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

# So neither will we.



**DILLON**
Living with Duchenne muscular dystrophy

SAREPTA THERAPEUTICS

August 2026

# 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 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 and next steps for multiple of our programs in 2026 and 2027.

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 products or product candidates in a timely manner or at all, which could impair our ability to generate sufficient revenue and have a successful business; 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; 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; 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 in sufficient quality and quantity or within sufficient timelines; 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.

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**~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.

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**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

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# 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

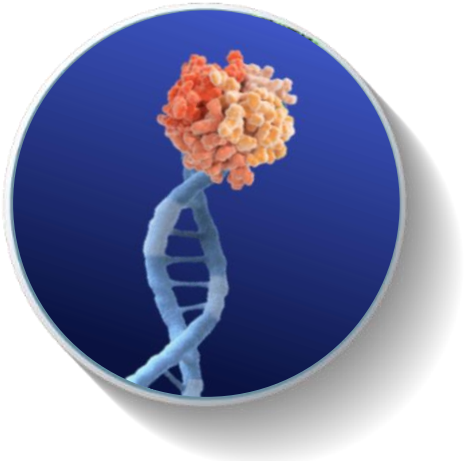
**Research & Manufacturing:** Andover, MA; Bedford, MA

**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. 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.

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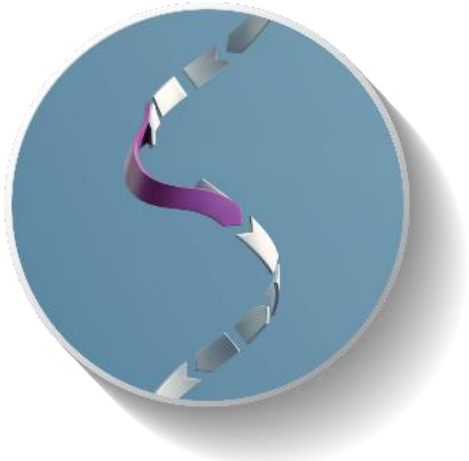
# Three distinct, proprietary scientific platforms



## siRNA

### Knockdown

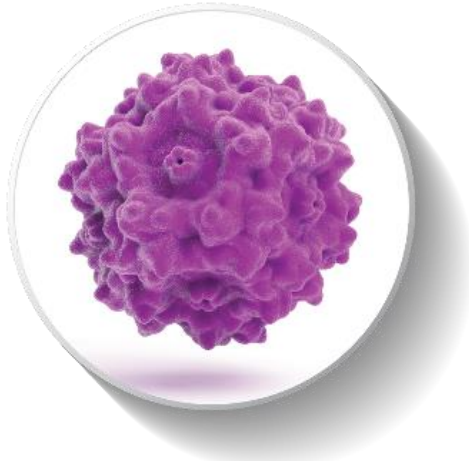
Suppresses overexpression of mutations



## RNA

### Skipping

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



## GENE THERAPY

### Replacement

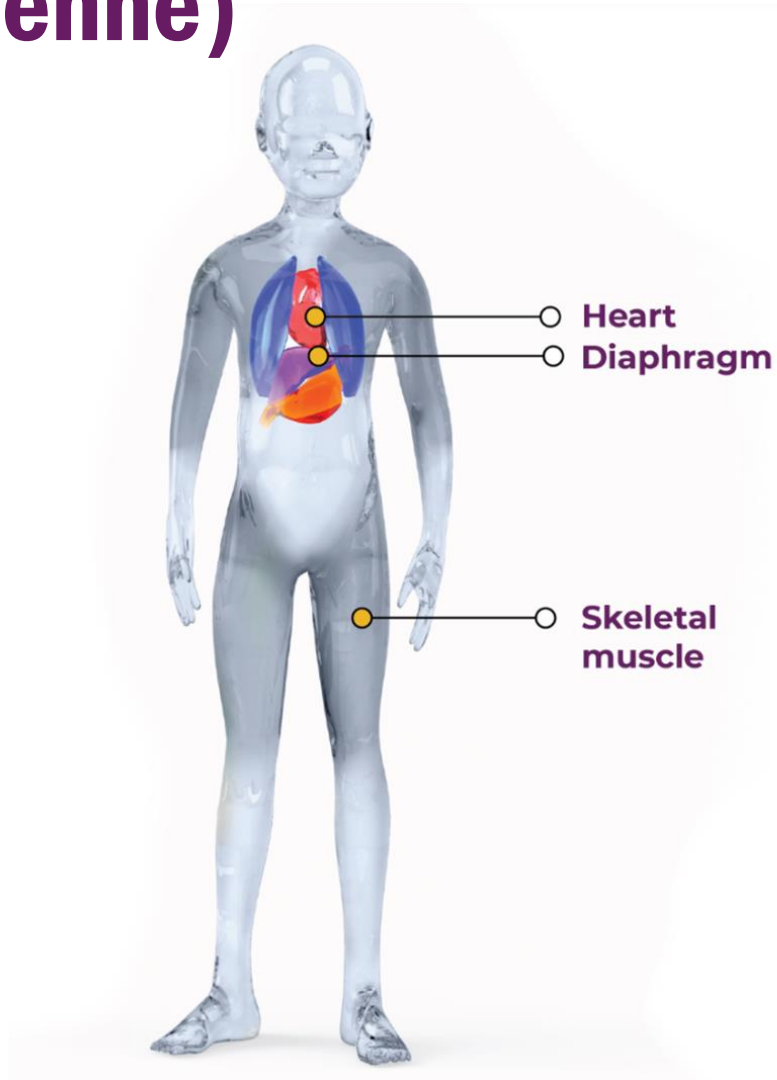
Adds a functional copy (a transgene) of a missing or malfunctioning gene

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# 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.


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# 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



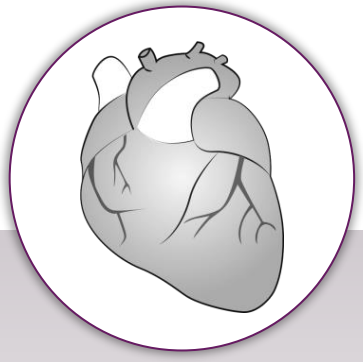
- Loss of ambulation
- Full-time wheelchair use
- Increasing loss of upper limb function

## 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

*Disease trajectory and manifestation may vary based on the disease's heterogeneity*


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.


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# Muscle biopsies of patients with Duchenne show continued damage at early ages

Biopsies showed fiber size variation, and progressive loss of muscle structure and integrity[a,b]

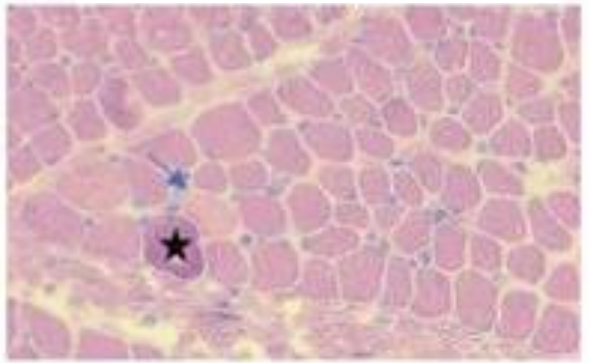
Blue arrows represent necrotic fibers

Black stars represent hypercontracted fibers

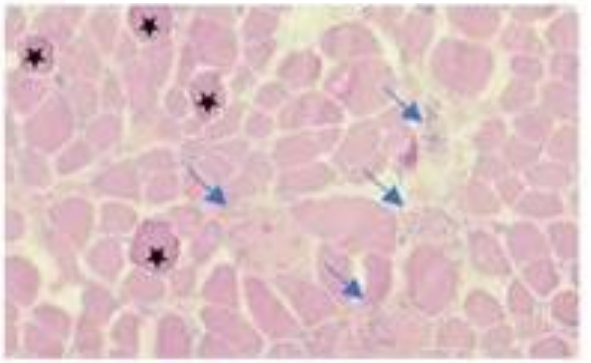
**Control Quadricep 4 Years**



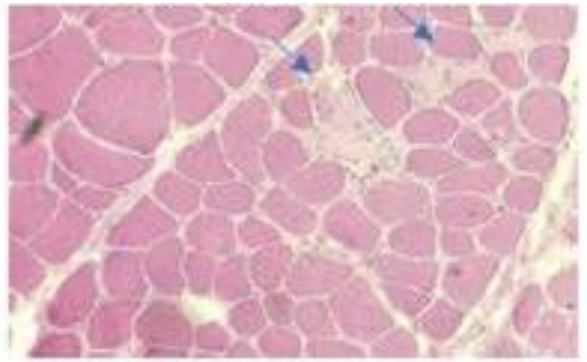
**DMD Quadricep 1 Year**



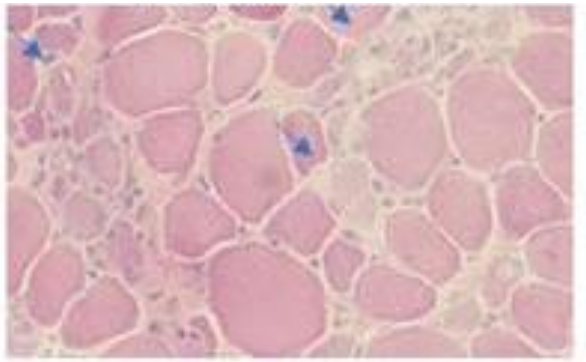
**DMD Quadricep 3 Years**



**DMD Quadricep 5 Years**



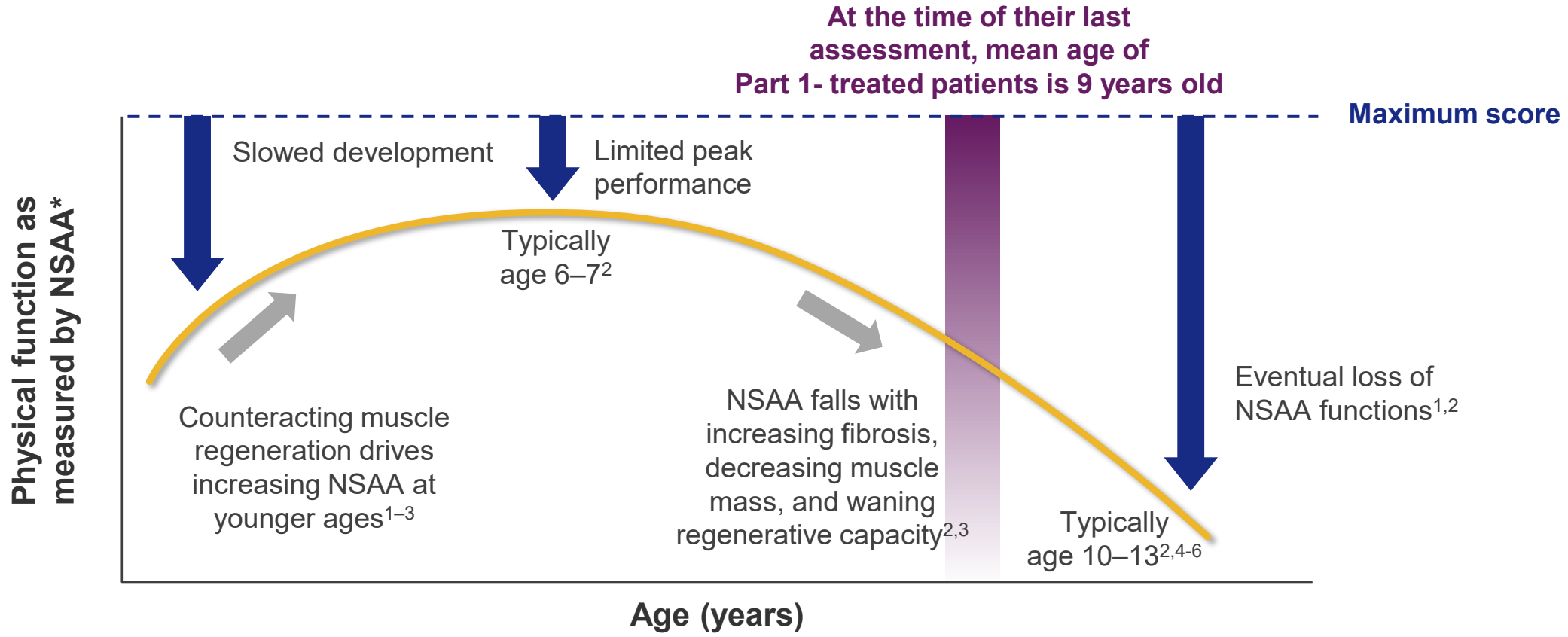
**DMD Quadricep 8 Years**



[a]Hematoxylin & Eosin (H&E) staining [b]Biopsy images shown are each from different patients
DMD, Duchenne muscular dystrophy. Cardone N, et al. *Acta Neuropathol Commun.* 2023;11(1);167.

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# Physical function typically peaks around age 6 in individuals with Duchenne[1-3]



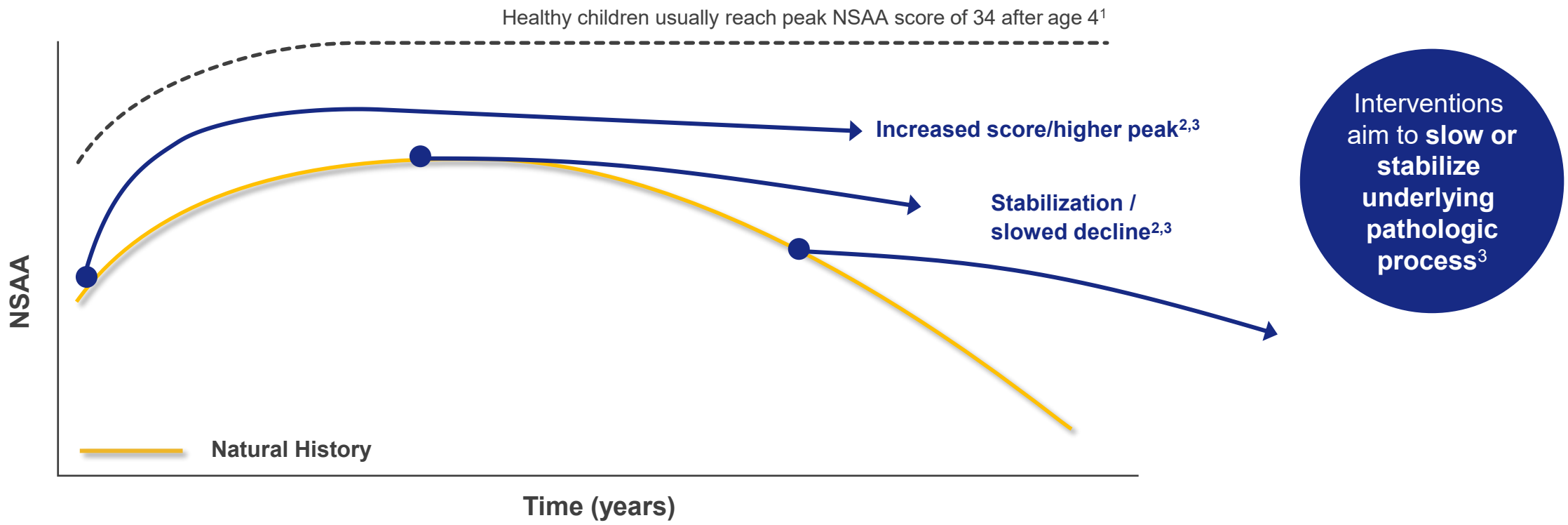

*NSAA is a composite endpoint evaluating physical function in ambulant children with Duchenne.[6]

NSAA, North Star Ambulatory Assessment.

1. McDonald CM, *et al. Lancet*. 2018;391(10119):451–61. 2. Muntoni F, *et al. PLoS One*. 2019;14(9):e0221097. 3. Rooney WD, *et al. Neurology*. 2020;94(15):e1622–33. 4. Emery AEH. *Lancet*. 2002;359(9307):687–95. 5. Niks EH and Aartsma-Rus A. *Expert Opin Biol Ther*. 2017;17(2):225–36. 6. Connolly AM, et al. Neuromuscul Disord. 2013;23(7):529-539

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# Potential outcomes based on timing of therapeutic intervention when attempting to stabilize Duchenne progression




**Change from baseline without context of expected course of disease may not be an appropriate method to assess treatment outcomes.[2]**


1. Mercuri E, et al. *PLoS One*. 2016;11(8):e0160195.
2. Muntoni F, et al. *PLoS One*. 2019;14(9):e0221097.
3. McDonald CM, et al. *Lancet*. 2018;391(10119):451-461.


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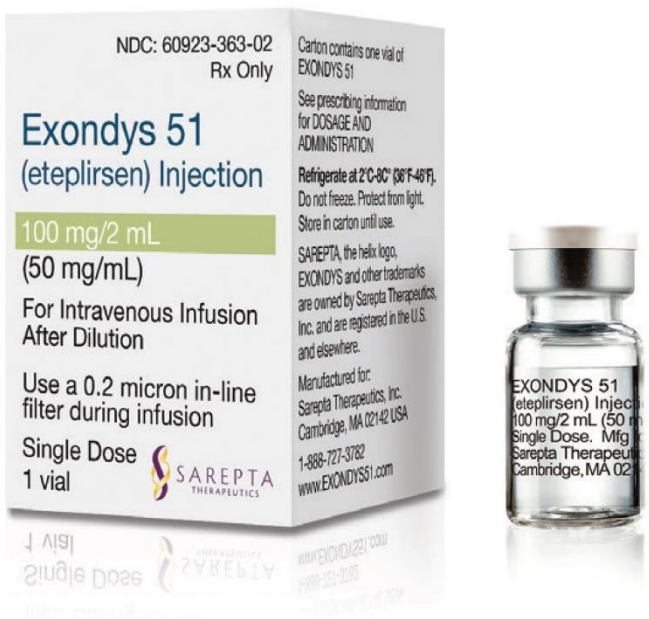



**PATIENTS LIVING WITH DUCHENNE TODAY*: 250,000 – 300,000 globally**

* Estimated global prevalence.

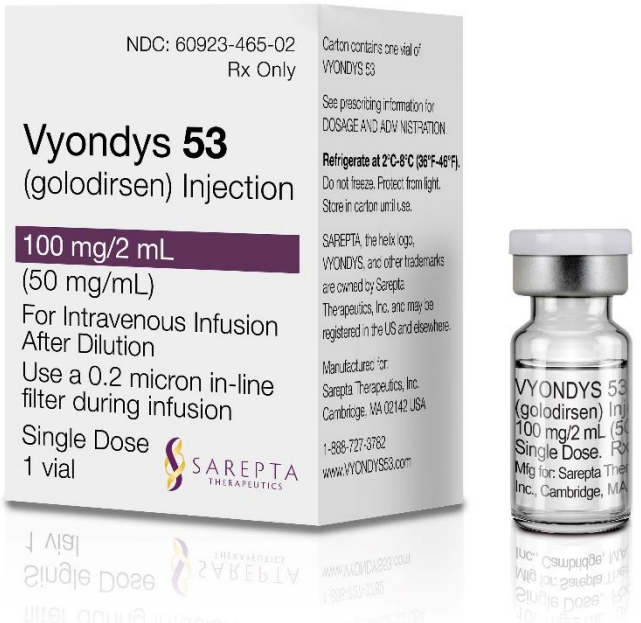
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# Serving approximately 30% of the Duchenne community with RNA-based therapies



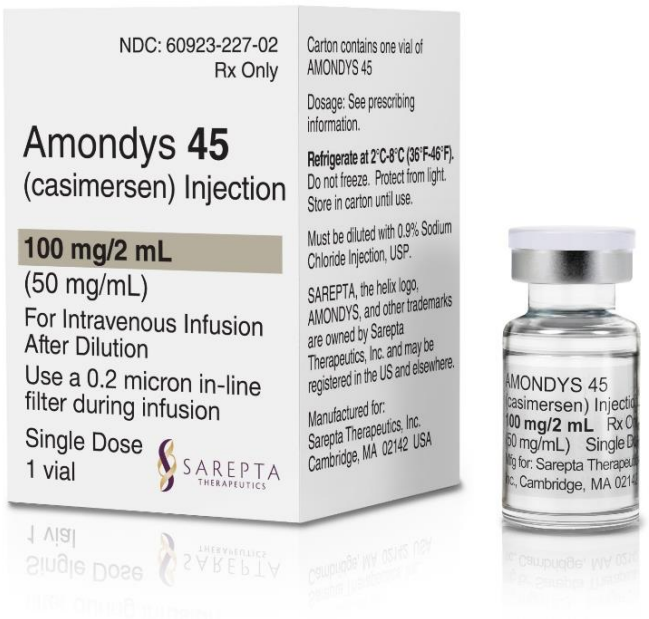

## September 2016

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)*



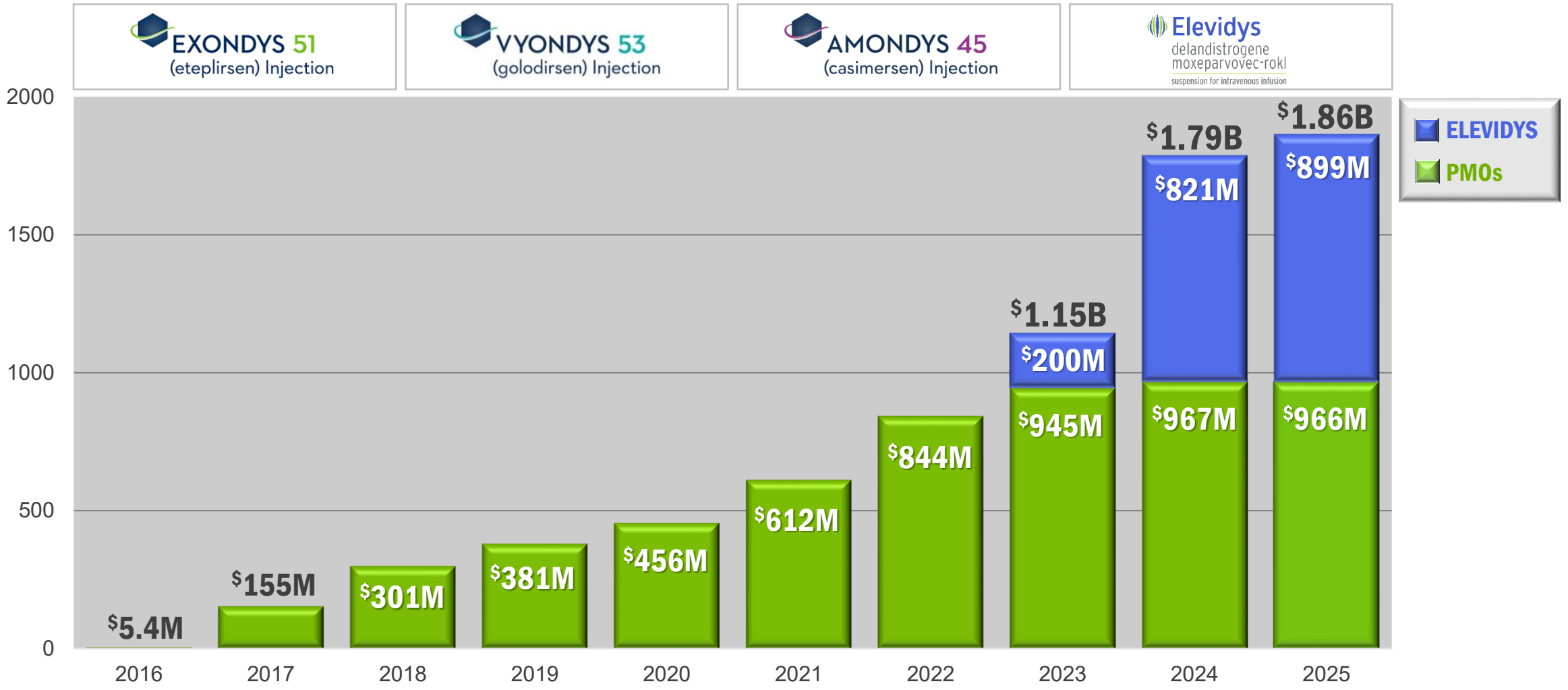

## February 2021

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.

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# Net product revenue from 2016 through 2025




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# Largest and most comprehensive clinical program in Duchenne

Clinical trial participants have ranged in age from 2 to 24 years old, with body weights ranging from 12 kg to close to 90 kg

## STUDY 101

Ages 4-7, ambulatory
Open-Label

**4**
PARTICIPANTS

## STUDY 102

Ages 4-7, ambulatory
Placebo-Controlled

**41**
PARTICIPANTS

## ENDEAVOR

Ages 3+, ambulatory and non-ambulatory
Open-Label

**58**
PARTICIPANTS

## EMBARK

Ages 4-7, ambulatory
Double-Blind, Placebo-Controlled

**126**
PARTICIPANTS

## ENVISION

Double-blind placebo-controlled safety and efficacy in ambulatory and non-ambulatory participants

**148**
PARTICIPANTS

## ENVOL

Safety and expression in participants under 4 years of age

**~21**
PARTICIPANTS

## EXPEDITION

Safety and efficacy in subjects who have previously received delandistrogene moxeparvovec in a clinical study (long-term follow-up study)

**400**
PARTICIPANTS

## ENDURE

Comparative effectiveness and safety of delandistrogene moxeparvovec vs. standard of care under conditions of routine clinical practice

**Up to 500**
PARTICIPANTS

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# EMBARK

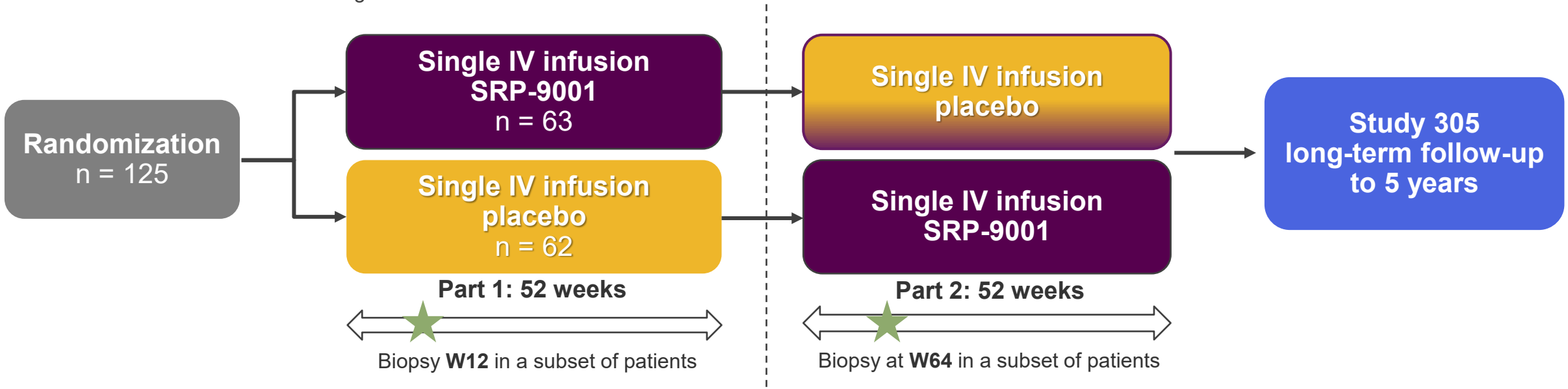
## SRP-9001-301

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# SRP-9001-301 study design

A completed Phase 3, multinational, double-blind, randomized, placebo-controlled study evaluating the safety and efficacy of ELEVIDYS (delandistrogene moxeparvovec-rokl), in boys with Duchenne 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

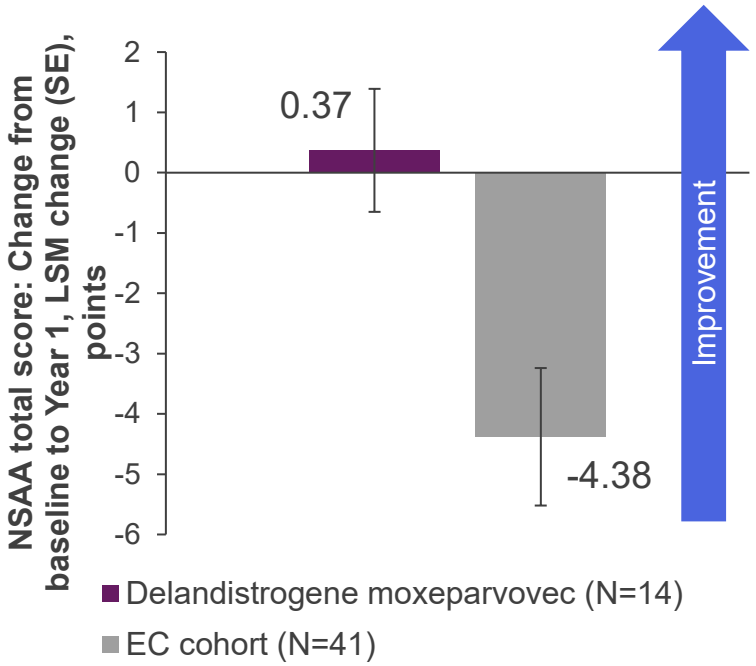
**Other timed secondary endpoints:**
- Stride Velocity 95th Centile (SV95C)
- 100-meter walk/run
- Ascend 4 Steps

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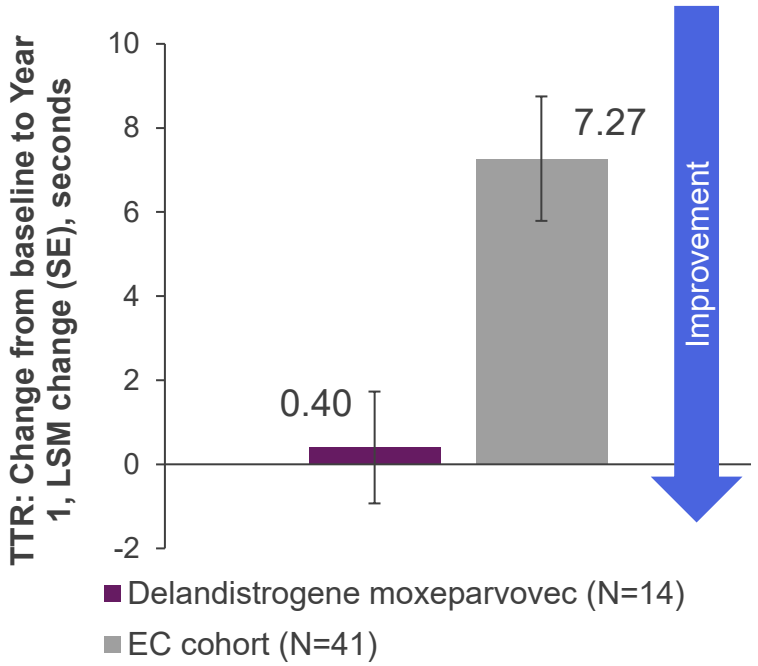
# One-year Follow-up: Functional outcomes of patients treated at ≥8 years of age

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

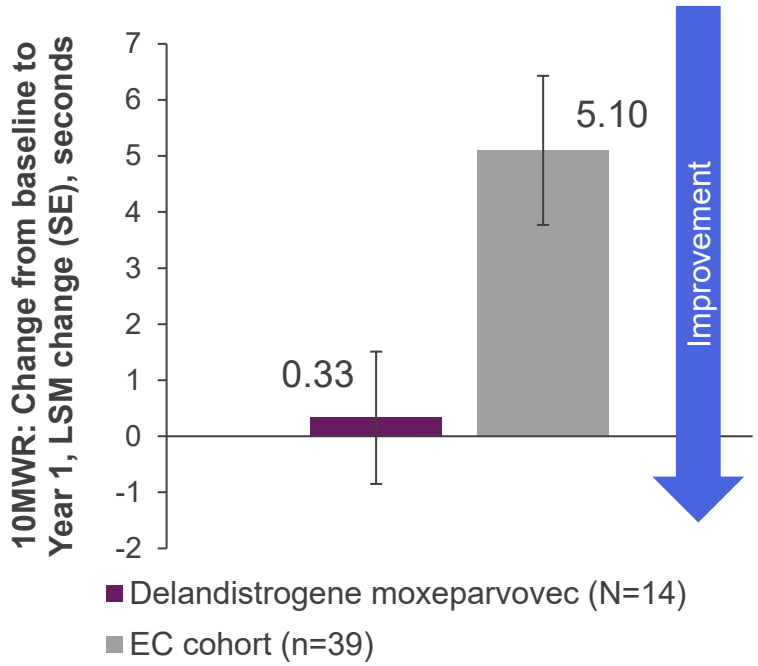
**NSAA Δ 4.75 points; *P*=0.0026**




**TTR Δ –6.87 s; *P*=0.0010**



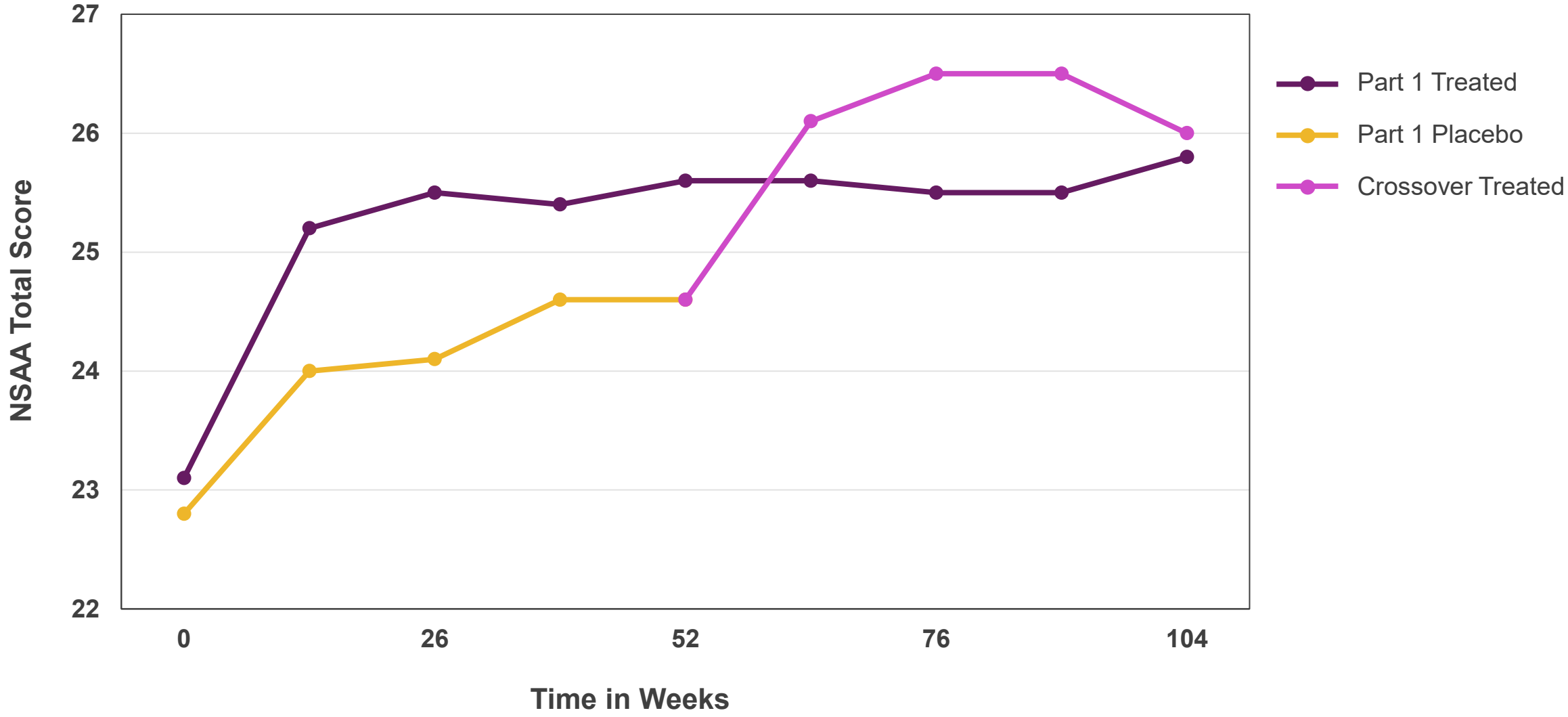

**10MWR Δ –4.76 s; *P*=0.0097**




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.
Mendell JR, et al. Oral presentation at: American Society of Gene and Cell Therapy Annual Meeting, May 13-17, 2025; [New Orleans, LA].

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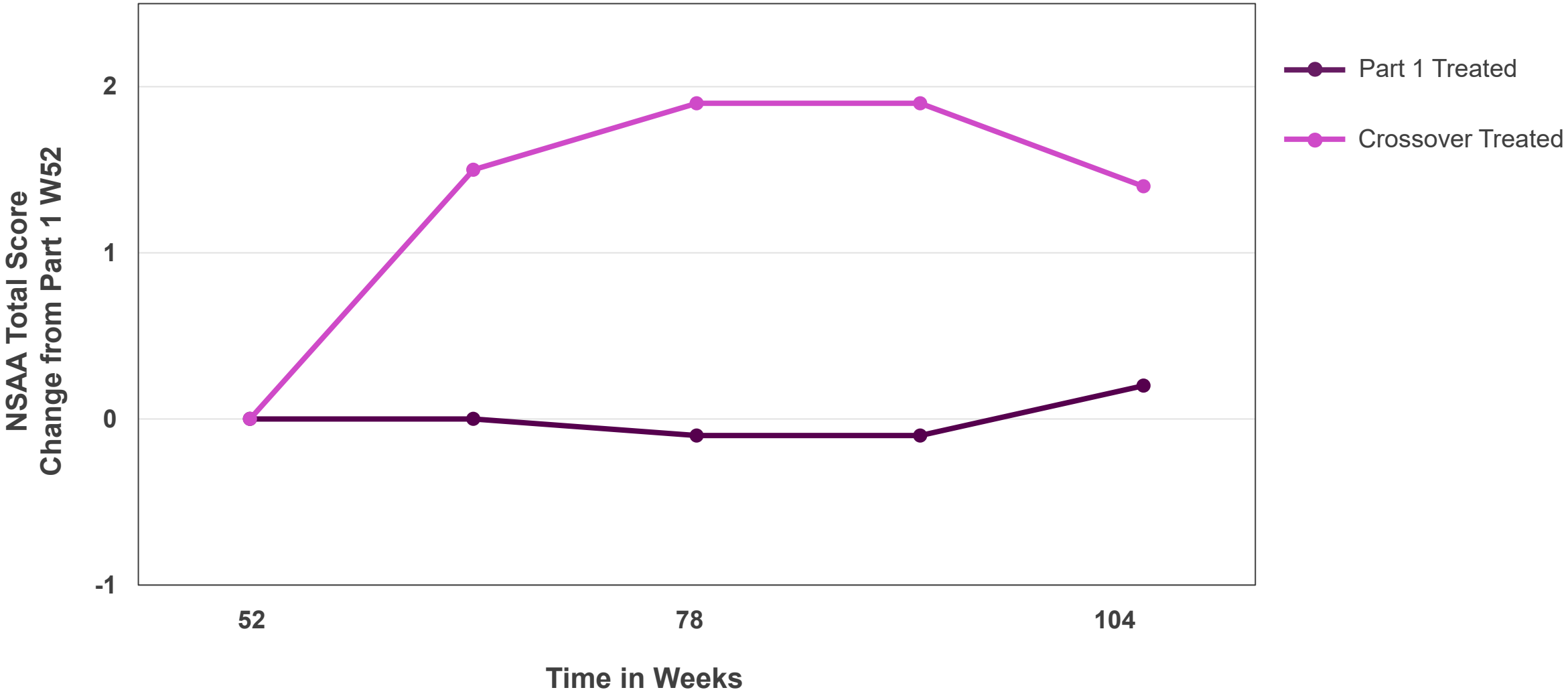
# EMBARK NSAA* Total Score: Baseline to Year 2, blinded study results




*North Star Ambulatory Assessment

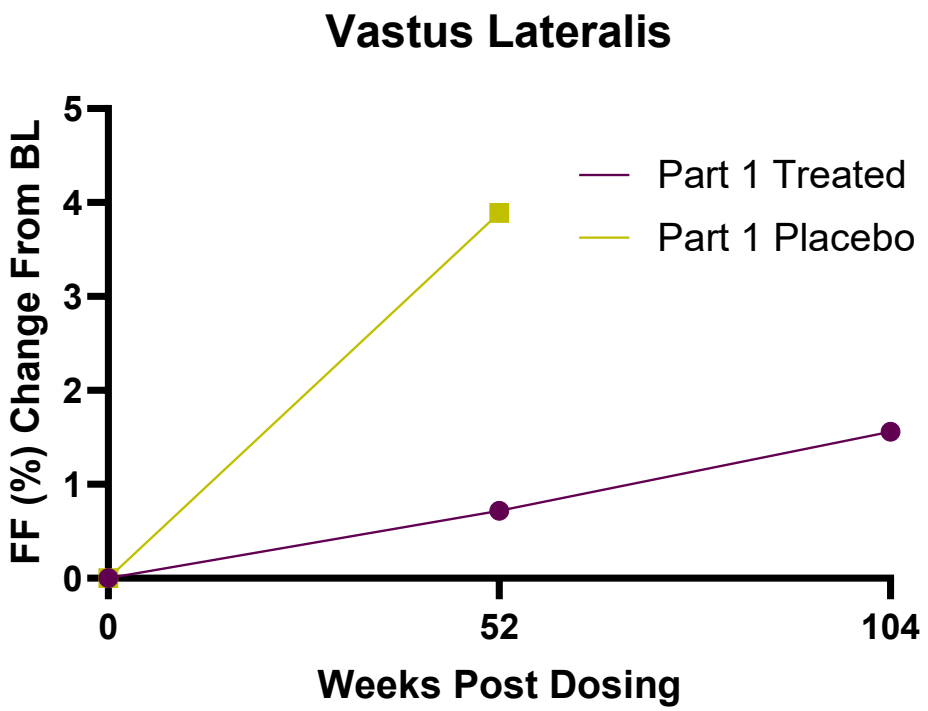
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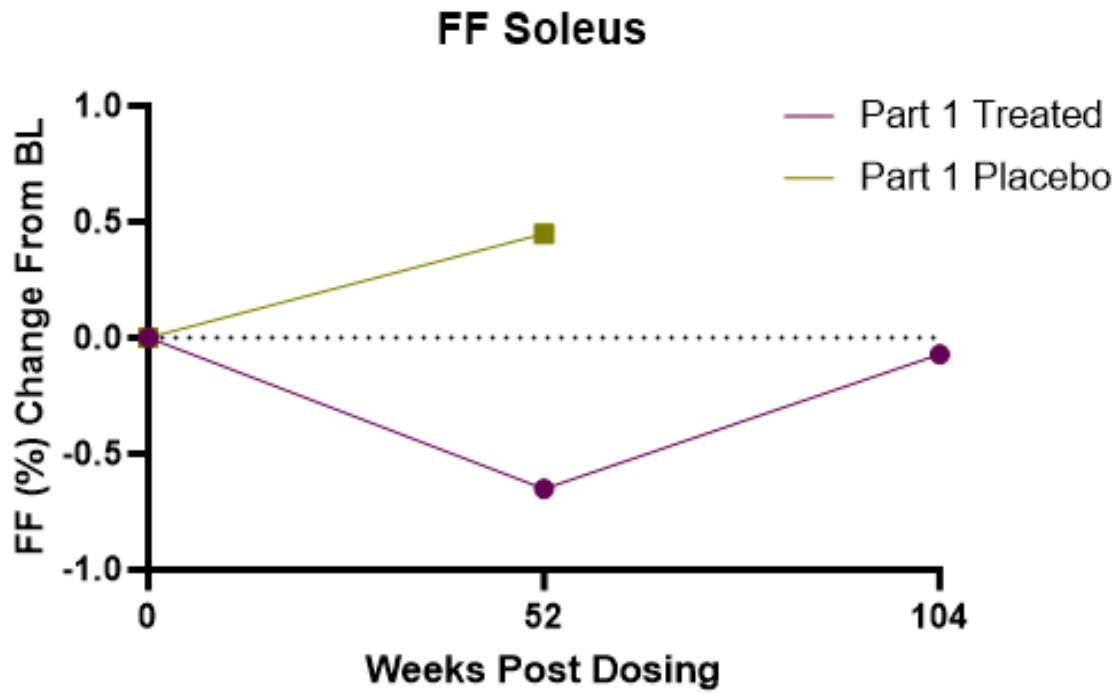
# NSAA increases in crossover treated patients following ELEVIDYS dosing




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# 2-Year Results: Musculoskelatal MRI - fat fraction (FF)




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

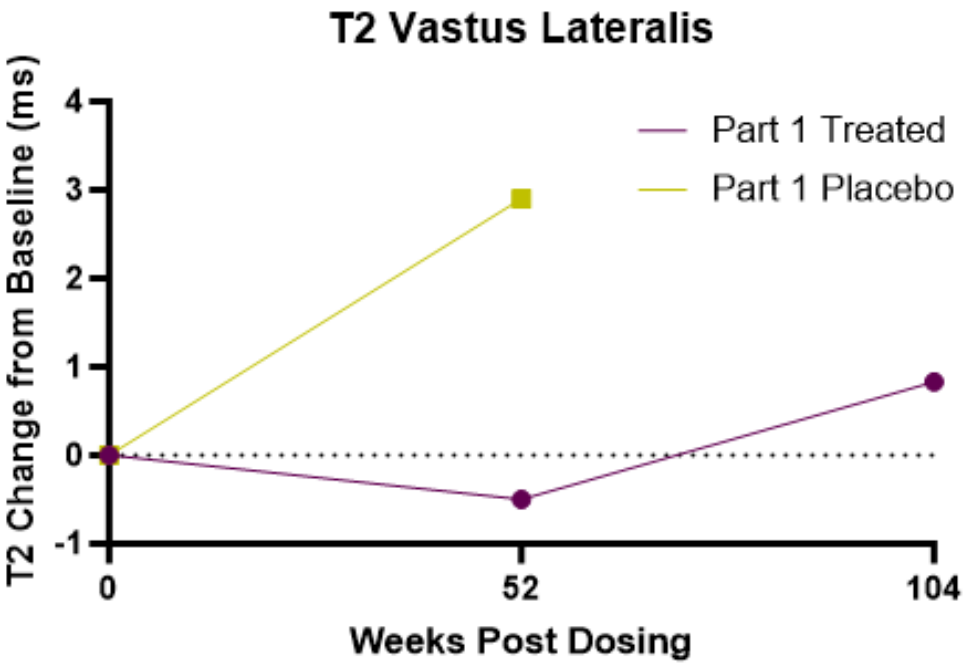
| | | |
|---|---|---|
| N=17 | N=15 | |
| N=16 | N=16 | N=15 |

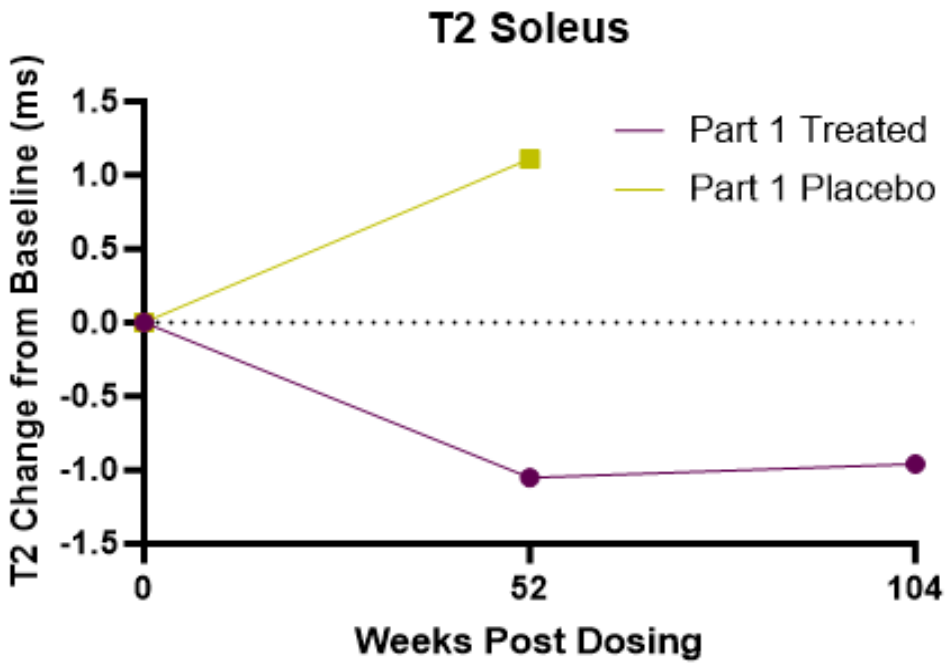
**Stabilization in MRI muscle FF in 9001 treatment group with two years values below those seen in part 1 placebo group**


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.


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# 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.

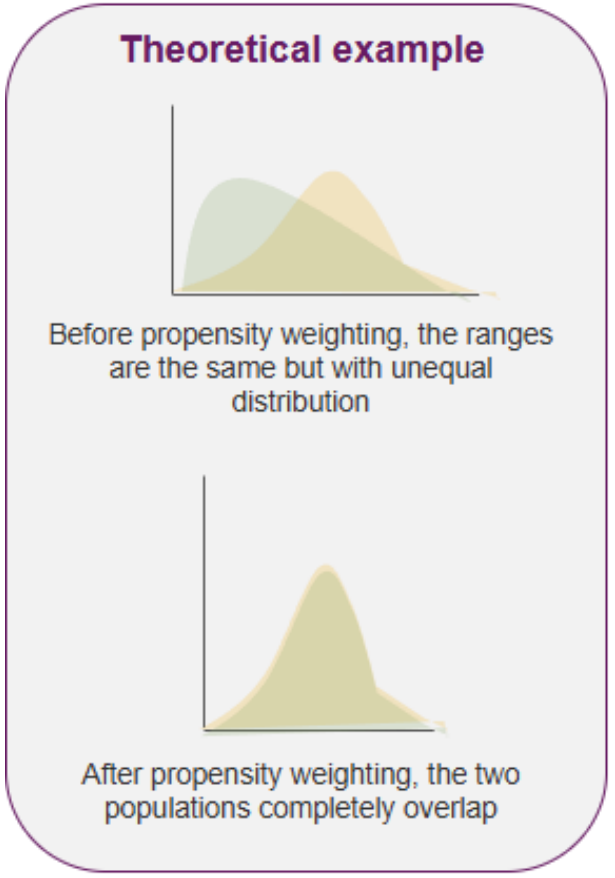

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# EMBARK Part 2 Results: Crossover-treated patients compared to external control, 1-year data

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# 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




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

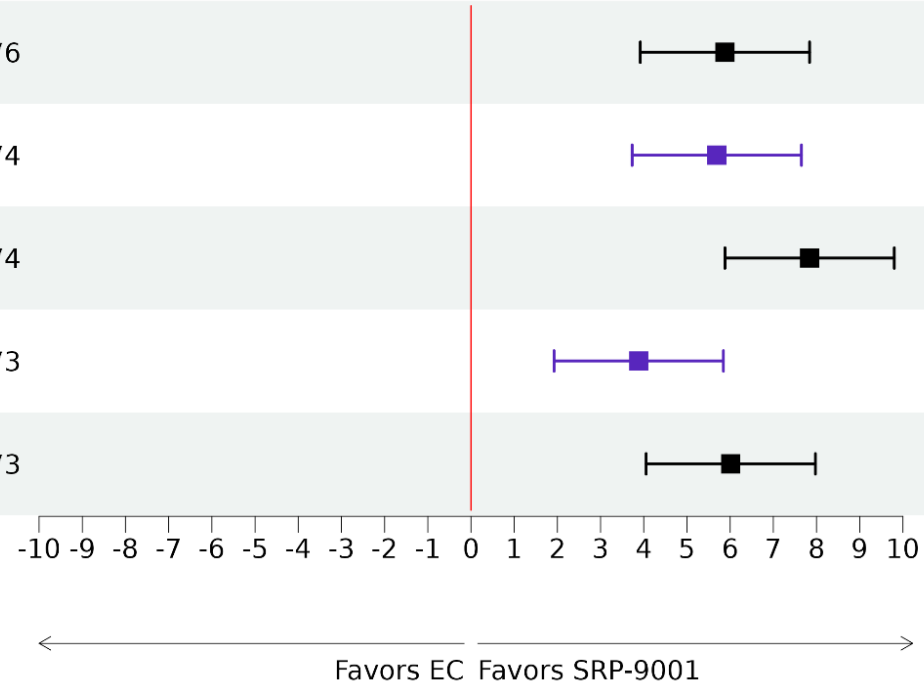
**Baseline Characteristics (Weighted)**
**Full Analysis Set**

| 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) |

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# 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 |

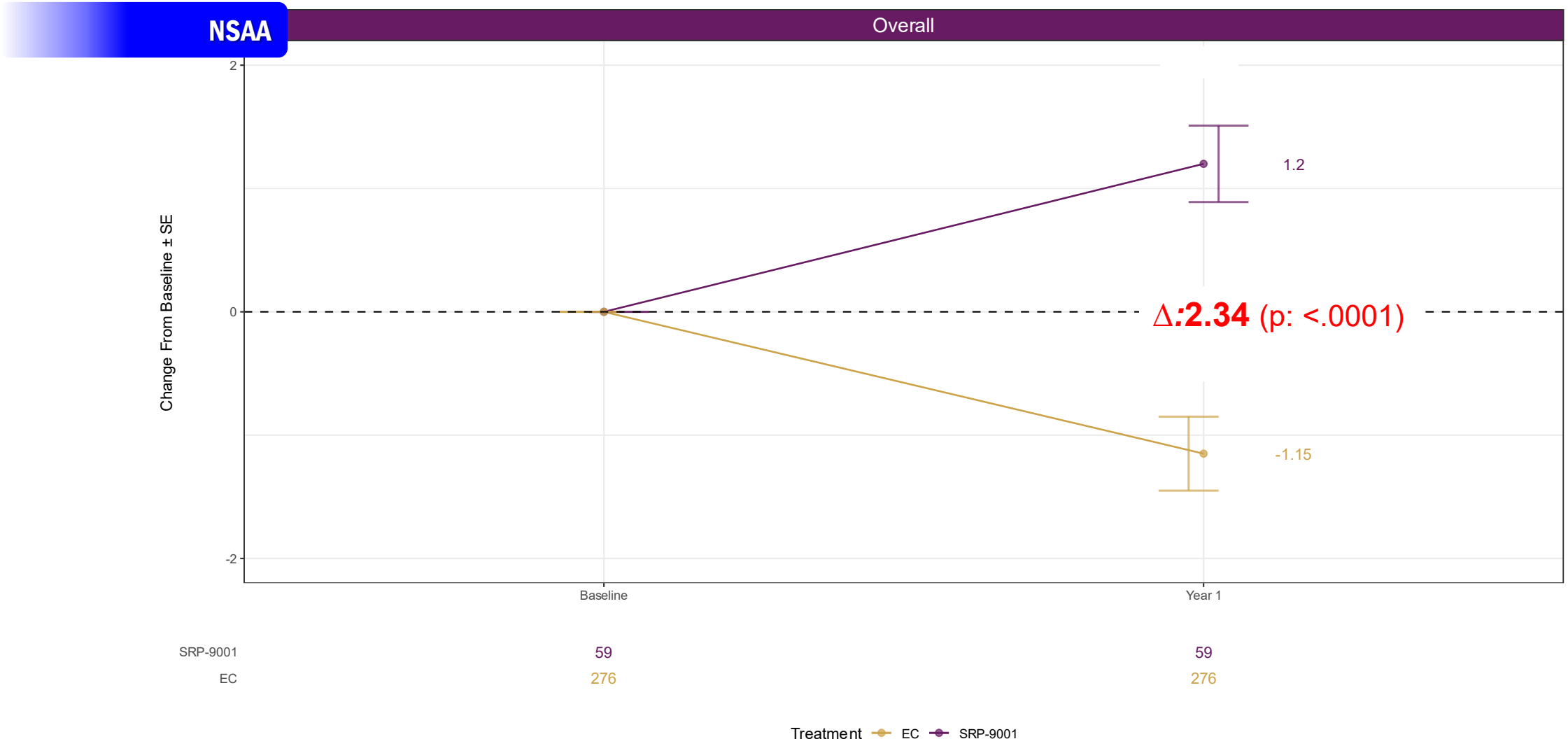



** Sign reversed to align favorable directions among effect endpoints*

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.

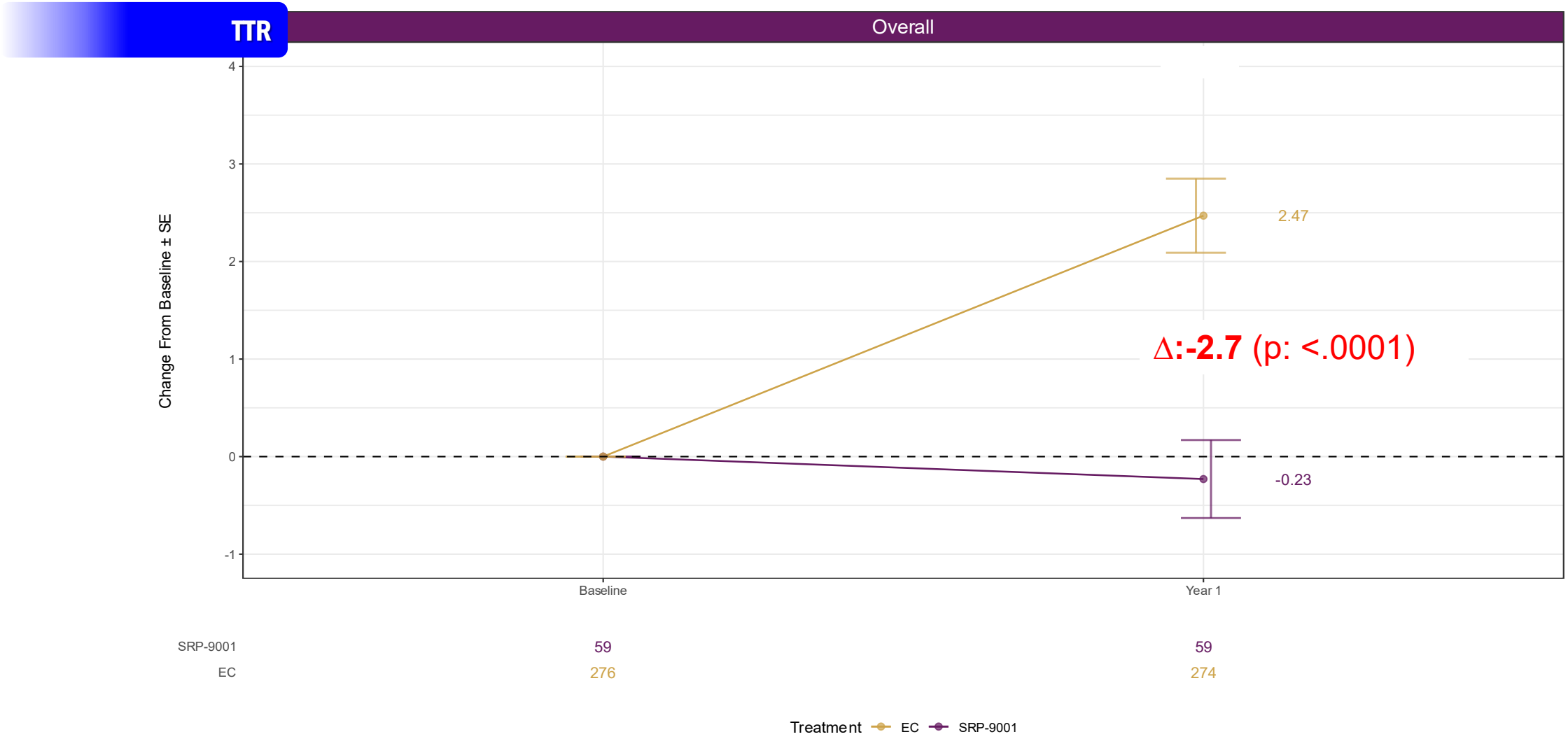
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# Statistically significant increase in NSAA one year after treatment compared to EC




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




Mendell, J.R., et al. Neurol Ther (2026).

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




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

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# 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)** |

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# Balanced baseline characteristics for Part 1 treated and EC

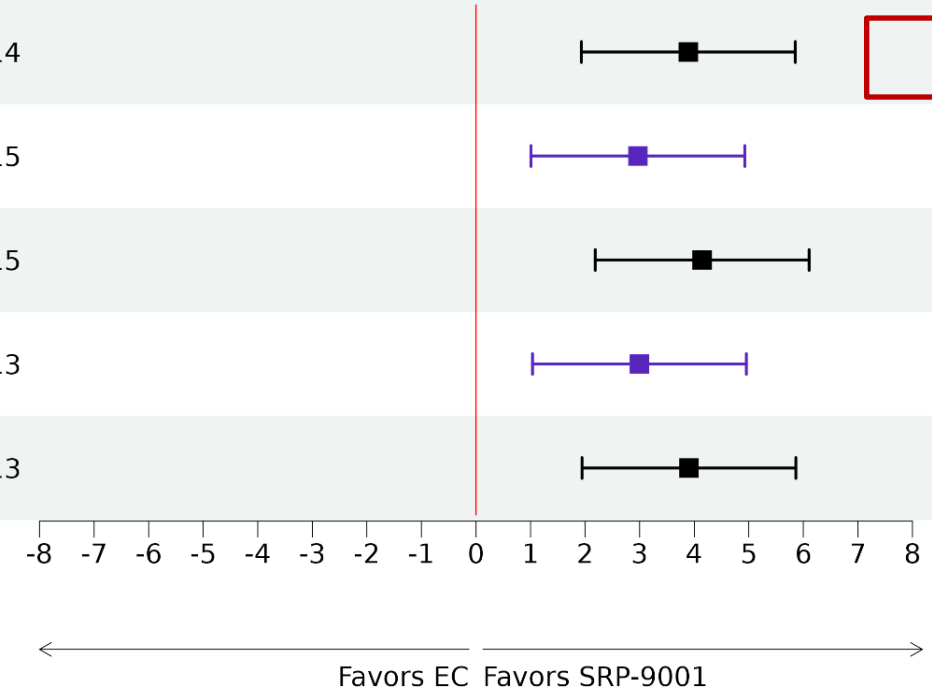
**Baseline Characteristics (Weighted)**
**Full Analysis Set**

| 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) |

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# 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.

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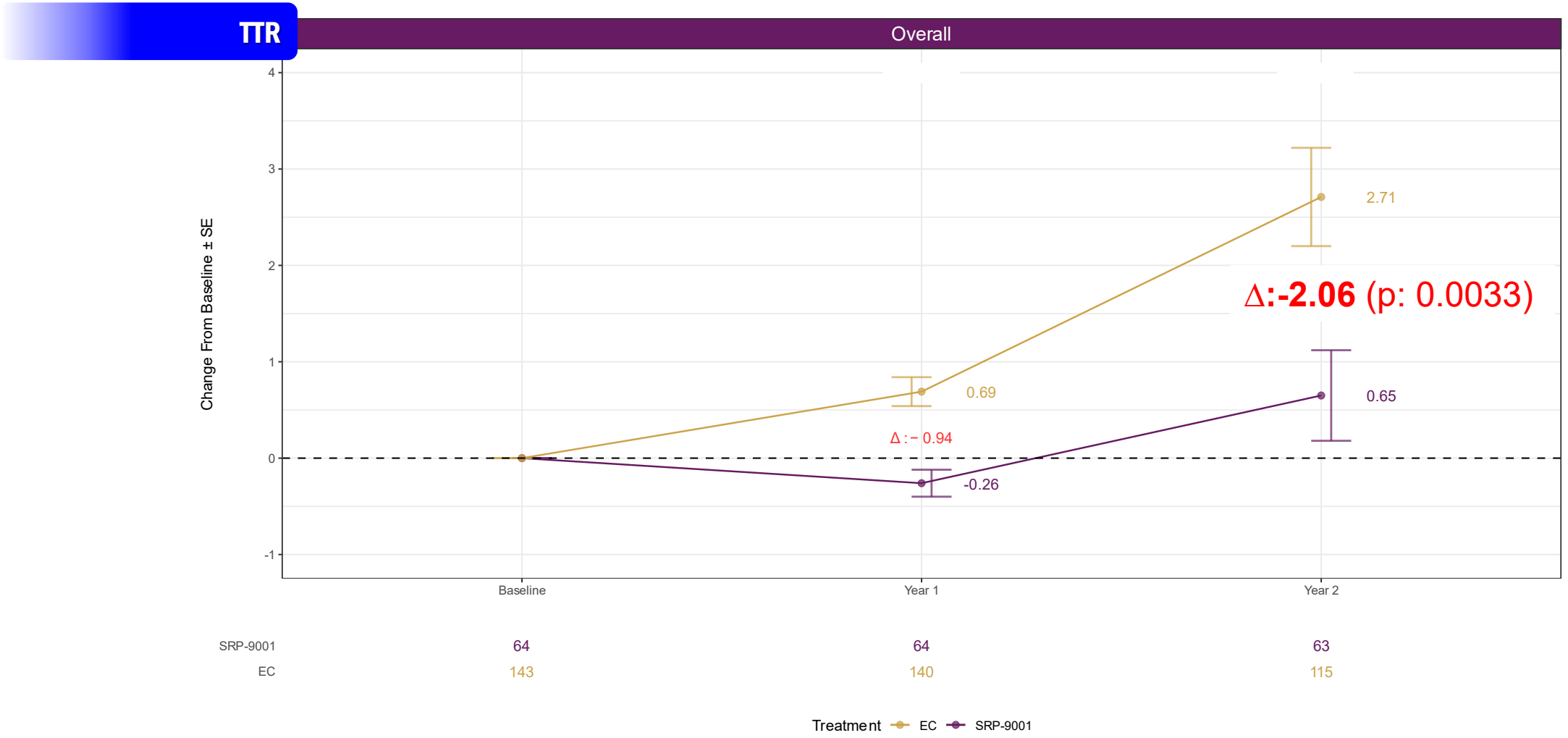
# NSAA improvements were sustained two years after treatment, showing a widening divergence from natural history




Mendell, J.R., et al. Neurol Ther (2026). https://doi.org/10.1007/s40120-025-00879-8.

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

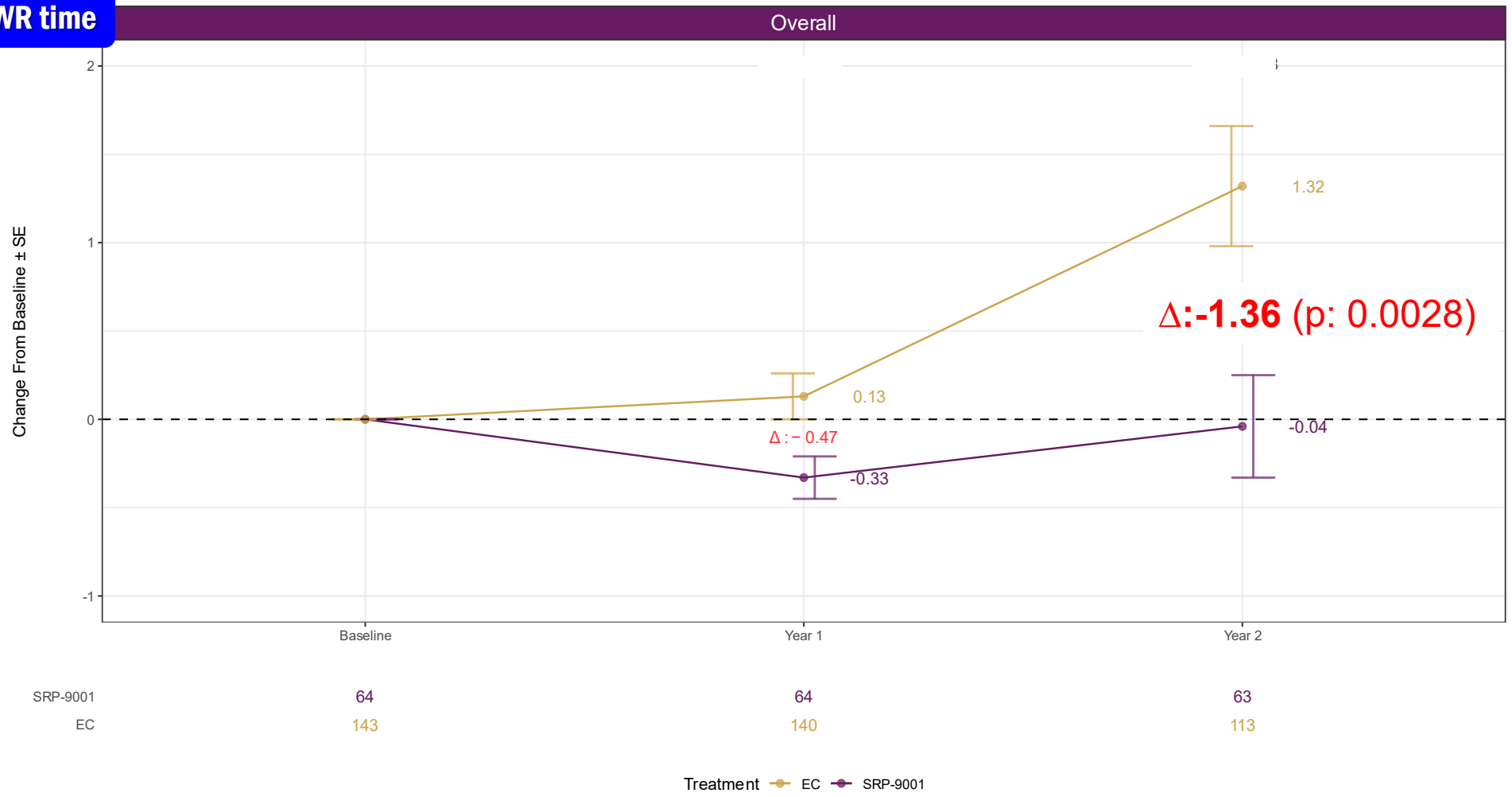



Mendell, J.R., et al. Neurol Ther (2026). https://doi.org/10.1007/s40120-025-00879-8.

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

**10MWR time**




Mendell, J.R., et al. Neurol Ther (2026). https://doi.org/10.1007/s40120-025-00879-8.

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# Cardiac MRI shows patients remain in normal range over 2 years of follow-up

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) |

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# Results from EMBARK:
# 3-Year Topline Data, Part 1-treated vs EC
## (Analysis Using LS-Mean by MMRM)

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# 3-year topline functional results from part 1 of EMBARK (Study 9001-301)

- On average, ELEVIDYS-treated patients remain above their baseline three years after treatment as measured by NSAA

- Statistically significant 73% slowing of disease progression as measured by TTR (time to rise)

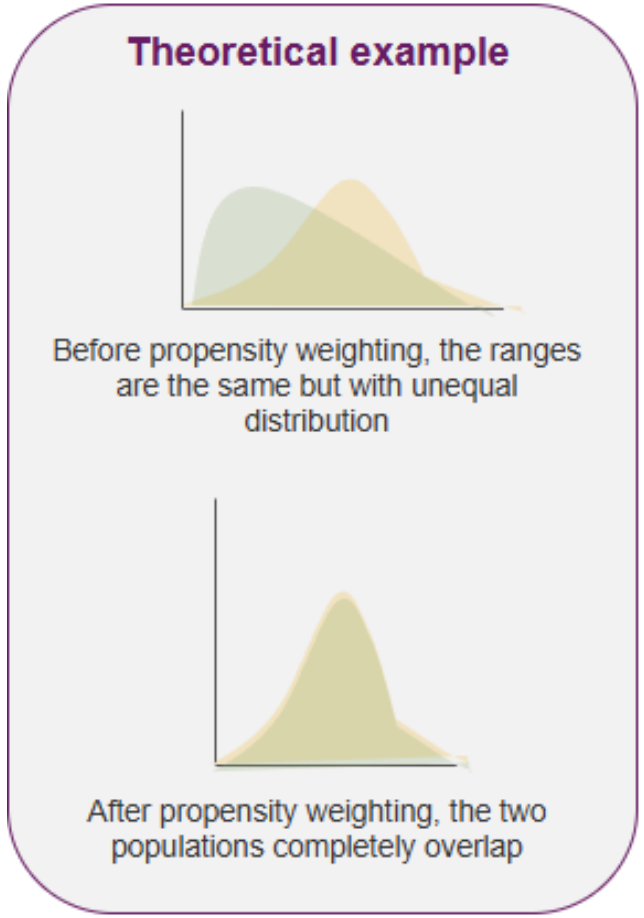
- Statistically significant 70% slowing of disease progression as measured by 10MWR (10-meter walk run)

**For the first time, a gene therapy for Duchenne has demonstrated a profound change in the trajectory of the disease out to three years**

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# Background on the external control (EC)

- 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 (n= 116)
  - DEMAND-III placebo arm (n= 186)
  - PRO-DMD (n= 269)
  - CINRG DNHS (n= 440)
  - FOR-DMD (n= 194)
- Propensity score weighting is used to decrease bias
- Protocols agreed to by regulatory authorities prior to the start of the study




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# Baseline characteristics balanced for part 1-treated and external control

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

| Characteristic, Mean (min, max) | EMBARK Part 1 Delandistrogene moxeparvovec (N=64) | EC cohort (N=143)† | Standardized mean difference after propensity-score weighting* |
|---|---|---|---|
| **Age, years** | 5.98 (4.07, 7.87) | 6.24 (4.24, 7.99) | –0.281 |
| **NSAA total score, points** | 23.3 (14, 32) | 23.5 (15, 32) | –0.045 |
| **TTR, time in seconds** | 3.51 (1.85, 5.75) | 3.52 (1.90, 5.70) | –0.011 |
| **10MWR, time in seconds** | 4.80 (3.20, 6.85) | 4.78 (3.00, 6.70) | 0.034 |
| **Weight, kg** | 21.20 (13.5, 37.4) | 22.18 (14.0, 36.0) | –0.198 |
| **Height, cm** | 108.65 (93.5, 127.0) | 110.60 (94.9, 131.1) | –0.285 |
| **BMI, kg/m$^2$** | 17.80 (13.69, 24.92) | 17.90 (13.74, 23.64) | –0.042 |

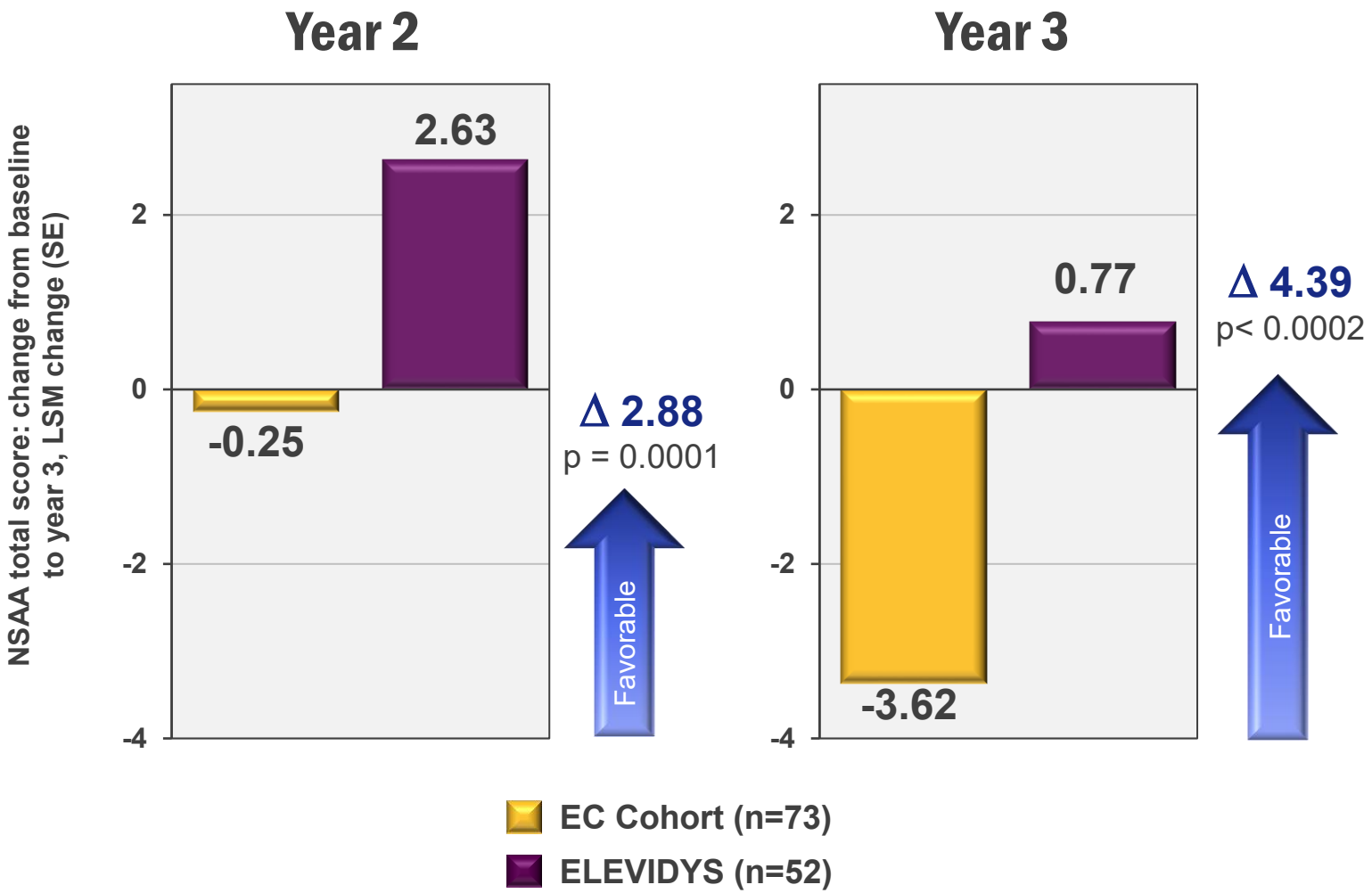
*Inverse probability of treatment weighting.
†Prior to propensity-score weighting, there were 155 patients in the EC cohort who met the entry criteria and had at least 1 post-baseline visit (FOR-DMD, n=89; BioMarin PRO-DMD-01, n=41; CINRG DNHS, n=25).
10MWR, 10-meter Walk/Run; BMI, body mass index; EC, external control; NSAA, North Star Ambulatory Assessment; TTR, Time to Rise.
Mendell et al. Poster presented at: Muscular Dystrophy Association Clinical and Scientific Conference, March 16-19, 2025; [Dallas, TX]; [Poster P169].

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# ELEVIDYS-treated patients (n=52) achieved a significantly higher NSAA total score compared to the external control group, with a p-value of 0.0002

NSAA Outcomes at Year 2 & Year 3 vs EC Results

Mean age of patients 9 years old at time of last assessment




## Key Observations:

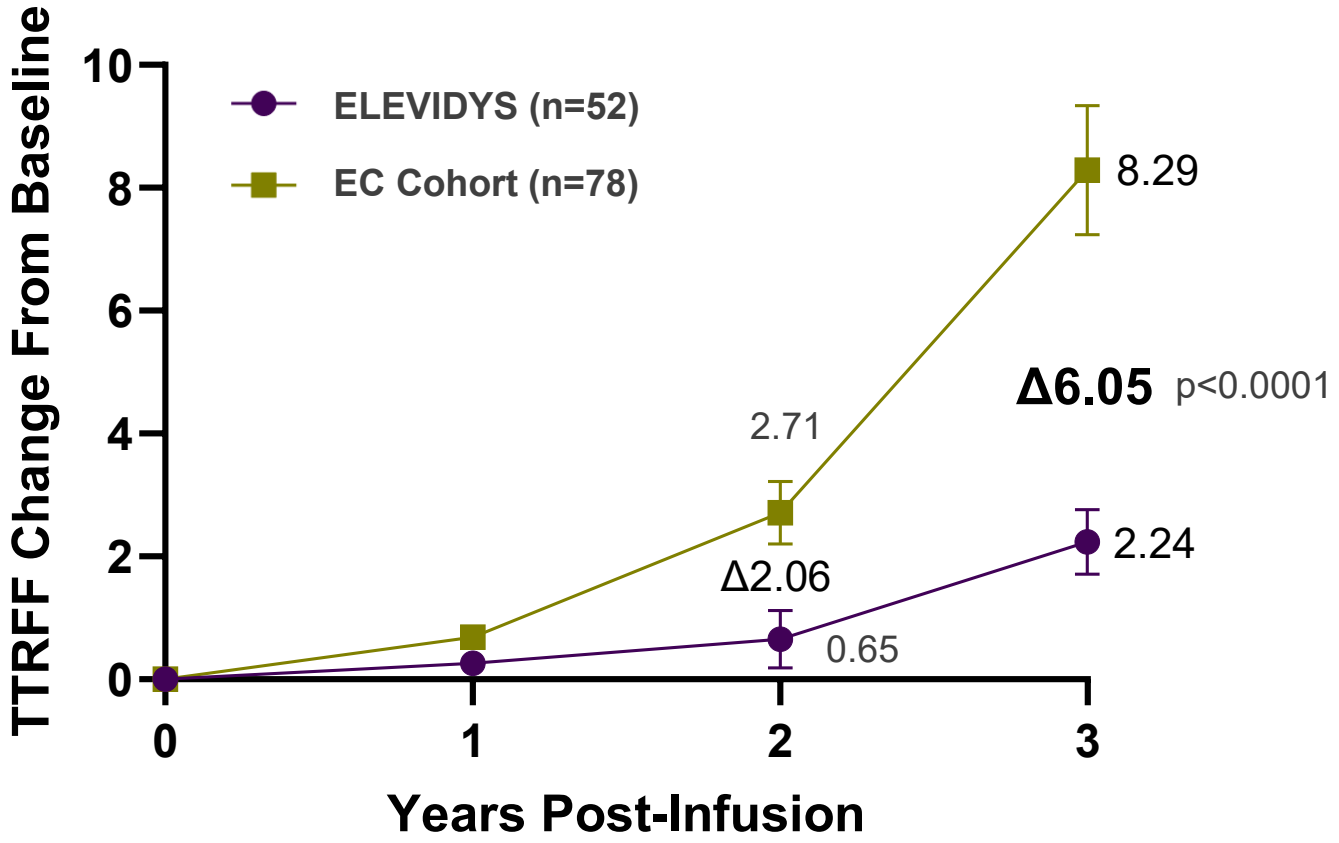
- The functional gap between treated and EC groups grew from a 2.88-point difference at Year 2 to a 4.39-point difference at Year 3.
- On average, ELEVIDYS-treated patients remain above their baseline while untreated peers declined to 3.62 points below baseline.

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# ELEVIDYS-treated patients demonstrated a highly significant 73% slowing of disease progression on TTR, with a p-value of < 0.0001

EMBARK Part 1: Time to Rise (TTR) Outcomes vs EC at Year 3 Results

**Mean age of patients 9 years old at time of last assessment**




## Key Observations:

- The performance gap nearly tripled in the third year, expanding from a 2.06-second difference at Year 2 to a 6.05-second difference at Year 3.
- ELEVIDYS-treated patients were able to far more rapidly rise from floor as compared to their untreated peers, who took an average of 8.29 seconds longer than baseline to stand compared to just 2.24 seconds for the treated group.

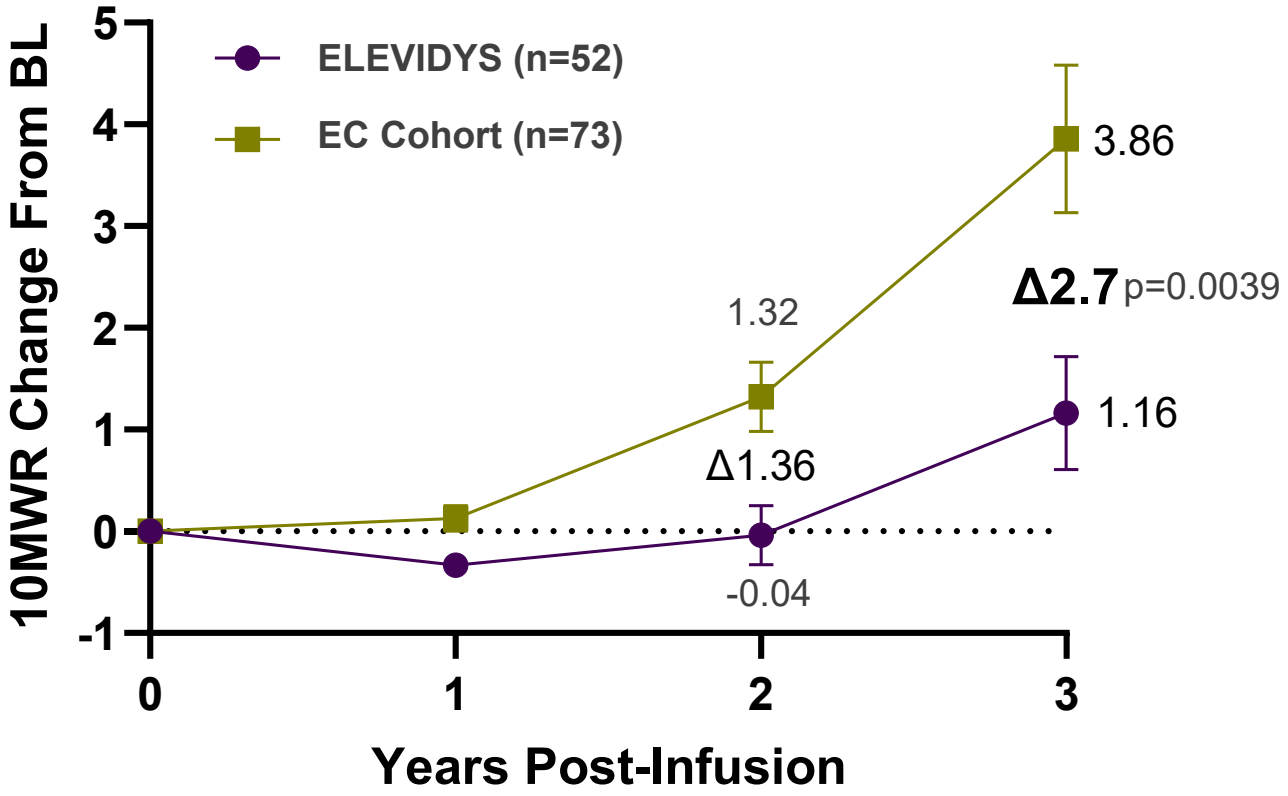
[a]All 64 patients treated with delandistrogene moxeparvovec and all 143 patients in the EC cohort were included in the analyses; MMRM methods account for missing data in these analyses. 12 patients treated with delandistrogene moxeparvovec in part 1 did not have 3-year follow-up data. In the EC cohort, 65 patients had missing year 3 data for TTR

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# ELEVIDYS-treated patients achieved a statistically significant 70% slowing of disease progression on 10MWR, with a p-value of 0.0039

EMBARK Part 1: 10-meter walk/run (10MWR) Outcomes vs EC at Year 3 Results

**Mean age of patients 9 years old at time of last assessment**




## Key Observations:

- Treated patients remained stable, with a decline of 1.16 seconds from baseline, whereas the untreated group declined over 3 times as much declining 3.86 seconds from their original time.

[a]All 64 patients treated with delandistrogene moxeparvovec and all 143 patients in the EC cohort were included in the analyses; MMRM methods account for missing data in these analyses. 12 patients treated with delandistrogene moxeparvovec in part 1 did not have 3-year follow-up data. In the EC cohort, 70 patients had missing year 3 data for 10MWR

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# Three-year safety for part 1-treated patients

| | Year 1 (EMBARK Y1) | Year 2 (EMBARK Y2)* | Year 3 (EXPEDITION Y1)^ |
|---|---|---|---|
| Patients with any SAEs | 14 | 5 | 4 |
| Patients with treatment-related SAEs | 7 | 1 | 0 |
| Treatment-related deaths | 0 | 0 | 0Ŧ |

- No new safety signals were observed
- The safety profile of ELEVIDYS as observed in participants dosed in EMBARK is fully consistent with our understanding of the identified and labelled risks of the medicine

*Only includes new events in year 2 of the study, excludes unresolved events that began in year 1
^Only includes new events in year 3 of follow-up, excludes unresolved events that began prior to this period
ŦOne treatment unrelated death of a Part 1-treated patient was disclosed in the community safety update webinar in August 2025 and on regulations.gov: https://www.regulations.gov/comment/FDA-2025-P-1929-0007

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# Long-term results from EMBARK demonstrate significant and growing functional benefit compared to EC

- At the time of their last assessment, mean age of patients treated in EMBARK is 9 years old, corresponding to a nearly universal period of functional decline in Duchenne
- On average, ELEVIDYS-treated patients remain above their baseline three years after treatment as measured by NSAA
- Statistically significant 73% slowing of disease progression as measured by TTR (time to rise)
- Statistically significant 70% slowing of disease progression as measured by 10MWR (10-meter walk run)
- Safety profile remains consistent

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# ENDEAVOR

## SRP-9001-103 Results

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# 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

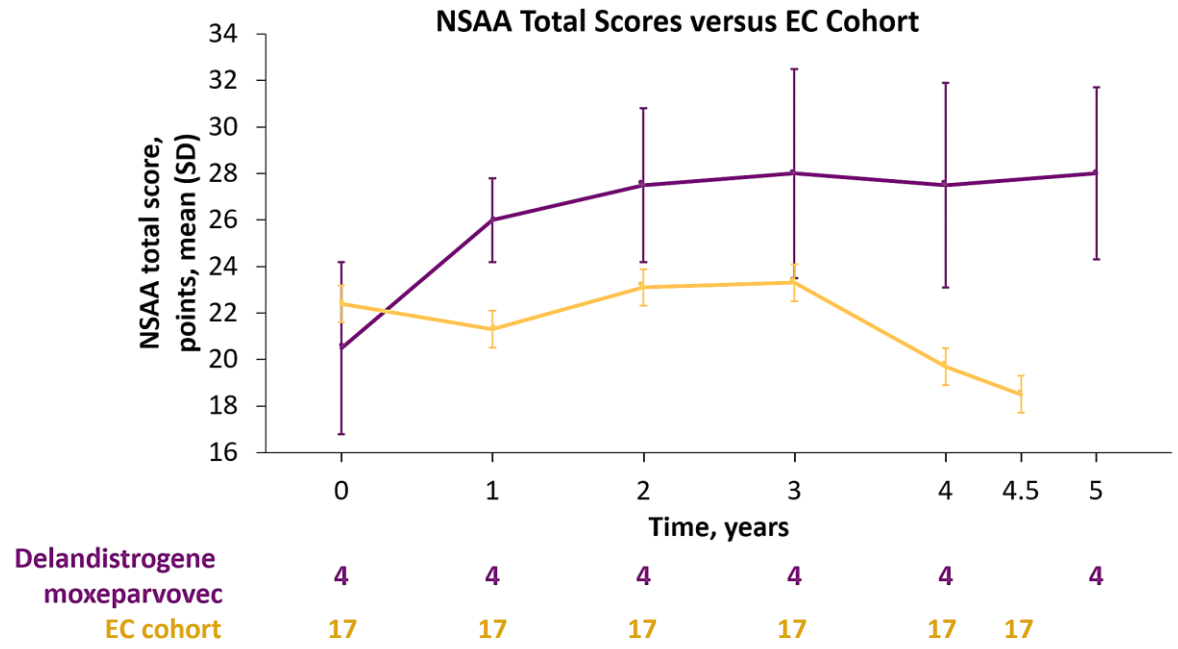
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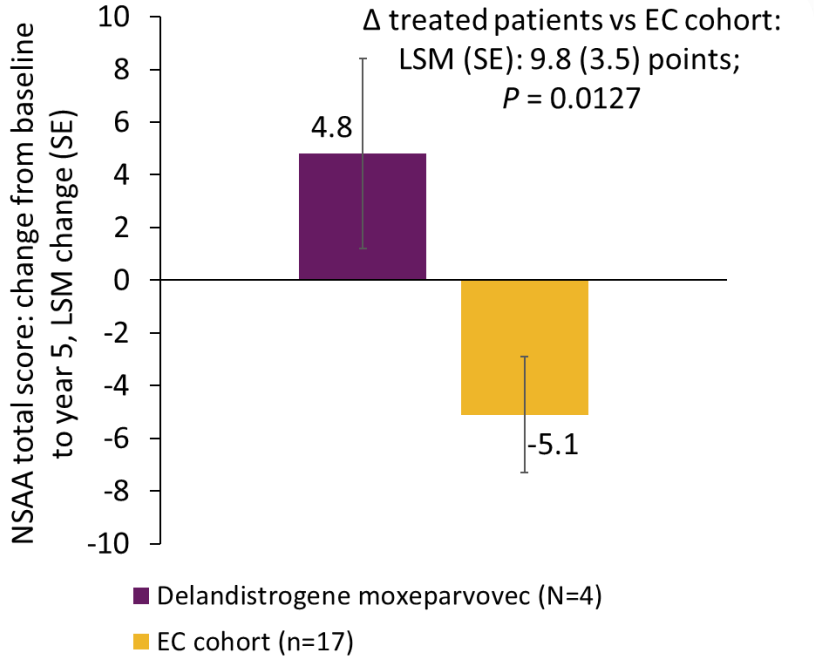
# SRP-9001-101
# Year 5 Results

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# 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.

Mendell JR, et al. Presented at the 2025 MDA Clinical and Scientif ic Conference, Dallas, TX, USA; March 16–19, 2025. P118.

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# ELEVIDYS Safety Data

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# 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.

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# 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) |

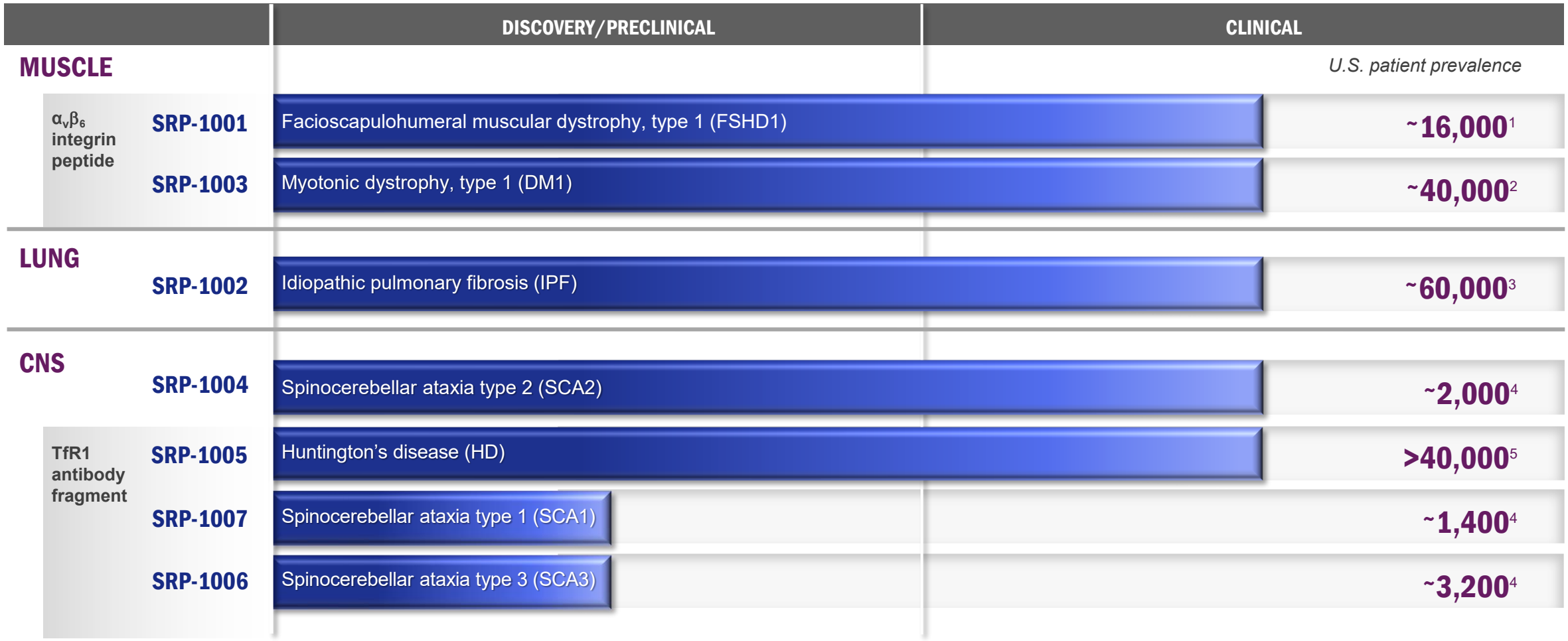
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# Key siRNA Programs

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

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# Advancing pipeline





1. Kabelac Z, et al. Neurology. 2020;94(15_Supplement)1561. (Diagnosed patients in the U.S.).
2. 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. (Diagnosed patients in the U.S.).
3. Data on file. (U.S.).
4. Ruano et al, Neuroepidemiology 2014. (Diagnosed patients in the U.S.).
5. https://hdsa.org/what-is-hd/. (People in the U.S. affected).


*Updated April 2026*

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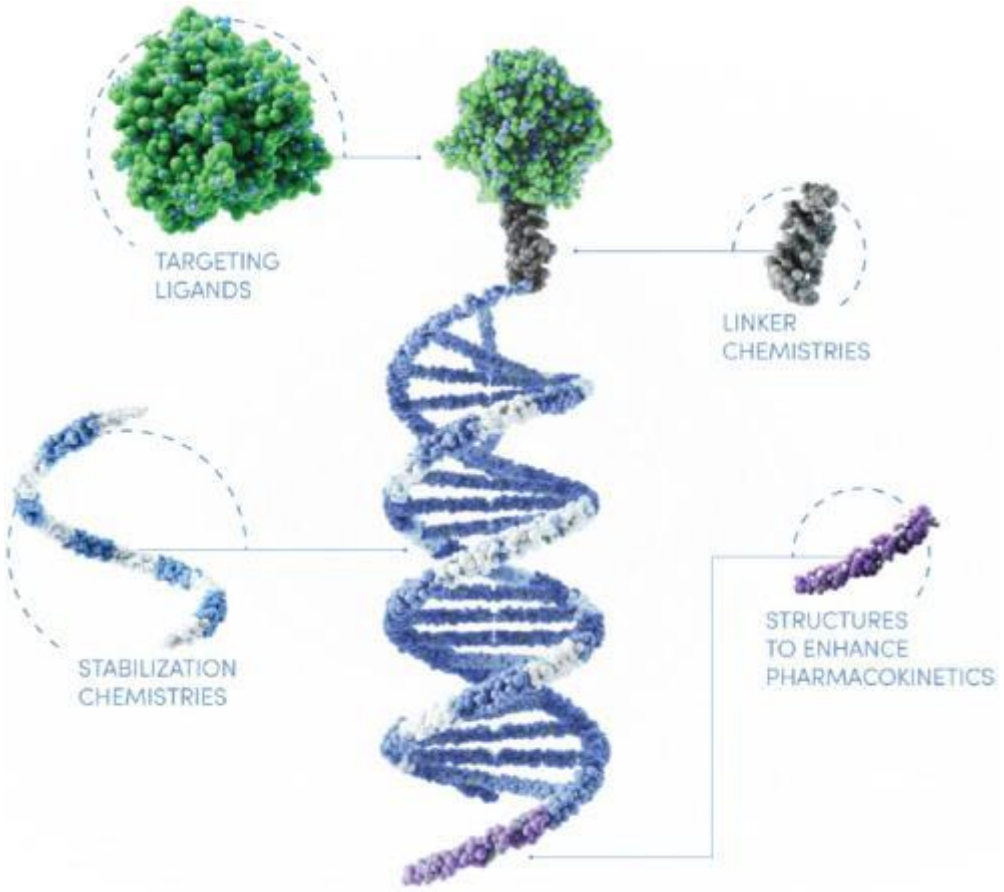
# Components of TRiM™ and the science that enables our pipeline

## Delivery

*Tissue-specific ligands (peptide, small molecule, Ab) designed to deliver siRNA to Liver, CNS, Muscle, Heart etc.*

## siRNA Chemistry

*Established and experimental chemical modifications designed to optimize potency, duration, and target specificity.*




## Linker

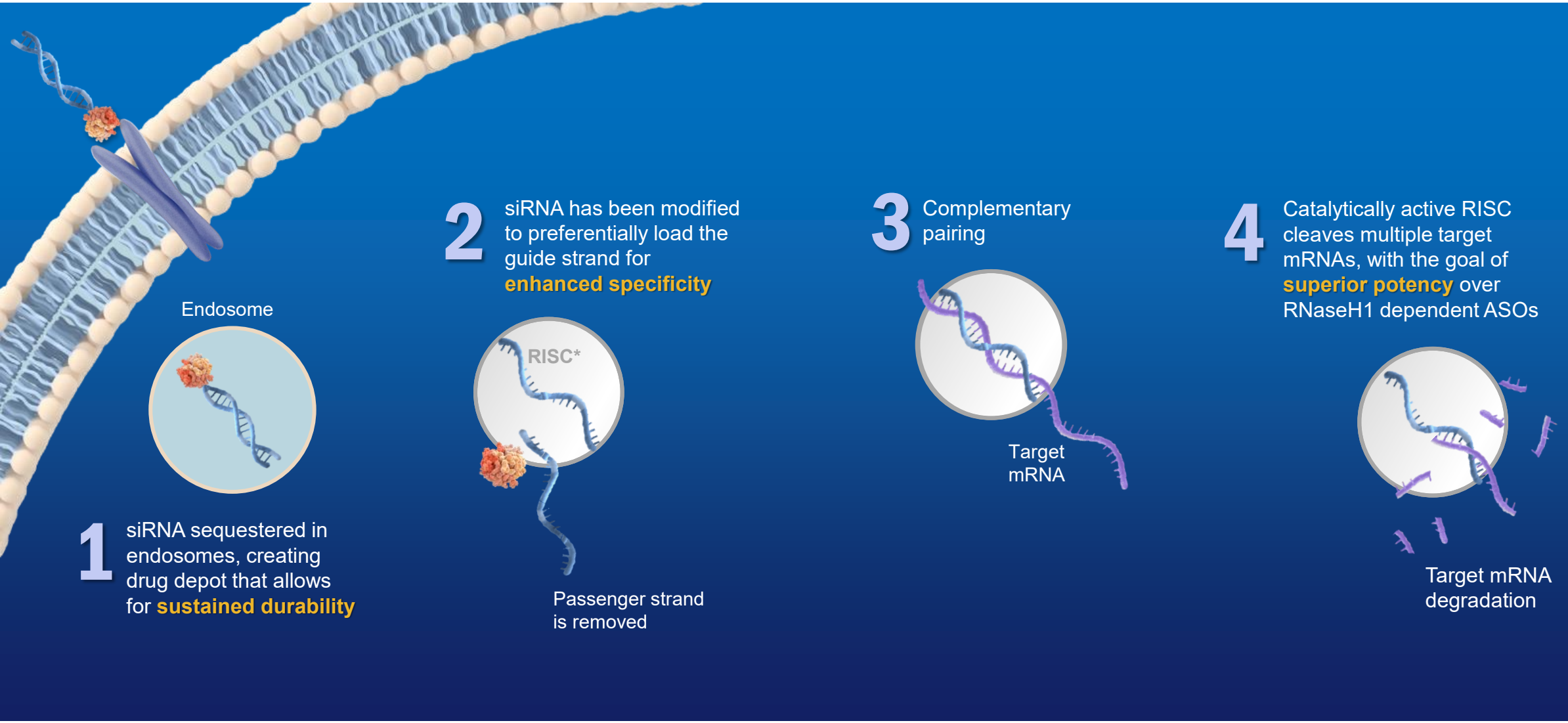
*Designed to provide stability/orientation. Linker is selected to optimize efficacy, reduce tox, and CMC complexity. Often, many known linkers are tested to select most optimal combination for each program.*

## PK/PD Structures

*Certain programs have novel features aimed at enhancing half life (e.g., lipid for SRP-1001).*

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# A Biology-First Approach: siRNA-mediated mRNA Degradation Designed to Enable Specific Target Knockdown



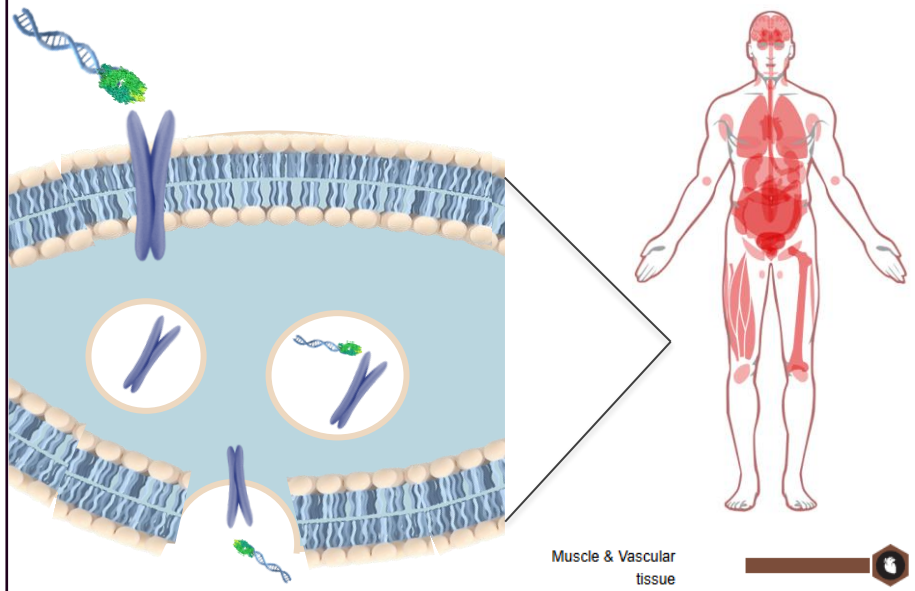

*RNA-induced Silencing Complex (RISC)

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# Targeting $\alpha_v\beta_6$ Integrin over TfR1 for Greater Muscle Uptake

High expression and surface availability of $\alpha_v\beta_6$ in muscle make it a preferred receptor for targeted siRNA delivery

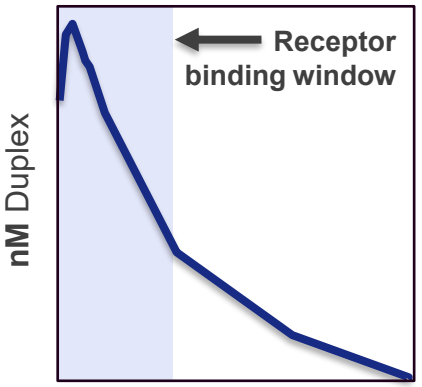
**TfR1: 5%[1]** of receptors available for binding on surface at any one time; majority are intracellular trafficking transferrin or being recycled to membrane



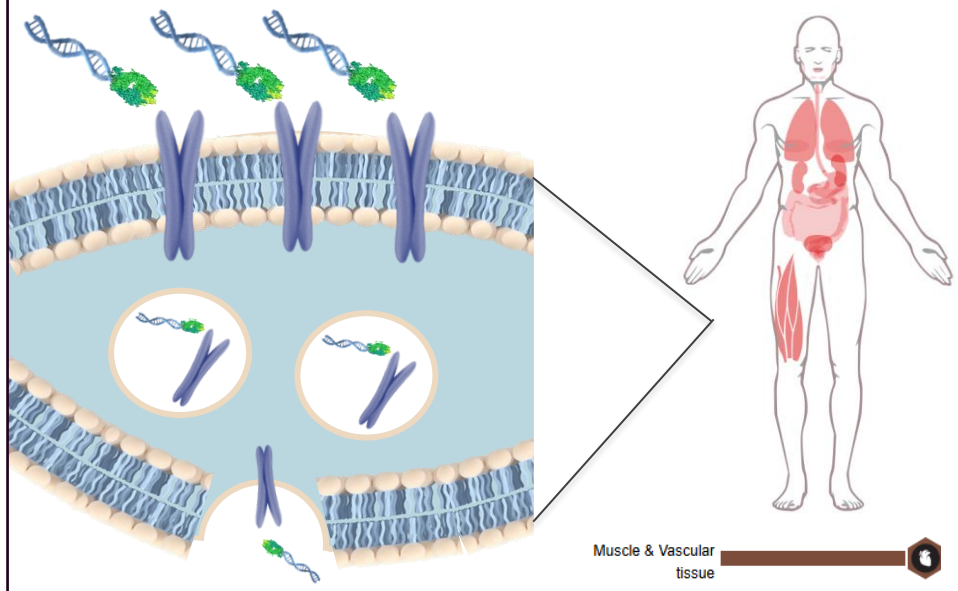

TFRC Protein Atlas

## IV Delivery

Receptor recycling times range from 30 minutes to a few hours[1,2], creating short window for receptor-mediated endocytosis




**$\alpha_v\beta_6$: ~40%[3]** of receptors available for binding on surface at any one time; higher muscle and vascular expression than TfR1




ITGB6 Protein Atlas

[1]https://doi.org/10.3390/ph14060535
[2]https://doi.org/10.3389/fcell.2022.920303
[3]http://dx.doi.org/10.1159/000443180

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# Potential advantages of siRNA integrin approach and best-in-class therapies to treat FSHD1 and DM1

## Better delivery to muscle with integrin $\alpha_v\beta_6$

| Optimal clinical impact | $\alpha_v\beta_6$ siRNA | TfR1mAb siRNA | TfR1fAb ASO |
|---|---|---|---|
| **Potency** | ✓ | ✓ | |
| **Better muscle penetration** *(e.g., delivers more Rx to muscle)* | ✓ | | |
| **Safety and lack of dose limiting toxicity** | ✓ | | |
| **Longer dose interval** | ✓ | | |

The tolerability of the $\alpha_v\beta_6$-targeting platform may allow for best-in-class efficacy, through higher doses and greater muscle concentration without dose-limiting AEs.

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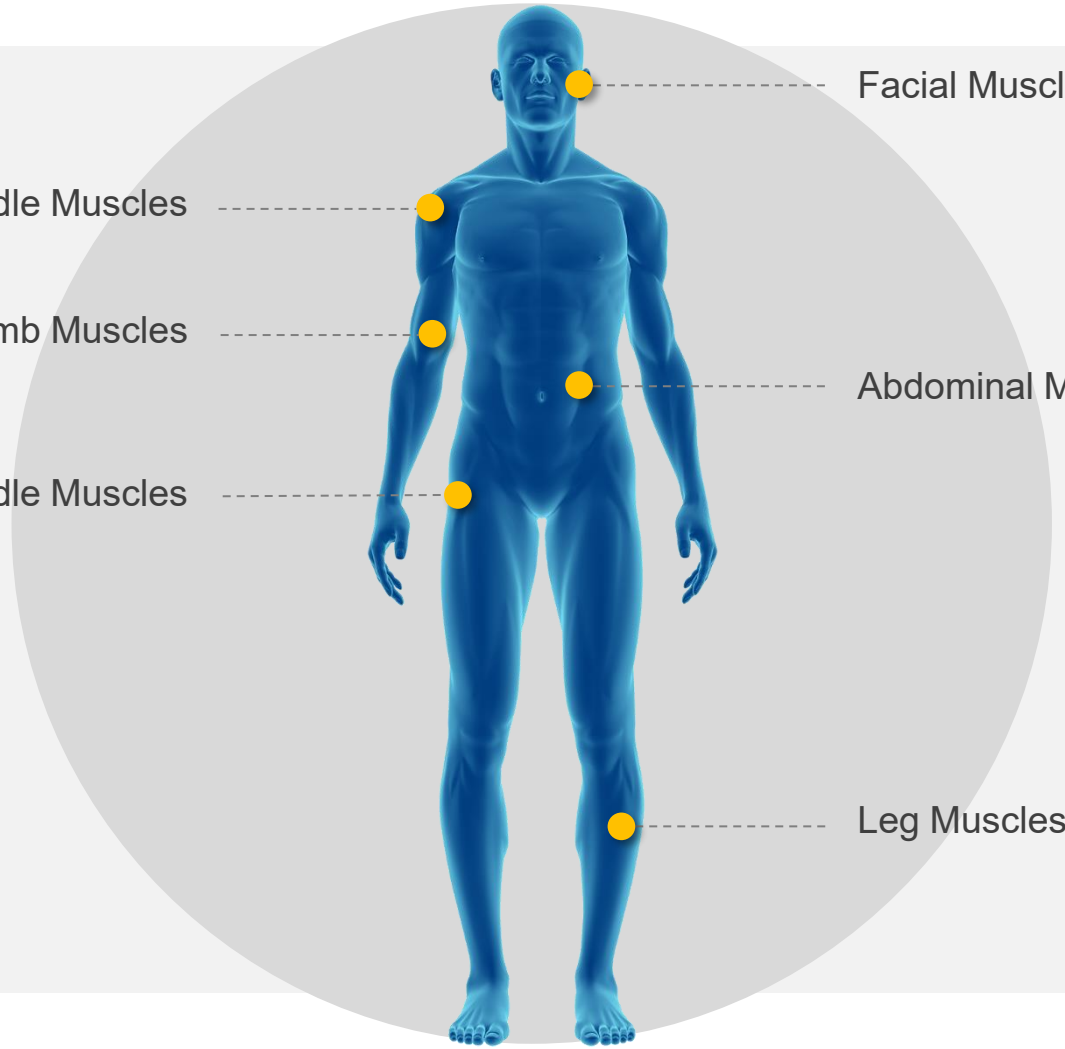
# SRP-1001: In clinical development for Facioscapulohumeral muscular dystrophy type 1 (FSHD1)

**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**

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# FSHD: Multiple skeletal muscles affected, beginning with the face



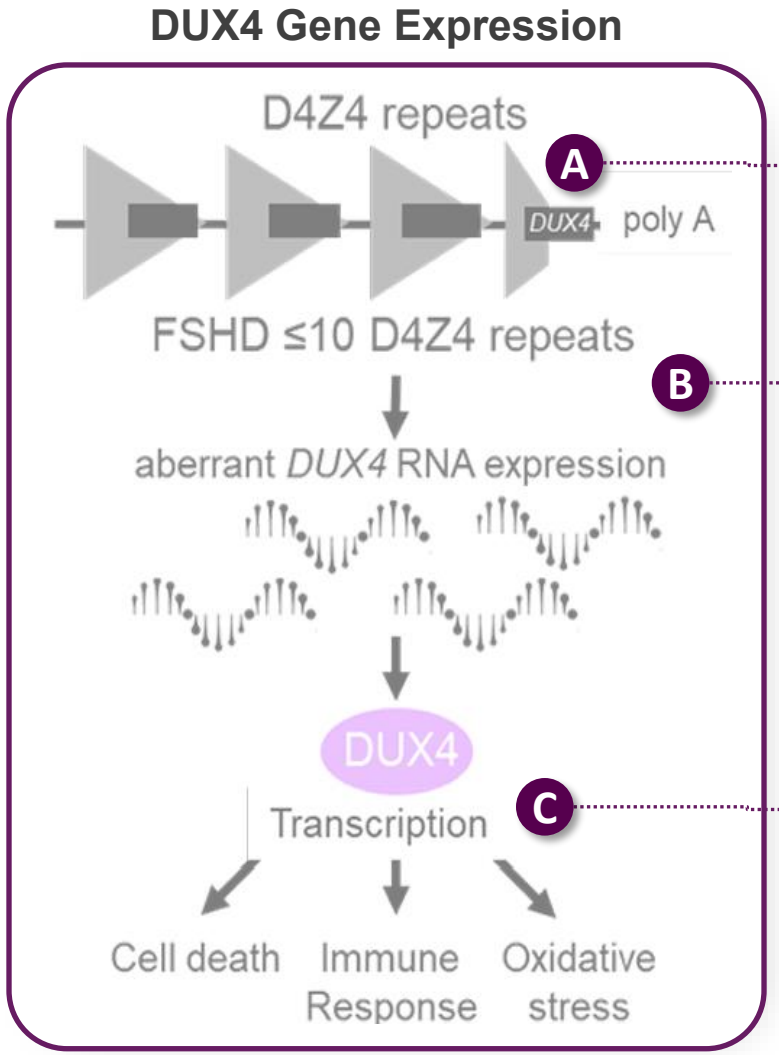

**Muscle Weakness and Mobility**

- ~50% of FSHD patients will progress to becoming dependent on a wheelchair after ~20 years
- >50% of FSHD patients have moderate to extreme level of mobility restrictions

"DUX4 Expression in FSHD Muscles: Focus on Its mRNA Regulation" *Journal of Personalized Medicine.*
"DUX4 Signaling in the Pathogenesis of Facioscapulohumeral Muscular Dystrophy", *International Journal of Molecular Sciences.* "Genetic Cause of FSHD", *FSHD Society*; Accessed March 2022.

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# FSHD is caused by the contraction of the D4Z4 repeat, leading to the abnormal expression of DUX4, which is typically silenced early in life



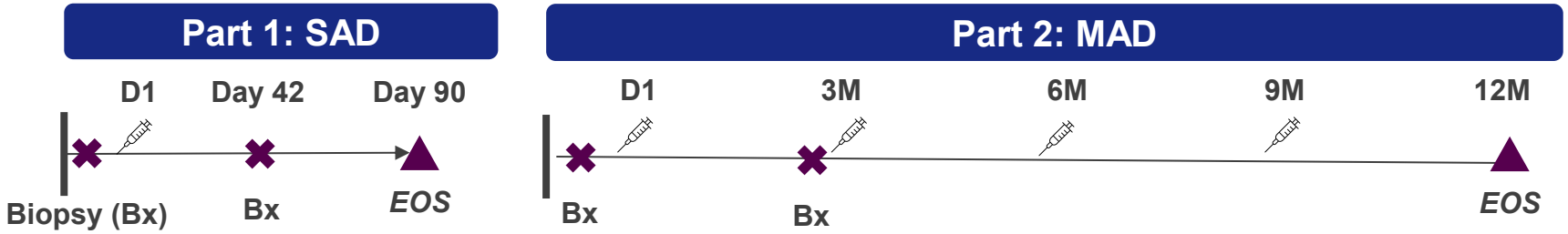

**DUX4 Transcription Factor**

**FSHD genotype leads to aberrant DUX4 expression**

**Downstream Cellular Consequences**

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# Study SRP-1001-101: A phase 1/2 randomized, placebo-controlled trial in participants aged 16-70 with FSHD1




## Cohort Design

**SAD**

**C1-4: n=6, 2:1**

- Cohort 1 (1.02 mg/kg siRNA)
- Cohort 2 (2.04 mg/kg siRNA)
- Cohort 3 (4.08 mg/kg siRNA)
- Cohort 4 (8.17 mg/kg siRNA)

**MAD**

**C5-7: n up to 12, 3:1**

- Cohort 5 (4.08 mg/kg siRNA Q3M)
- Cohort 6 (8.17 mg/kg siRNA Q3M)
- Optional Cohort 7 (8.17 mg/kg siRNA Q3M), 16-70 y/o

## Endpoints

**Primary**:
- Safety and tolerability

**Secondary**:
- PK in plasma

**Key Exploratory Endpoints:**
- siRNA muscle concentration
- Circulating DUX4 biomarker & DUX4 regulated gene expression
- Serum CK
- Functional: RWS, 6MWT, QMT, TUG
- PROs: Pain VAS, CIS, PGIC

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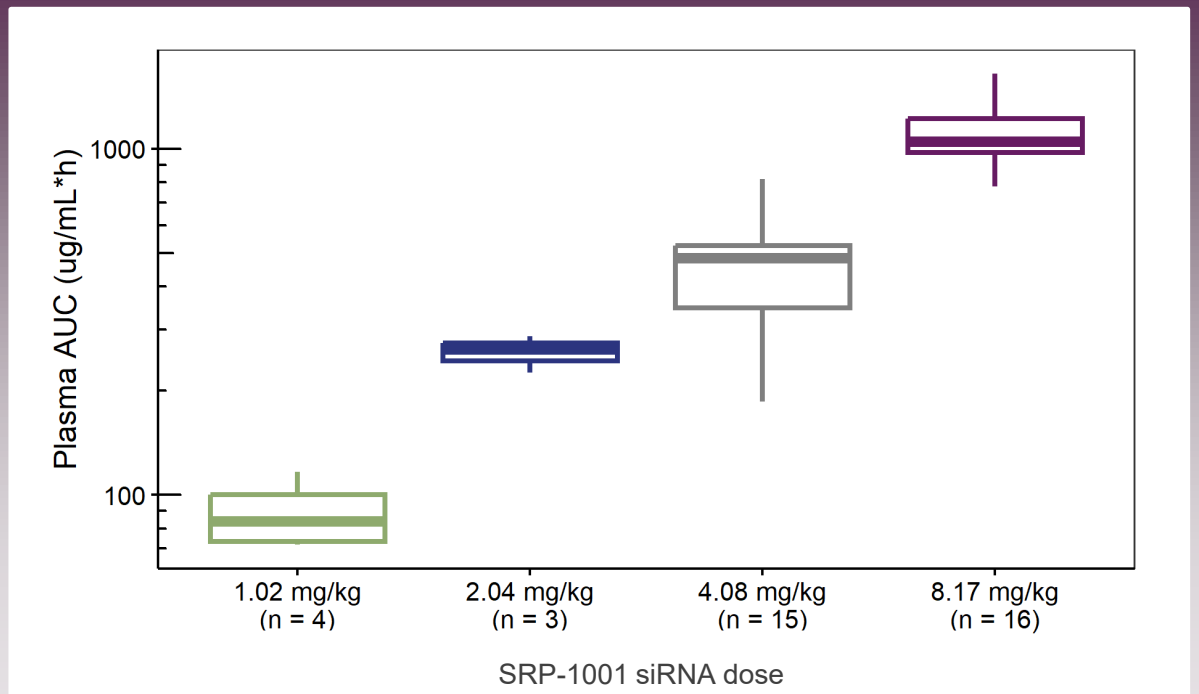
# Baseline characteristics

| | SAD | | | | MAD | | Overall | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort 1 (1.02 mg/kg) N=5 | Cohort 2 (2.04 mg/kg) N=4 | Cohort 3 (4.08 mg/kg) N=4 | Cohort 4 (8.17 mg/kg) N=5 | Cohort 5 (4.08 mg/kg) N=11 | Cohort 6 (8.17 mg/kg) N=11 | Pooled Placebo N=16 | Treated N=40 | Total N=56 |
| Age (years) | 36.2 (14.15) | 49.0 (6.00) | 42.8 (9.29) | 34.4 (11.44) | 50.2 (9.13) | 51.0 (13.35) | 42.8 (13.75) | 45.8 (12.41) | 44.9 (12.75) |
| Female, n (%) | 0 | 2 (50.0) | 1 (25.0) | 0 | 2 (18.2) | 2 (18.2) | 5 (31.3) | 7 (17.5) | 12 (21.4) |
| Weight (kg) | 84.320 (12.6428) | 84.750 (25.9976) | 78.063 (7.1672) | 81.664 (15.0810) | 83.050 (12.9954) | 82.645 (15.7689) | 80.627 (14.2110) | 82.596 (14.3478) | 82.033 (14.2076) |
| BMI (kg/m²) | 25.66 (4.868) | 27.88 (7.571) | 26.20 (2.035) | 24.46 (3.812) | 26.10 (3.546) | 26.85 (3.177) | 25.07 (4.036) | 26.23 (3.910) | 25.90 (3.945) |
| CSS at Baseline | 4.4 (1.95) | 6.5 (1.29) | 5.8 (2.06) | 6.6 (1.14) | 6.1 (1.14) | 5.2 (1.33) | 5.0 (1.67) | 5.7 (1.51) | 5.5 (1.57) |

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# SRP-1001 shows consistent dose-dependent increase in plasma exposure up to the highest dose cohort tested so far

## Plasma Exposure by Dose Level




Dose-dependent increase in plasma AUC up to 8 mg/kg, representing the highest siRNA dose evaluated to date for FSHD

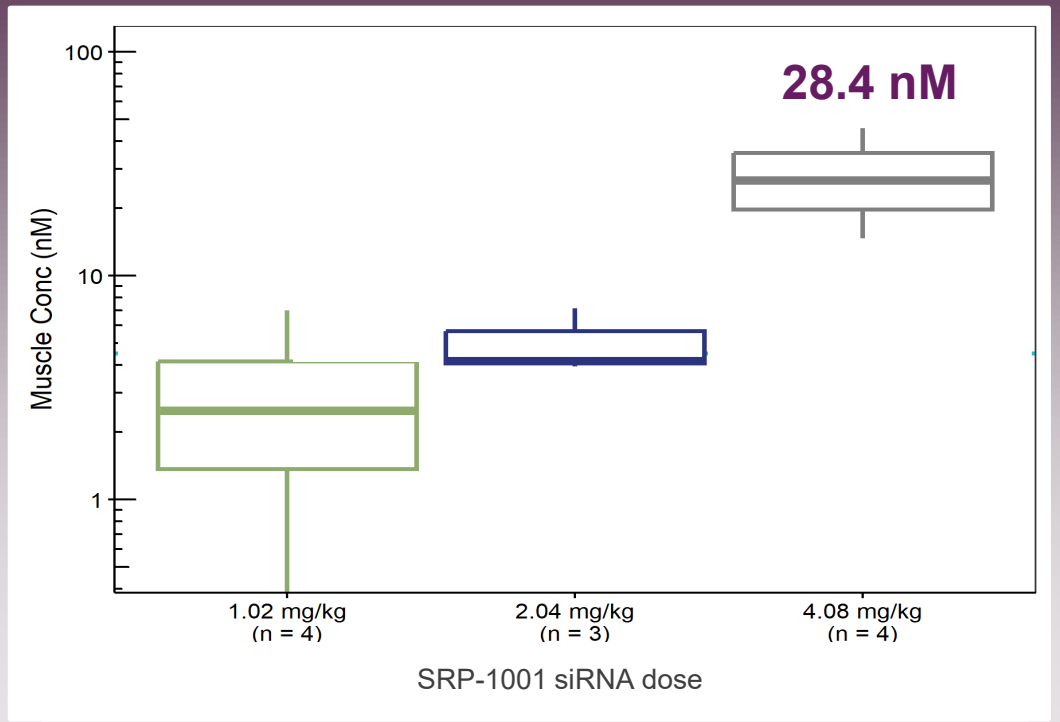
AUC = area under the plasma concentration-time curve between time zero to 8 hours. Plasma PK includes data following Day 1 dose across SAD and MAD cohorts.

One subject in Cohort 1 and 2 (2.08 mg/kg) with all BLOQ samples was excluded from the analysis.

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# Single dose of SRP-1001 delivers 6-fold greater siRNA muscle concentration than multiple doses of transferrin-targeting ligand

## SRP-1001 Muscle Concentration by Dose Level




- Dose-dependent increase in muscle concentration up to 4.08 mg/kg, representing the highest siRNA dose with muscle PK data to date
- At 42 days, SRP-1001 has achieved **28.4 nM** muscle concentration without dose-limiting toxicities that would limit further dose escalation. In comparison, the TfR1 mAb-siRNA construct has reported a median of **4.5 nM** muscle concentration at its chosen pivotal trial dose (n=7)

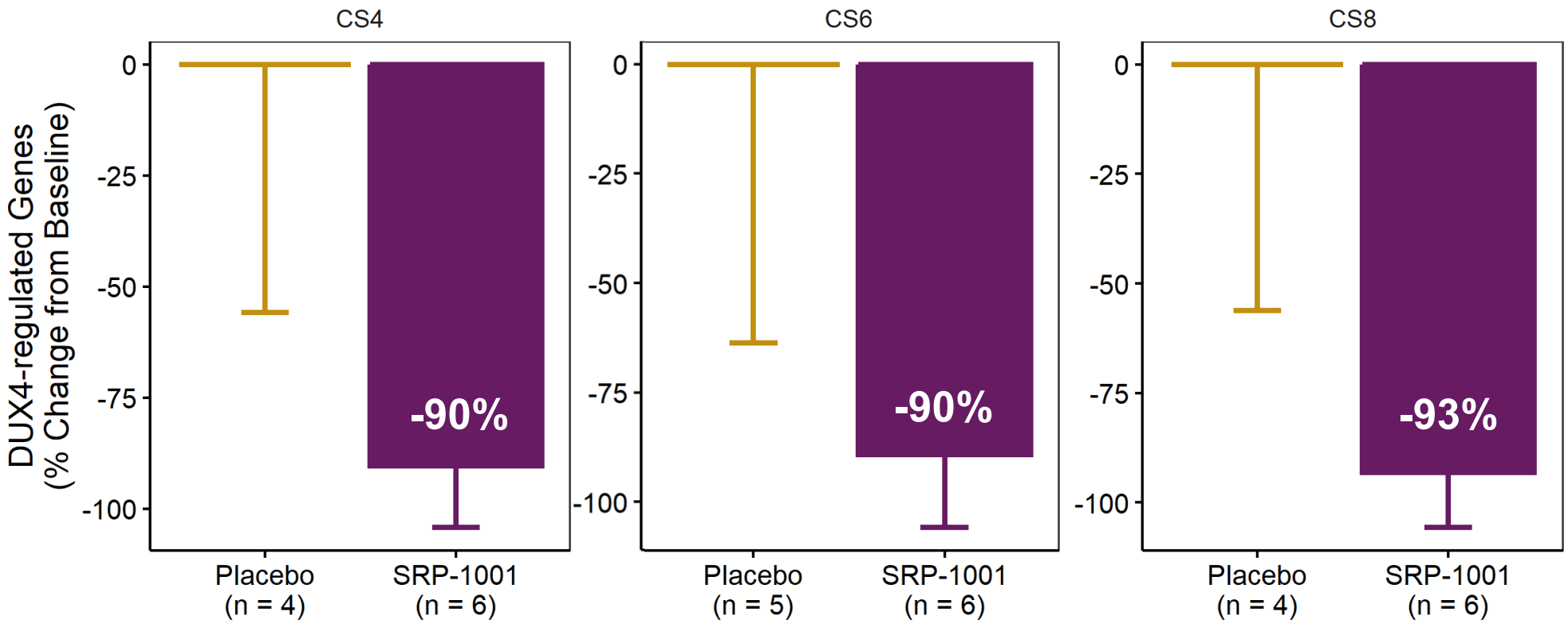
Muscle PK includes data from SAD cohorts.

Delivering on the RNA Revolution, Avidity corporate presentation, August 2024.
Data are derived from different clinical trials conducted at different times, with differences in trial design and patient populations. As a result, cross-trial comparisons may not be reliable, and no head-to-head clinical trials have been conducted.

One subject in Cohort 1 (1.02 mg/kg) and 2 (4.08 mg/kg) with BLOQ samples was excluded from the analysis.

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# SRP-1001 suppresses DUX4-regulated genes after a single dose



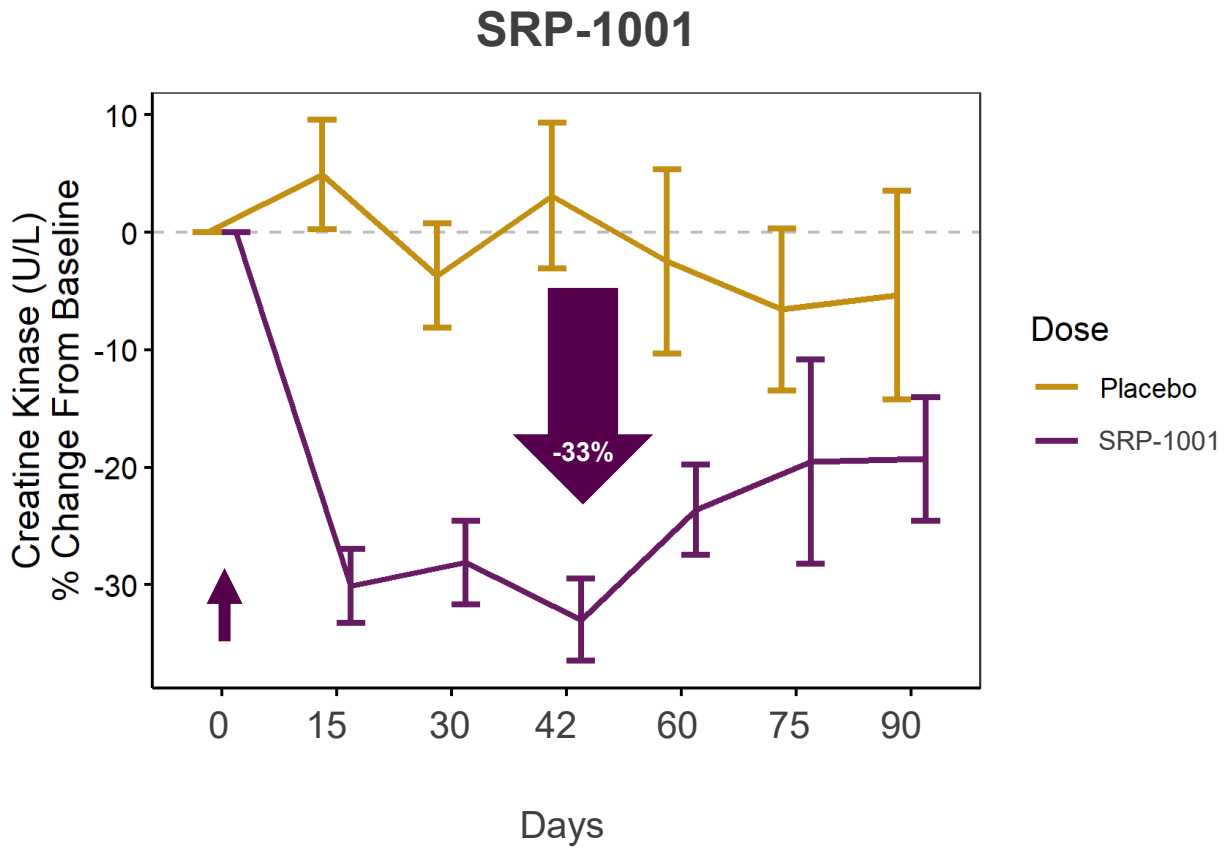

SRP-1001 treatment cohorts pooled from siRNA dose cohort 1 (1.02 mg/kg), cohort 2 (2.04 mg/kg), and cohort 3 (4.08 mg/kg).

- *qPCR composite scores for CS4 (MBD3L2, TRIM43, KHDC1L, LEUTX), CS6 (MBD3L2, KHDC1L, CCNA1, PRAMEF5/6, SLC34A2, ZSCAN4), and CS8 (MBD3L2, TRIM43, KHDC1L, LEUTX, CCNA1, PRAMEF5/6, SLC34A2, ZSCAN4) were calculated as the sum across contributing target genes and normalized to baseline and placebo.
- One subject in Cohort 1 (1.02 mg/kg) excluded with all BLOQ plasma and muscle samples. One subject in Cohort 2 (2.08 mg/kg) with all BLOQ plasma and muscle samples was excluded from the analysis. Additional subjects excluded if BLOQ for dux4 genes.
- Muscle Dux4 regulated genes were characterized in MRI-guided biopsy samples collected from lower-body muscles.

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# SRP-1001 drives rapid reduction in serum creatine kinase (CK) with a single dose of SRP-1001

SRP-1001 achieved a 33% reduction in CK vs placebo at Day 42




Data represent mean percent change from baseline ± SEM. Placebo (n = 16) and SRP-1001 treatment cohorts pooled from siRNA doses at 4.08 mg/kg and 8.17 mg/kg (n = 31) following a single dose administration.

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# SRP-1001-101: Reassuring safety profile to date with no serious related TEAEs

| TEAE Category | SAD (Active and Placebo) | | | | MAD (Active and Placebo) | | Overall |
|---|---|---|---|---|---|---|---|
| | Cohort 1 (1.02 mg/kg) N=7 n (%) | Cohort 2 (2.04 mg/kg) N=7 n (%) | Cohort 3 (4.08 mg/kg) N=6 n (%) | Cohort 4 (8.17 mg/kg) N=7 n (%) | Cohort 5 (4.08 mg/kg) N=14 n (%) | Cohort 6 (8.17 mg/kg) N=15 n (%) | Total N=56 n (%) |
| Any TEAE | 7 (100) | 4 (66.7) | 5 (83.3) | 5 (71.4) | 10 (71.4) | 12 (80.0) | 43 (76.8) |
| Serious TEAE | 0 | 1 (14.3) | 0 | 0 | 0 | 0 | 1 (1.8) |
| Related TEAE [1] | 2 (28.6) | 0 | 1 (16.7) | 0 | 6 (42.9) | 1 (6.7) | 10 (17.9) |
| Related Serious TEAE [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Related TEAE Leading to Drug Withdrawal | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Related TEAE Leading to Study Discontinuation | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Related TEAE Leading to Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

% = 100 x n/N, N = number of subjects in the population, n = number of subjects reporting event.
Treatment-emergent AEs will be defined as AEs with onset after administration of the study drug, or when a pre-existing medical condition increases in severity or frequency after study drug administration.
Adverse Events are coded using MedDRA Version 25.0.
[1] AE is considered treatment-related if the relationship to the study drug is 'Related' or missing. Subjects are counted only once at the maximum relationship.
[2] AE records with missing severity values will be imputed as 'Severe'. Subjects are counted only once at the maximum severity.

## Majority of TEAEs were mild to moderate in severity

- 1 (1.8%) serious TEAE (chest discomfort) was considered not related to study drug, and is also the only severe TEAE in the study
- Most (observed in ≥ 10% of subjects) common TEAEs
  - Headache (16.1%)
  - Upper respiratory tract infection (14.3%)
- No TEAEs occurred ≥ 20% of participants
- No related TEAEs led to death, study drug discontinuation or study discontinuation

**TEAEs do not appear to be dose dependent based on TEAE frequencies at the different SAD and MAD doses**

**SRP-1001 is safe and well tolerated to date in the ongoing study**

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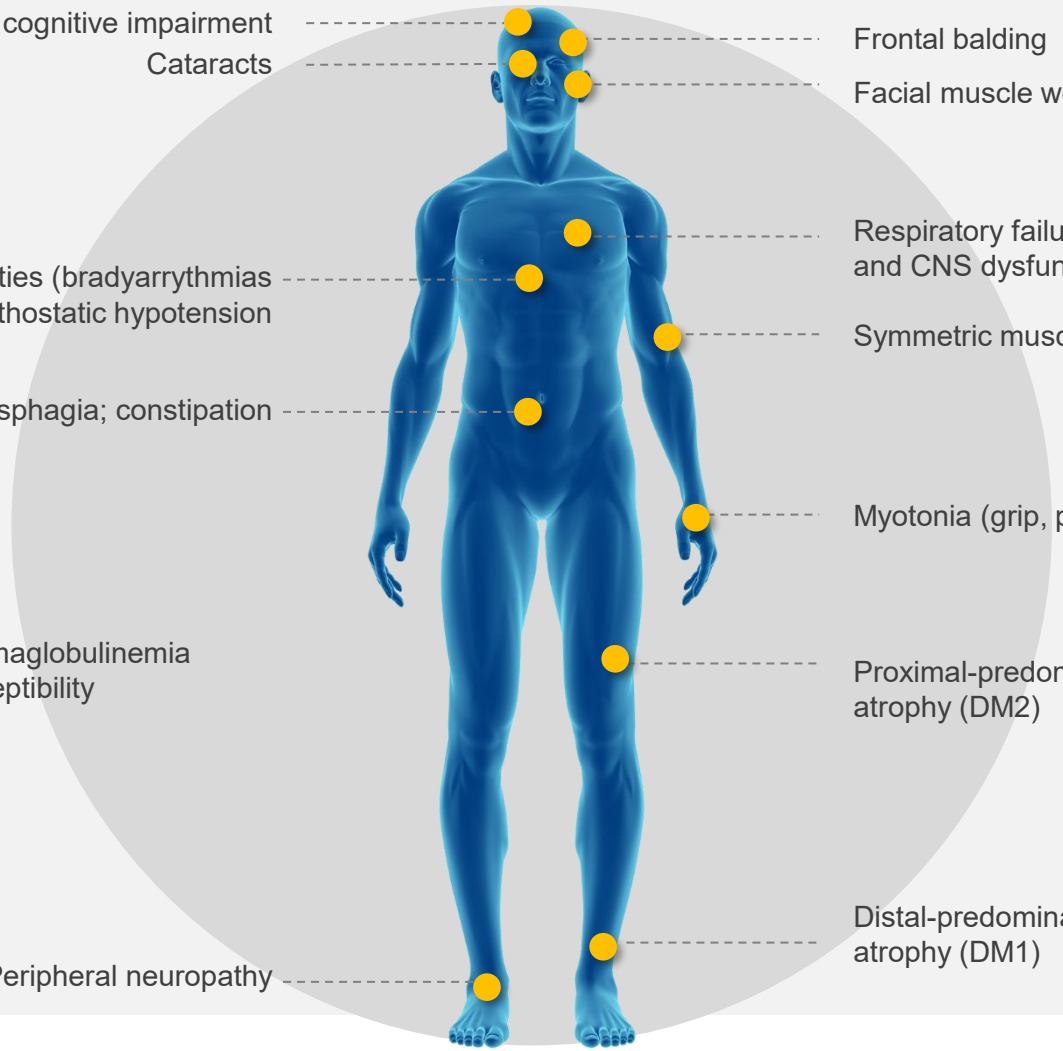
# SRP-1003: In clinical development for myotonic dystrophy type 1 (DM1)

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

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

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# DM1: A multi-system disorder impacting skeletal and smooth muscle along with other organs



Fatigue, apathy, cognitive impairment

Cataracts

Cardiac conduction abnormalities (bradyarrythmias and ventricular tachycardia); orthostatic hypotension

GI dysmotility; dysphagia; constipation

Peripheral neuropathy

Frontal balding

Facial muscle weakness; TMJ dysfunction

Respiratory failure (skeletal muscle weakness and CNS dysfunction)

Symmetric muscle pain

Myotonia (grip, percussion, electrical)

Proximal-predominant muscle weakness and atrophy (DM2)

Distal-predominant muscle weakness and atrophy (DM1)

**Systemic Symptoms**

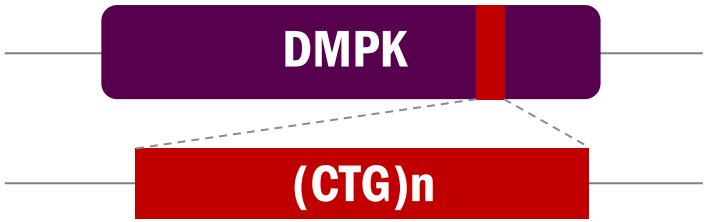
- Endocrine dysfunction
- IgG and IgM hypogammaglobulinemia
- Increased cancer susceptibility

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# DM1: Expanded DMPK Repeat, Leading to Multi-System Impact

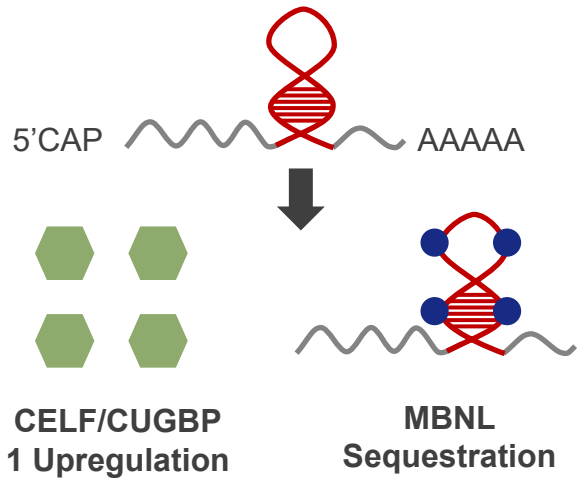
Targeting and knockdown of DMPK leads to therapeutic benefit

## DM1 Genetic Cause




### DNA

Expanded tri-nucleotide repeat in the *DMPK* gene (50 – 1000 repeats)



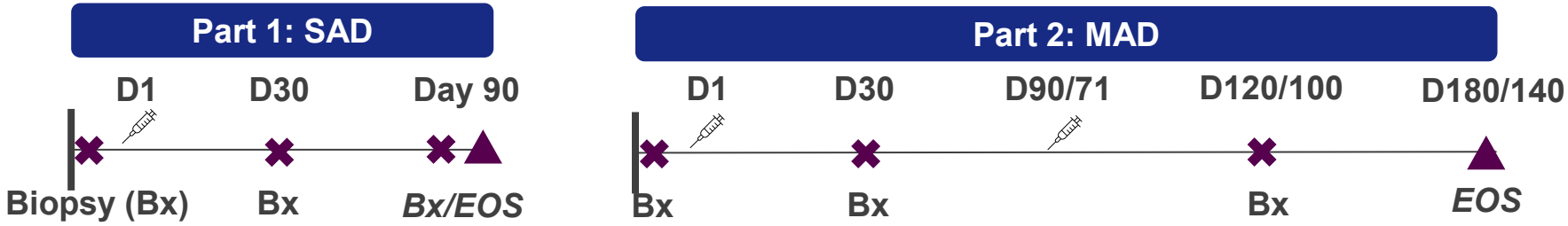

### RNA

Repeats accumulate in the nucleus and create 3D structures that bind MBNL and alter CUGBP1 expression

**Downstream mis-splicing of proteins implicated in cognitive, skeletal, and cardiac muscle function**

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# Study SRP-1003-101: A phase 1/2 randomized, placebo-controlled trial in participants aged 18-65 with DM1




## Cohort Design

**SAD**

**Cohort 1**
**(1.02 mg/kg siRNA) n=12**

**Cohort 2**
**(2.05 mg/kg siRNA) n=6**

**MAD**

**Cohort 3**
**(3.07 mg/kg siRNA Q12W) n=6**

**Cohort 4**
**(4.10 mg/kg siRNA Q12W) n=6**

**Cohort 5**
**(8.20 mg/kg siRNA Q10W) n=12**

## Endpoints

**Primary**:
- Safety and tolerability

**Secondary**:
- PK in plasma

**Key Exploratory Endpoints:**
- siRNA muscle concentration
- DMPK mRNA KD
- DMPK splicing indices
- Functional (secondary in C5): vHOT, QMT, 10MWR, TUG
- PROs: CIS, PGIC, DM1-Activ-C, MDHI (MDHI and DM1-Activ-C secondary for C5)

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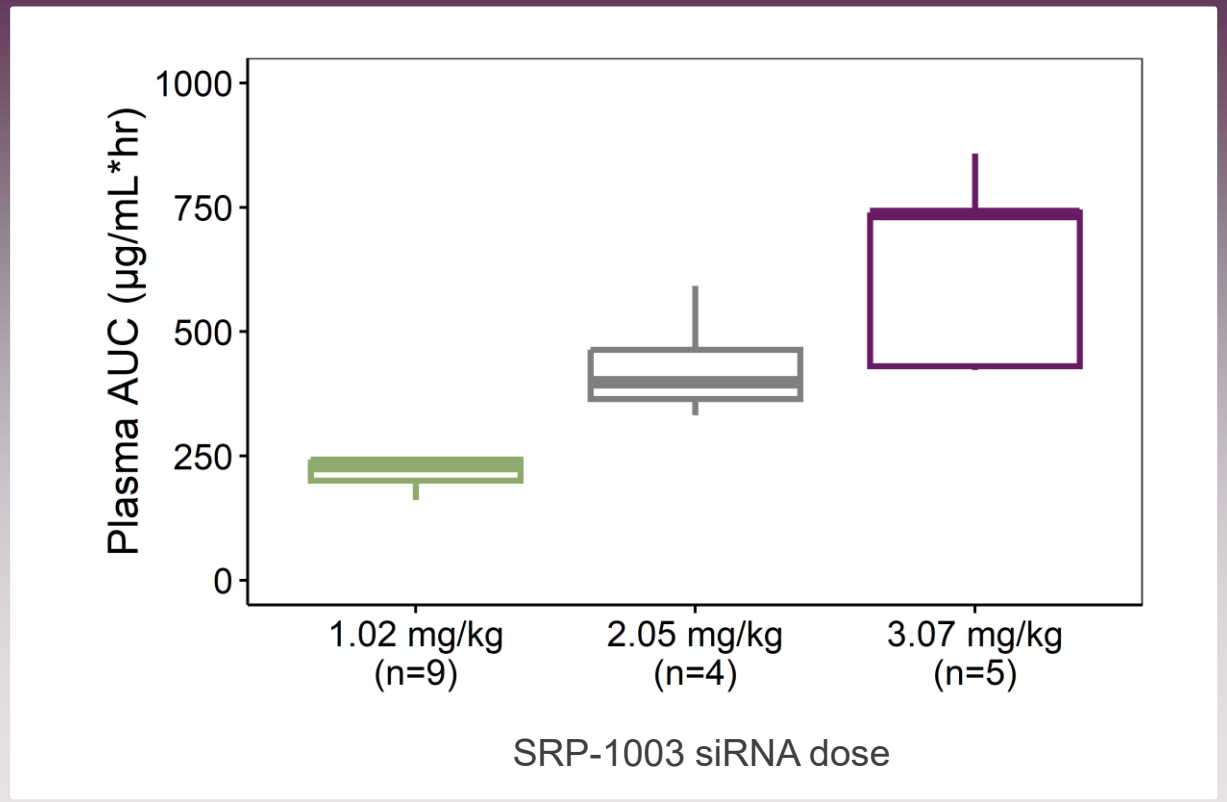
# Baseline characteristics

| | SAD | | MAD | | | |
|---|---|---|---|---|---|---|
| Mean (sd) or Freq (%) | Cohort 1 (1.02 mpkg) N=10 | Cohort 2 (2.04 mpkg) N=6 | Cohort 3 (<=3.07 mpkg) N=5 | Cohort 4 (<=4.10 mpkg) N=4 | Placebo N=11 | Total N=36 |
| **Age (years)** | 39.2 (11.84) | 36.0 (9.06) | 47.0 (12.04) | 41.8 (7.09) | 36.3 (9.16) | 39.1 (10.32) |
| **Female, n (%)** | 6 (60.0) | 1 (16.7) | 1 (20.0) | 1 (25.0) | 5 (45.5) | 14 (38.9) |
| **Weight (kg)** | 74.97 (19.112) | 63.92 (12.982) | 78.34 (6.201) | 72.45 (21.849) | 75.31 (15.826) | 73.42 (15.992) |
| **BMI (kg/m²)** | 25.84 (3.862) | 20.77 (3.132) | 25.88 (4.272) | 25.23 (5.814) | 25.68 (4.656) | 24.88 (4.465) |

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# SRP-1003 shows dose-dependent increase in plasma exposure, reinforcing cross-program consistency in the TRiM™ platform

## Plasma Exposure by Dose Level

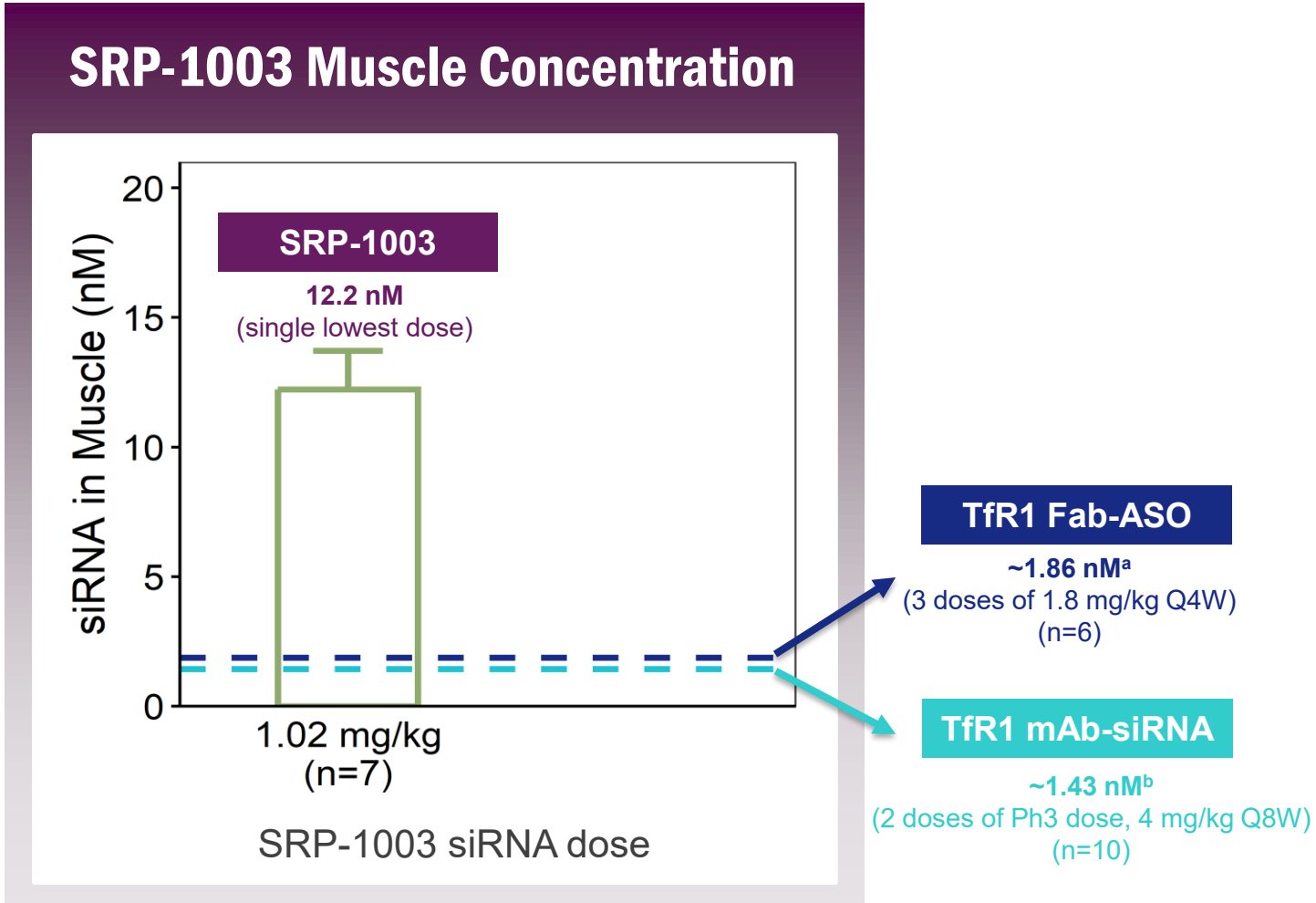



Dose-dependent increase in plasma AUC up to 3.07 mg/kg, representing the highest SRP-1003 dose cohort with data to date

AUC = area under the plasma concentration-time. N=1 in cohort 1 excluded due to study conduct.

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# Superior muscle delivery with a single low dose of SRP-1003




- SRP-1003 in the lowest dose cohort (1.02 siRNA mg/kg) mediates robust siRNA delivery into the muscle
- A single low dose of SRP-1003 significantly outperforms repeated dosing of TfR1 mAb-siRNA and TfR1 Fab-ASO in muscle drug delivery

a Initial data from the ACHIEVE Trial of DYNE-101 in Adults With Myotonic Dystrophy Type 1 (DM1), World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024; (original values reported in ng).
b An Antibody–Oligonucleotide Conjugate for Myotonic Dystrophy Type 1, *New England Journal of Medicine*, Downloaded from nejm.org, February 23, 2026.
Data are derived from different clinical trials conducted at different times, with differences in trial design and patient populations. As a result, cross-trial comparisons may not be reliable, and no head-to-head clinical trials have been conducted. One subject excluded due to study conduct.

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# SRP-1003-101: Reassuring safety profile with no serious related TEAEs to date

| TEAE Category | SAD (Active and Placebo) | | MAD (Active and Placebo) | | Overall |
|---|---|---|---|---|---|
| | Cohort 1 (1.02 mg/kg) N=14 n (%) | Cohort 2 (2.04 mg/kg) N=9 n (%) | Cohort 3 (≤3.07 mg/kg) N=7 n (%) | Cohort 6 (≤4.10 mg/kg) N=6 n (%) | Total N=36 n (%) |
| Any TEAE | 12 (85.7) | 6 (66.7) | 7 (100) | 3 (50.0) | 28 (77.8) |
| Serious TEAE | 2 (14.3) | 0 | 0 | 0 | 2 (5.6) |
| Related TEAE [1] | 2 (14.3) | 0 | 3 (42.9) | 0 | 5 (13.9) |
| Related Serious TEAE [1] | 0 | 0 | 0 | 0 | 0 |
| Related TEAE Leading to Drug Withdrawal | 0 | 0 | 0 | 0 | 0 |
| Related TEAE Leading to Study Discontinuation | 0 | 0 | 0 | 0 | 0 |
| Related TEAE Leading to Death | 0 | 0 | 0 | 0 | 0 |

% = 100 x n/N, N = number of subjects in the population, n = number of subjects reporting event.
Treatment-emergent AEs will be defined as AEs with onset after administration of the study drug, or when a pre-existing medical condition increases in severity or frequency after study drug administration.
Adverse Events are coded using MedDRA Version 25.0.
[1] AE is considered treatment-related if the relationship to the study drug is 'Related' or missing. Subjects are counted only once at the maximum relationship.

## Majority of TEAEs were mild to moderate in severity

- Three serious TEAEs in 2 subjects (5.6%) **unrelated to study drug**
  - Fatal Arrhythmia
  - Limb abscess
  - Emotional distress
- Most common TEAEs (observed in ≥ 10% of subjects)
  - Headache and URTI (13.9% each)
- No TEAEs occurred ≥ 20% of participants

**TEAEs do not appear to be dose dependent based on TEAE frequencies at the different SAD/MAD doses**

**SRP-1003 appears safe and well tolerated to date in the ongoing study**

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# Summary: Conclusions from clinical data to date for FSHD1 and DM1

- Well-tolerated with no dose-limiting toxicity allowing us to continue dose escalating and the potential to drive differentiated efficacy

- Superior muscle concentration

- Successful target engagement with emerging biomarker evidence of potentially meaningful treatment efficacy

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# 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**

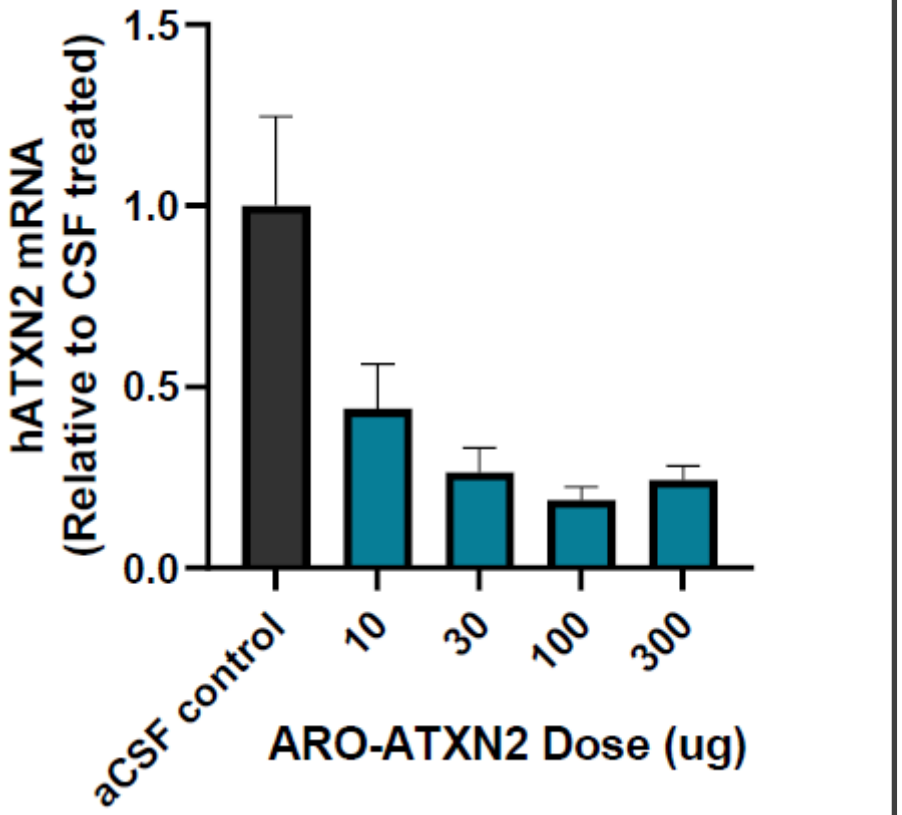

1. National Institute of Neurological Disorders and Stroke.
2. Cleveland Clinic.
3. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Spinocerebellar ataxia type 2. Available from: https://medlineplus.gov/genetics/condition/spinocerebellar-ataxia-type-2/#causes.
4. Ruano et al,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


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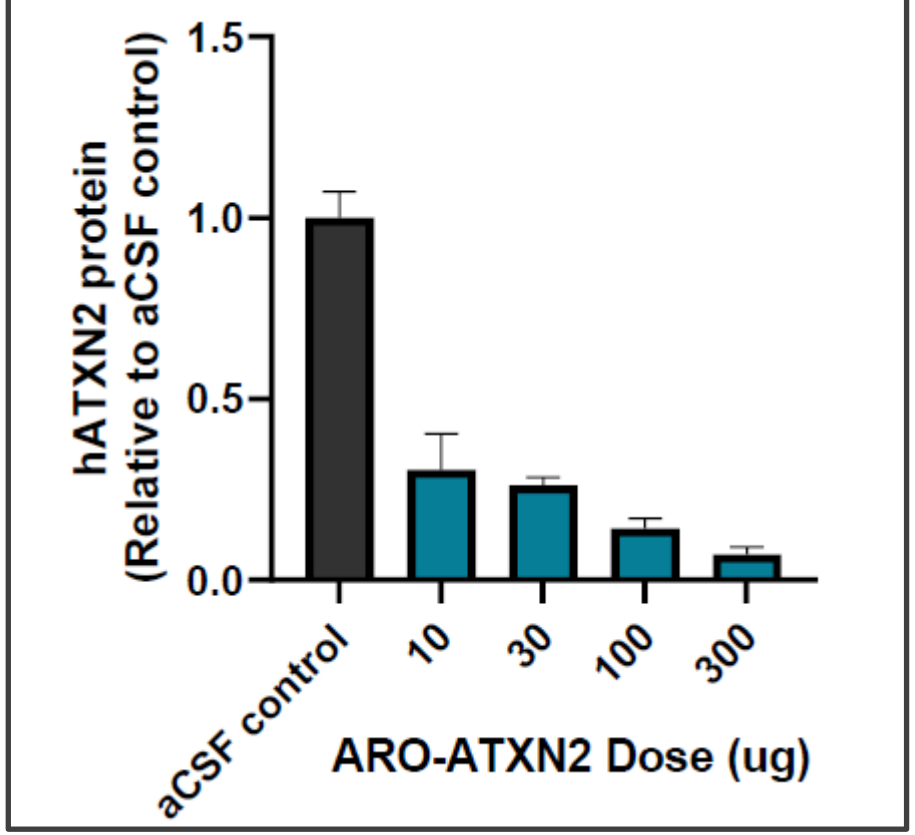
# SRP-1004 reduces ATXN2 in a mouse brain

Mouse model engineered to express human ATXN2

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



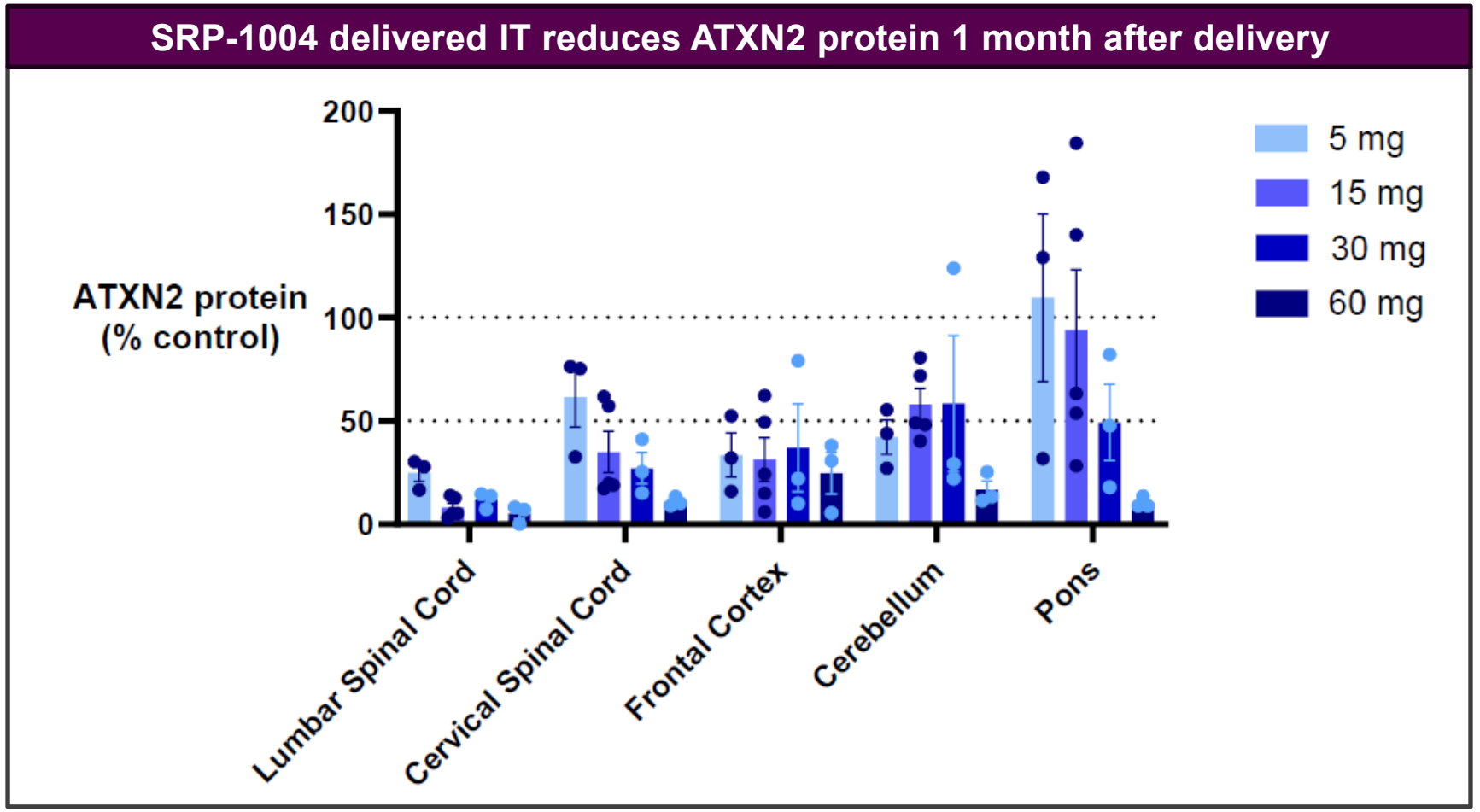

**SRP-1004 delivered ICV reduces ATXN2 protein 2 weeks after delivery**




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

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

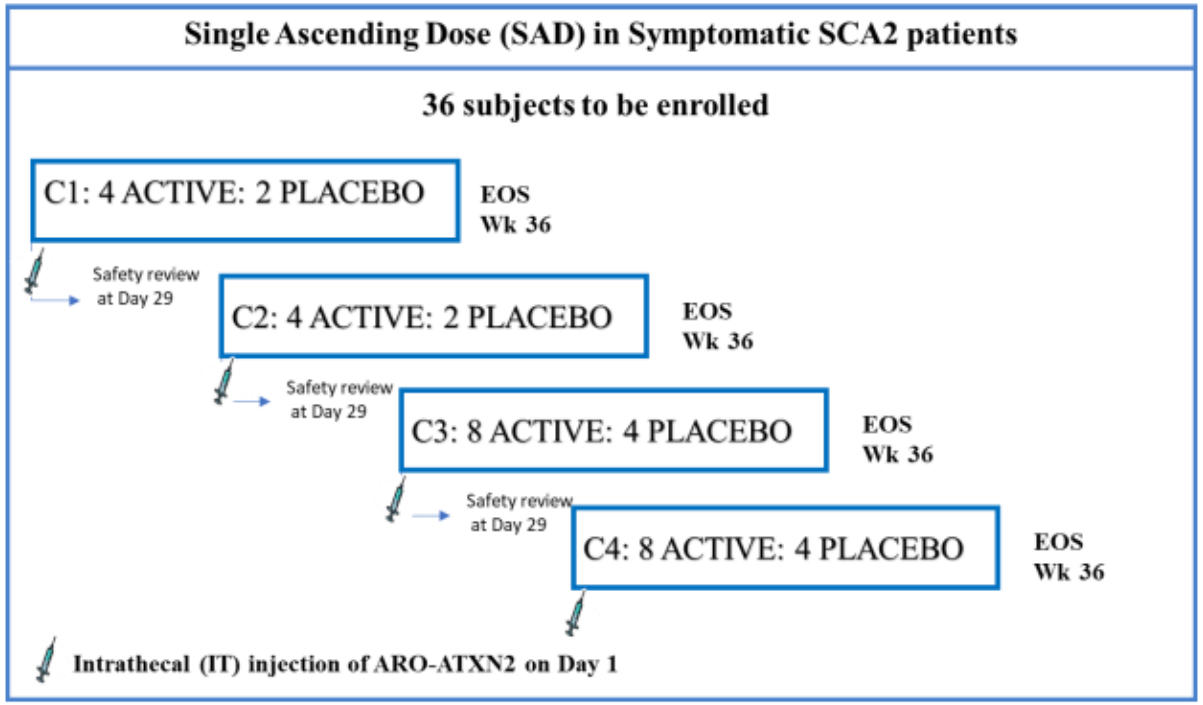



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# SRP-1004: Spinocerebellar ataxia type 2 (SCA2)

## 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 |

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# 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:**
**Phase 1**

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

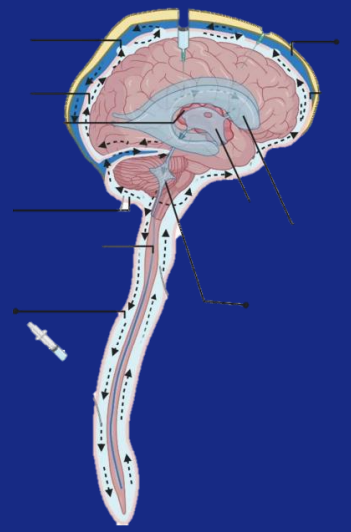
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# TfR1-Binding Designed to Optimize CNS Delivery in Huntington's Disease

## CNS-SC platform demonstrates improved delivery to deep brain in NHP compared to direct CSF injection

SRP-1005 HD program employs a subcutaneous route of administration delivering siRNA across the BBB to the source of disease in the deep brain.

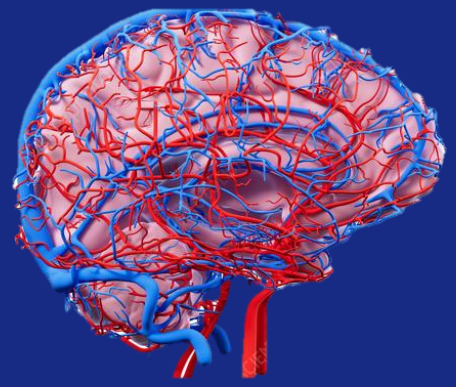
### CSF delivery via IT injection



Accessing the brain via intrathecal injection (IT) is limited by CSF flow

J. Pers. Med. 2022, 12(12), 1979; https://doi.org/10.3390/jpm12121979

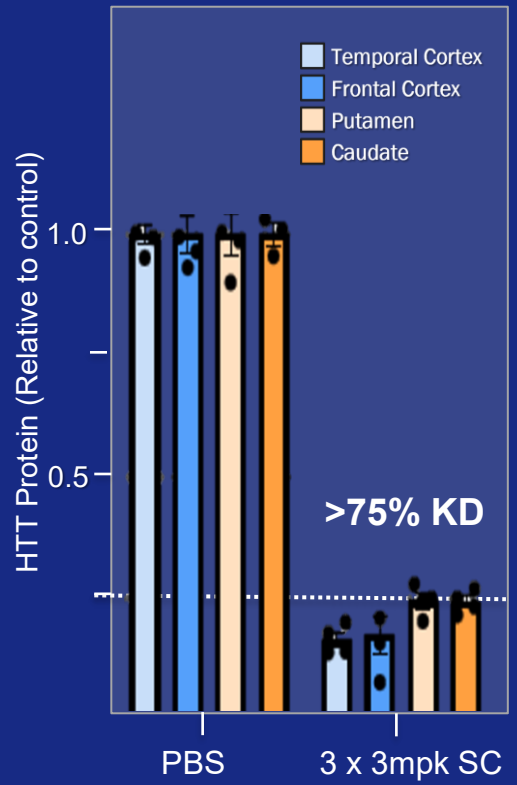
### Systemic delivery via SC injection



Accessing the brain via the blood-brain barrier through TfR1-mediated crossing potentially leads to greater deep brain distribution

Thom Leach / Science Photo Library

### SRP-1005 in NHP




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# 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-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

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# Dragging tomorrow into today

#DraggingTomorrowIntoToday

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