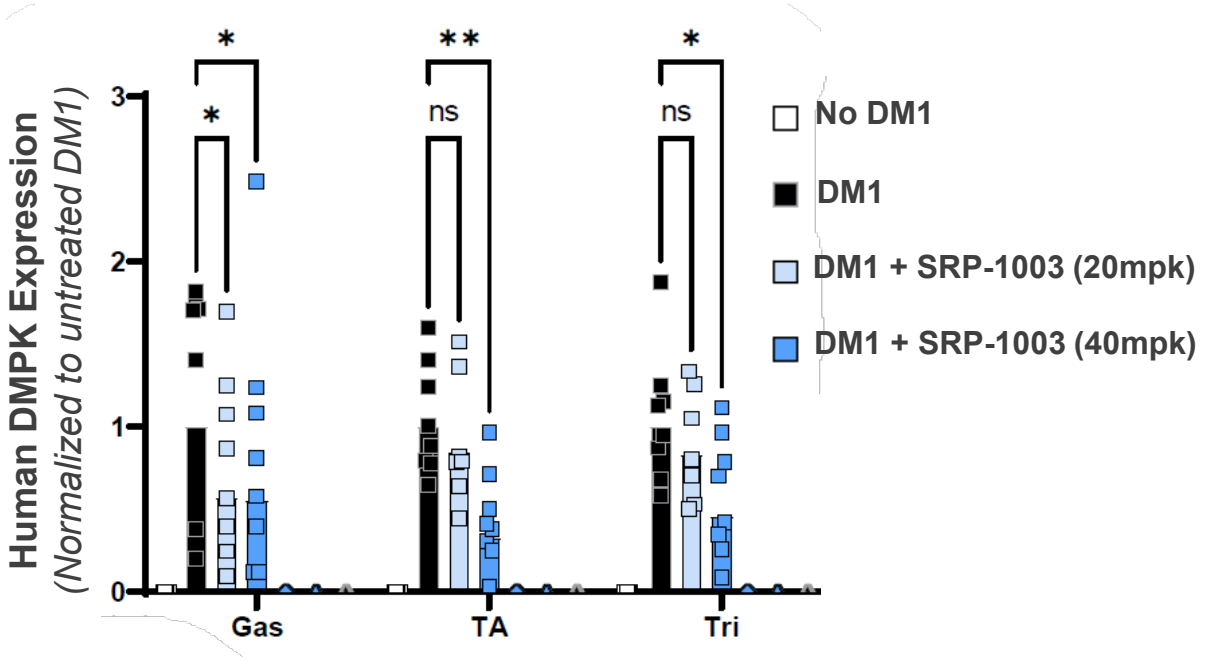
DMPK mRNA is knocked down to around 80% in NHP skeletal muscle



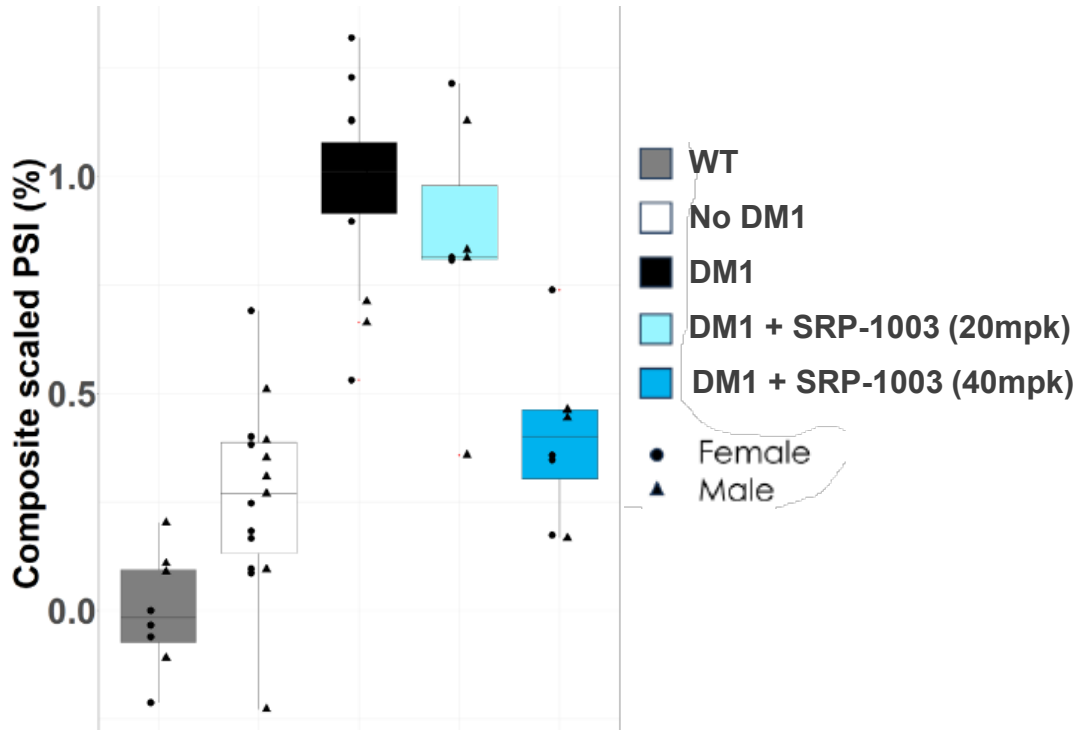
# Reducing DMPK fixes splicing deficit in a DM1 mouse

DM1 mouse model engineered to induce expression of human DMPK with expanded CUG repeats

## SRP-1003 reduces pathological DMPK mRNA in the nucleus of a DM1 mouse model (>50% at high dose)



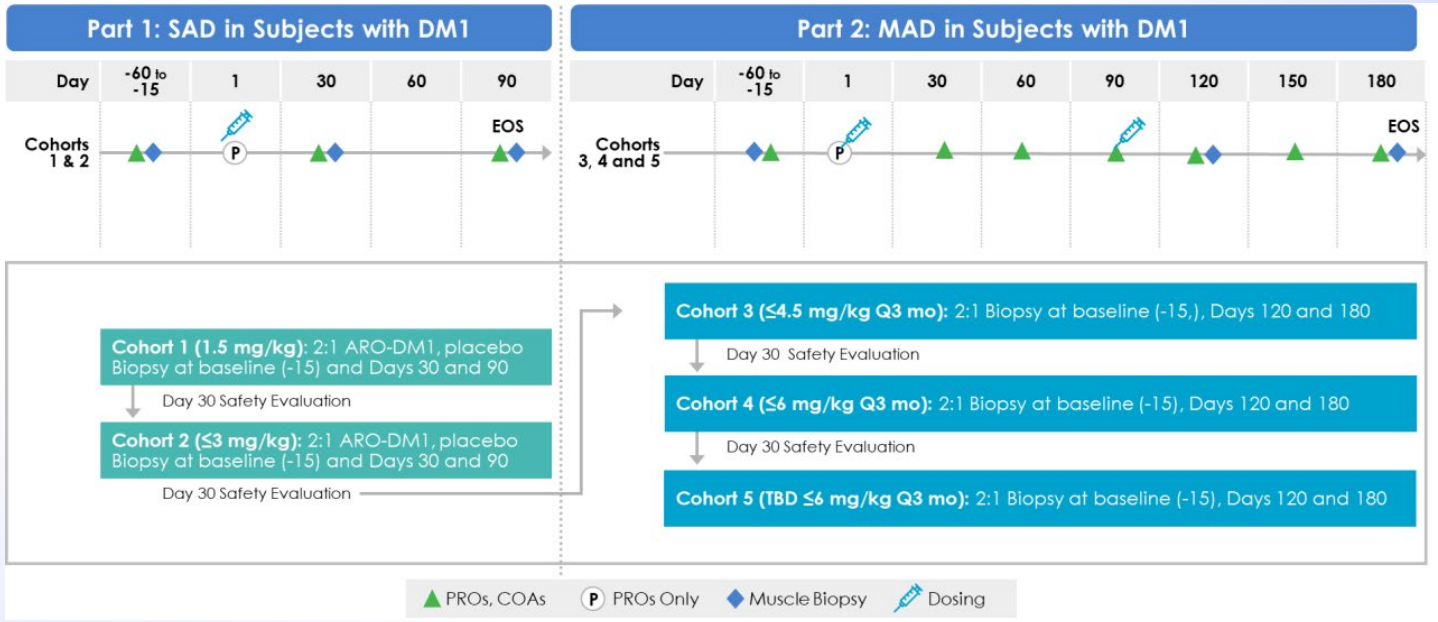

## SRP-1003 reverses splicing deficits in DM1 mouse model (~60% mis-splicing repair at high dose)



# SRP-1003: Myotonic dystrophy type 1 (DM1)

## Proof of concept (POC) and confirmation of registrational dose

- **Development Status:** Phase 1/2
- **Design:** Placebo-controlled single ascending dose (Part 1) with placebo-controlled multiple ascending dose (Part 2)
- **Participants:** Cohorts 1-2 fully enrolled
- **Primary endpoint:** Safety
- **Select key endpoints:**
  - *DMPK* mRNA knockdown
  - Change in DMPK mediated splicing indices
  - VHOT and other measures of physical function
- **Near-term Milestone(s):**
  - First Participant In Cohort 3 – Q4 2025
  - Preliminary Phase 1 data – 2H 2025




| Total Participants | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 | Cohort 5 |
|---|---|---|---|---|---|
| | SAD Cohorts | | MAD Cohorts | | |
| **Randomized** | 14/13 | 8/6 | 0/6 | 0/6 | 0/6 |

# Spinocerebellar ataxia type 2 (SCA2)

**Spinocerebrellar ataxia (SCA) is a group of rare, genetic neurodegenerative disorders** leading to severe disability and premature death.[1]

- In SCA, the nerve fibers carrying messages to and from the brain are affected, resulting in degeneration of the cerebellum (the coordination center of the brain). [1]
- There are more than 40 types of SCA.[2] SCA2 is caused by mutations in the ATXN2 gene.[3]
- SCA2 symptoms include movement, vision, speech and swallowing problems, as well as peripheral neuropathy, tremor and muscle wasting; and may include short-term memory problems and dementia.[1]
- There is currently no cure and there are no disease-modifying treatments.

**~2,000**

Diagnosed SCA2 patients in the U.S. [4]

**10-20 years**

After diagnosis, patients become dependent on a wheelchair [1]

**PROGRAM:**
**SRP-1004** RNAi targets production of toxic ATXN2 protein that causes the disease.

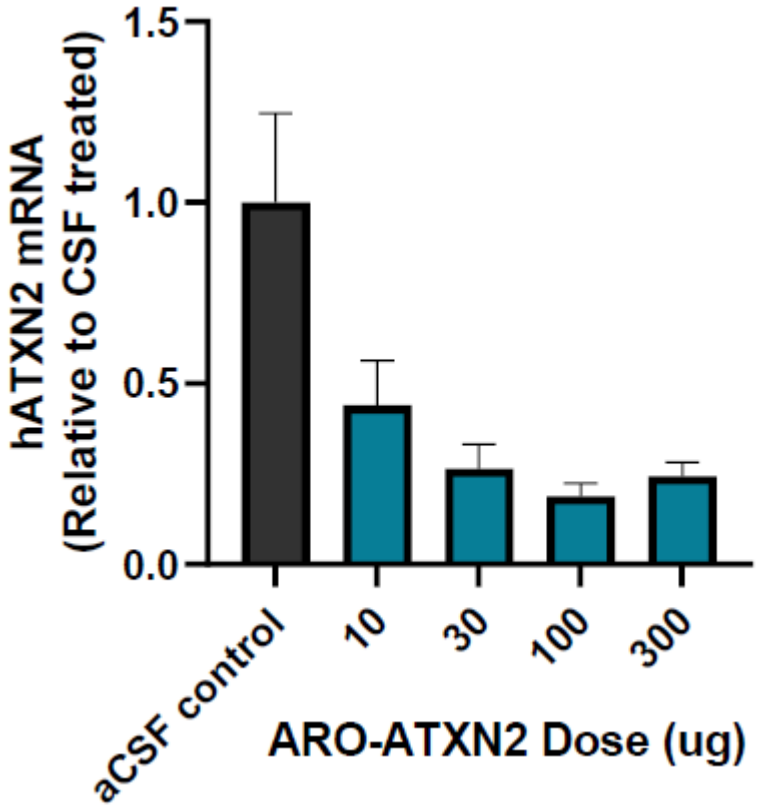
**STAGE:**
**Phase 1**

1. National Institute of Neurological Disorders and Stroke
2. Cleveland Clinic
3. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Spinocerebellar ataxia type 2. Available from: https://medlineplus.gov/genetics/condition/spinocerebellar-ataxia-type-2/#causes
4. Ruano et al, Neuroepidemiology 2014

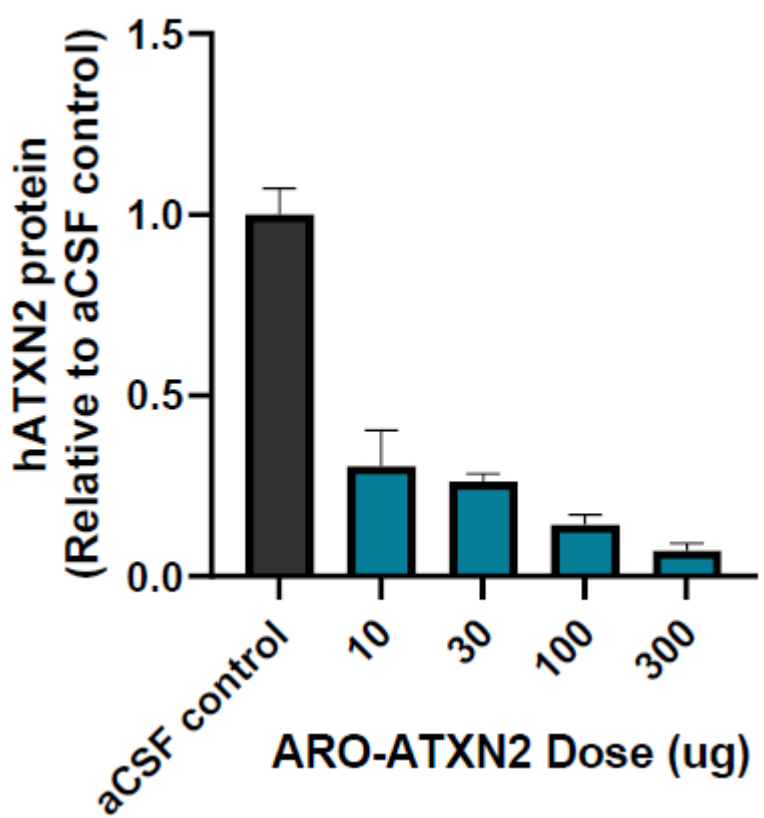
# SRP-1004 reduces ATXN2 in a mouse brain

Mouse model engineered to express human ATXN2

**SRP-1004 delivered ICV reduces ATXN2 mRNA 2 weeks after delivery**



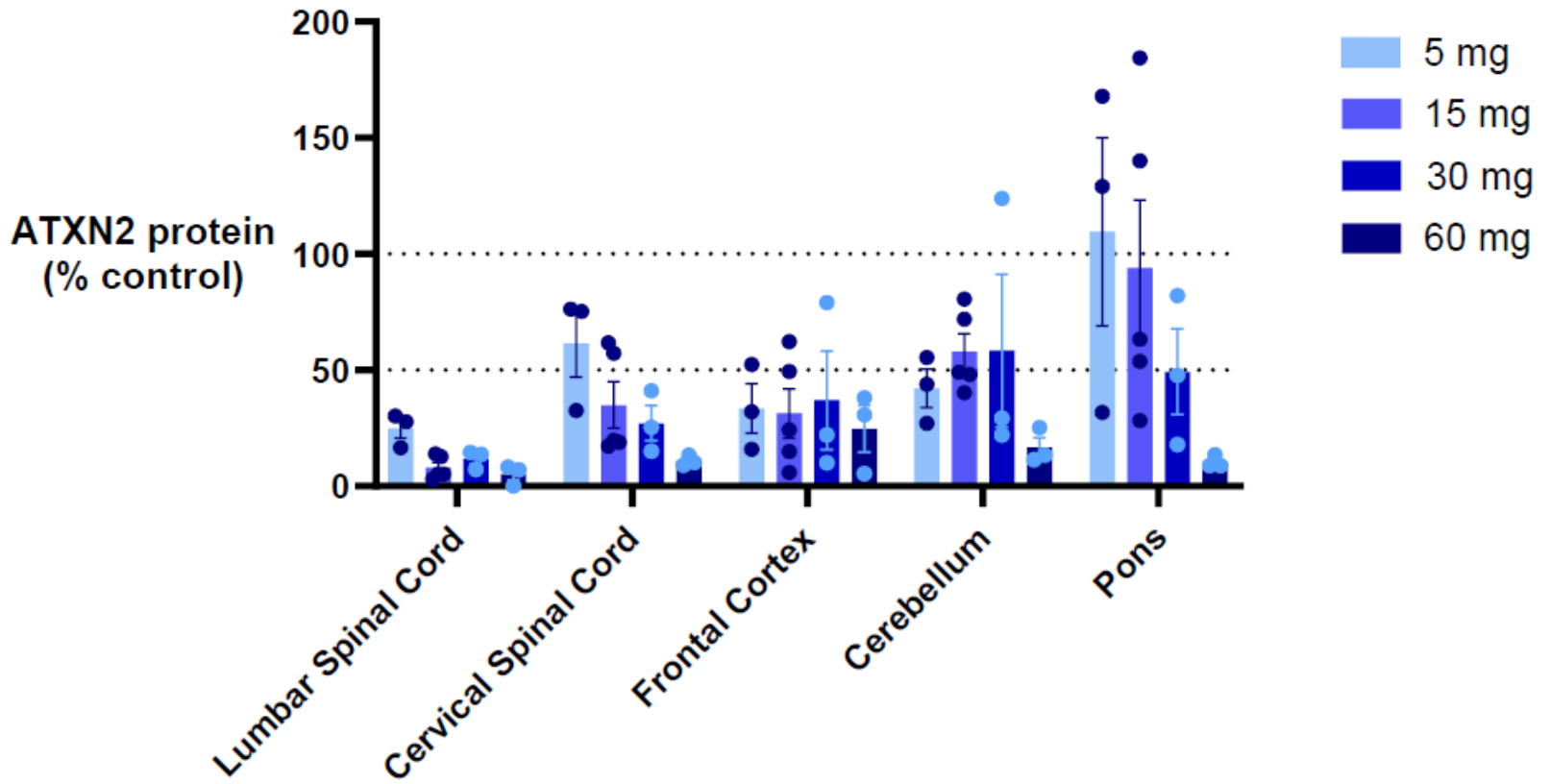

**SRP-1004 delivered ICV reduces ATXN2 protein 2 weeks after delivery**



# SRP-1004 lowers ATXN2 in NHP brain regions important in disease

>80% reduction in key brain regions (i.e. cerebellum) involved in SCA2 pathology

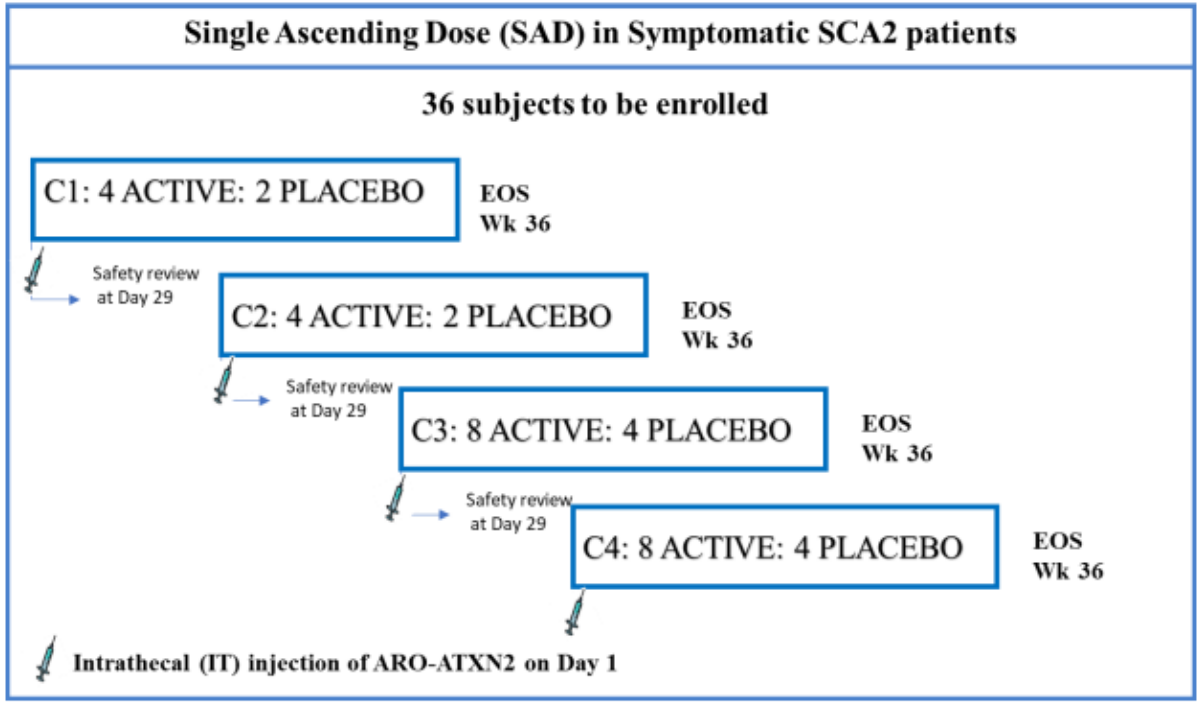
**SRP-1004 delivered IT reduces ATXN2 protein 1 month after delivery**



# SRP-1004: Spinocerebellar ataxia type 2 (SCA2)

## POC and confirmation of registrational dose

- **Development Status:** Phase 1
- **Design:**
  - Randomized placebo-controlled single ascending dose
  - Multiple ascending dose Part 2 being added
- **Participants:** Cohort 1 fully enrolled
- **Primary endpoint:** Safety
- **Select key secondaries:**
  - *CSF* ATXN2 protein levels
- **Next Milestone(s):**
  - First Participant In (FPI) Cohort 2 – Q3 2025
  - Preliminary data




Abbreviations: C=Cohort; EOS=end of study; Wk=week; SCA2=spinocerebellar ataxia type 2.
Note: EOS (Week 36) is equivalent to Day 253.

| Total Participants | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|---|---|---|---|---|
| | SAD Cohorts | | | |
| Randomized | 6/6 | 0/6 | 0/12 | 0/12 |

# Huntington's Disease (HD)

**A fatal genetic disorder that causes brain cells to gradually break down and die.**
HD deteriorates a person's physical and mental abilities, and a person with HD is described as having ALS, Parkinson's and Alzheimer's disease simultaneously. [1]

- HD is caused by a mutation in the gene for a protein called huntingtin. The defect causes the building blocks of DNA called cytosine, adenine and guanine (CAG) to repeat many more times than typical. [1]
- People typically develop motor symptoms in their 40s and 50s, but subtle changes, such as depression, disinhibition, minor involuntary movements and difficulty thinking through complex problems, may arise much earlier. [1]
- As HD progresses, people develop problems with swallowing, balance and voluntary motor tasks. Chorea, or irregular movements, becomes more pronounced; and in the late stages of HD, individuals are often nonverbal and bedridden. [2]
- There is currently no cure and there are no disease-modifying treatments.

**40,000+**
people in the U.S. affected[1]

**15-20 years**
Median survival after symptom onset [2]

**PROGRAM:**
**SRP-1005 Subcutaneous ROA** delivers siRNA across the blood brain barrier to the source of disease in the deep brain.

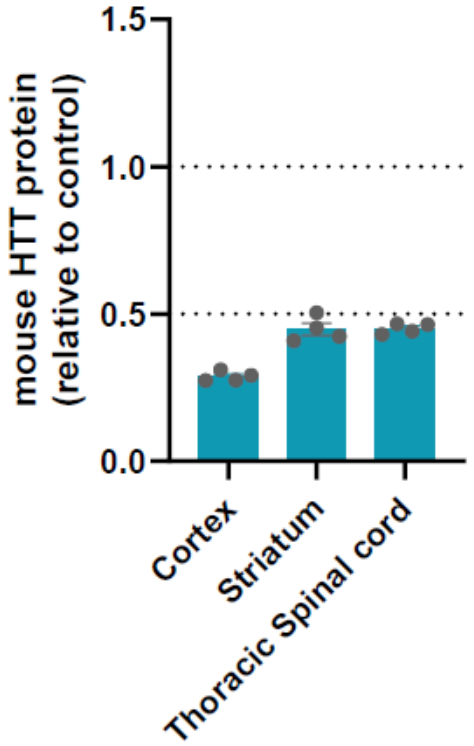
**STAGE:**
**Preclinical**

1. https://hdsa.org/what-is-hd/
2. https://medlineplus.gov/genetics/condition/huntingtons-disease

# SRP-1005 reduces HTT in mouse brain

HTT siRNA linked to an antibody fragment targeting TfR1 enabling entry into the brain

**SRP-1005 delivered subcutaneously reduces mouse HTT protein 1 month post delivery**



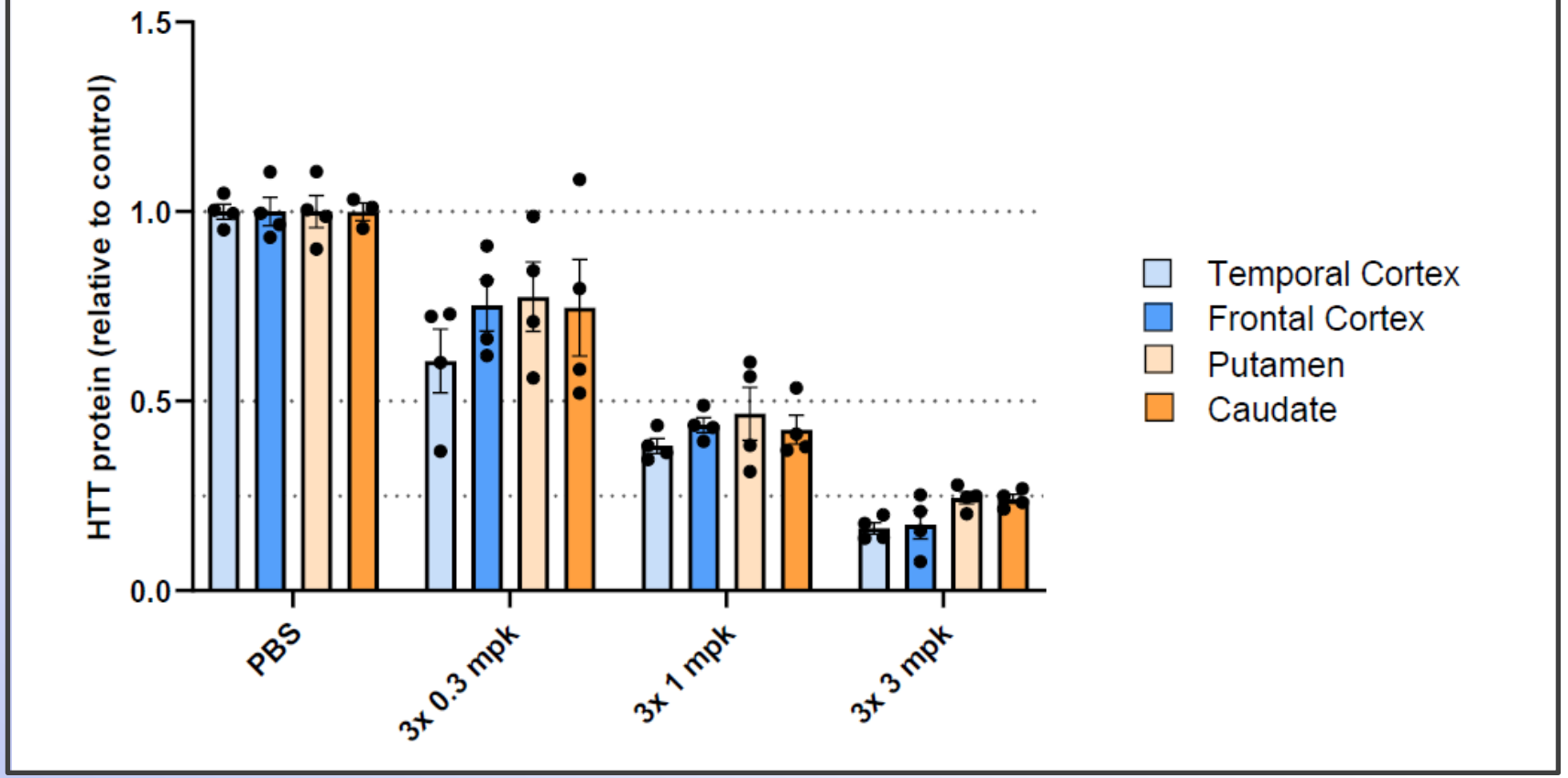

4 x 3mg/kg qd Subcutaneous Doses
Day 29, n=4/Group, Mean±SEM

Mouse model engineered to express human TfR1

# SRP-1005 reduces HTT in NHP brain regions important to disease

SRP-1005 binds to NHP TfR1 to access the brain and reduce HTT protein levels

**SRP-1005 delivered SC (3 weekly doses) reduces HTT protein in key brain regions 43 days post delivery**



# Bolstering pipeline with preclinical programs and up to 6 discovery targets in muscle (skeletal and cardiac) or CNS

## PRECLINICAL PROGRAMS

- Preclinical CNS leverages TfR1-binding for optimal CNS delivery
- Subcutaneous delivery reaches across the blood brain barrier

**SRP-1005 for Huntington's Disease (HD)**

**SRP-1007 for Spinocerebellar ataxia type 1 (SCA1)**

**SRP-1006 for Spinocerebellar ataxia type 3 (SCA3)**

## DISCOVERY TARGETS

- Up to 6 targets in muscle (skeletal and cardiac) or CNS
- Sarepta and Arrowhead will work together exclusively to develop therapies for skeletal muscle diseases


# Dragging tomorrow into today

#DraggingTomorrowIntoToday