Breakthroughs in Becker: Unveiling New Natural History Insights and a Novel Agent’s Clinical Progress

Symposium at World Muscle Society Conference

Vienna, Austria

Wednesday 08 October 2025

Disclosures

Roxana Donisa Dreghici is an employee of Edgewise Therapeutics and holds stock.

Program Overview

Introduction
Roxana Donisa Dreghici, MD

Becker Muscular Dystrophy Natural History & Modeling
Erik Niks, MD, PhD

Advancements with an Investigational Agent: Sevasemten Clinical Program Update
Craig McDonald, MD

Panel Discussion Q&A
Moderated by Roxana Donisa Dreghici, MD

Roxana Donisa Dreghici, MD
VP Clinical Development
Edgewise Therapeutics

Erik Niks, MD, PhD
Pediatric and adult neurologist
Leiden University Medical Center

Craig McDonald, MD
Professor and Chair, PM&R
University of California Davis, California

This presentation is intended for HCP audiences. Sevasemten is an investigational agent that is not currently approved in any territory.

Session Objectives

- Expand awareness of the most current Becker muscular dystrophy (Becker) natural history studies and how they support the severity of Becker.
- Increase understanding of functional assessments, such as the North Star Ambulatory Assessment (NSAA), and their clinical meaningfulness in Becker.
- Learn about the utilization of the recent natural history studies in the development and validation of a new Becker NSAA prediction model.
- Share updates from the sevasemten clinical program and discuss the application of the prediction model to the latest Becker data.

Sevasemten is an investigational agent that is not currently approved in any territory.

Becker Muscular Dystrophy Natural History & Modeling

Erik H. Niks, MD, PhD

Edgewise THERAPEUTICS

Disclosures

Participant in advisory boards for Edgewise Therapeutics, BioMarin, Entrada, Pfizer, Roche, Italfarmaco, Sarepta, and Solid Bioscience.

Principal investigator at LUMC for clinical trials from Edgewise Therapeutics, Italfarmaco, Entrada, Sarepta, Solid Bioscience, Fibrogen, NS Pharma, Reveragen, Santhera, ML Bio, Janssen, Alexion, and Argenx.

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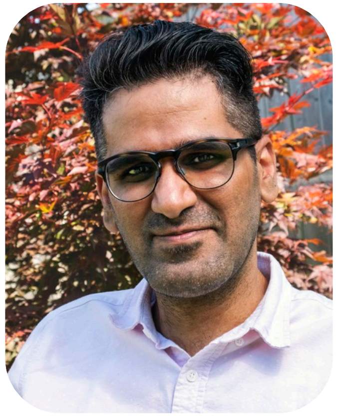
No personal financial interest. Reimbursement received by LUMC.

Becker Muscular Dystrophy is a Serious, Progressive, and Debilitating Neuromuscular Disease



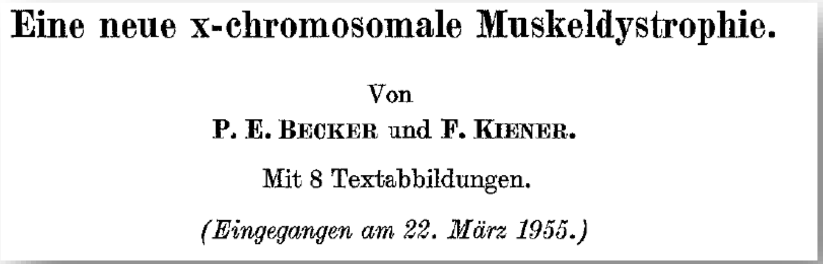
- BMD is an X-linked recessive disease caused by mutations in the *DMD* gene, affecting approximately 1:18,000 male births.
- BMD is a multi-systemic disease that can lead to irreversible loss of muscle function and cardiomyopathy.
- There is currently no approved treatment for BMD.
- Disease management consists of symptom management aimed at preserving cardiac function and physiotherapy to preserve mobility as much as possible.

BMD, Becker Muscular Dystrophy

Magot A, et al. J Neurol. 2023;270(10):4763-4781.

Becker Muscular Dystrophy is Hallmarked by Variable Onset and Progression

- Original publication on 14 male patients
- Onset 12-25 years
- Hypertrophic calves & waisting of quadriceps



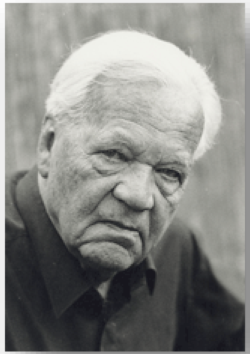
Eine neue x-chromosomale Muskeldystrophie.

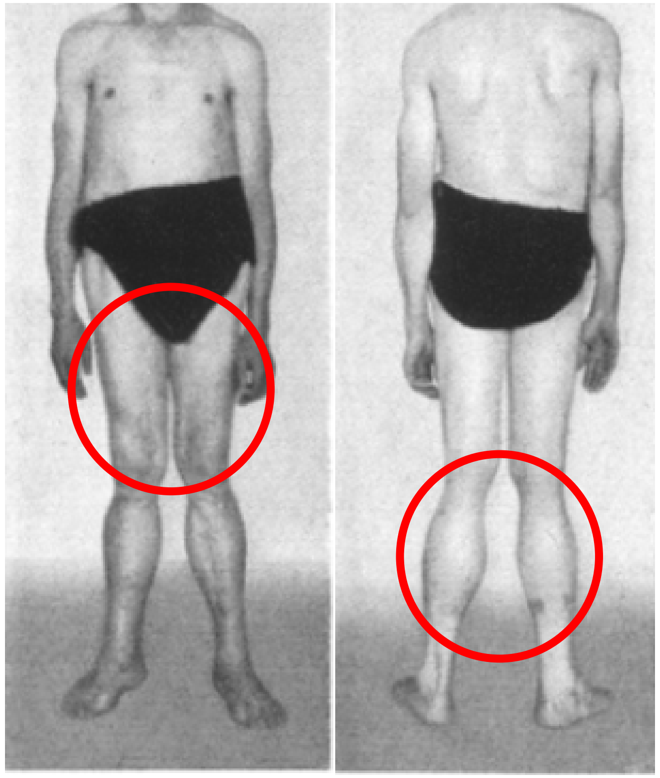
Von

P. E. BECKER und F. KIENER.

Mit 8 Textabbildungen.

(Eingegangen am 22. März 1955.)





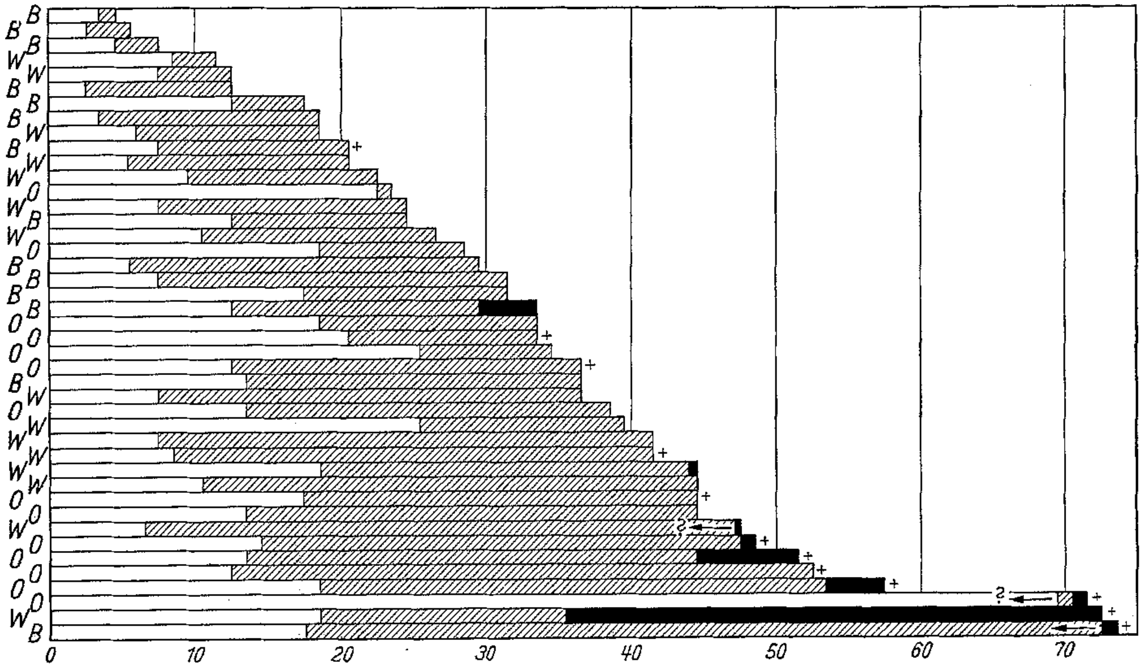
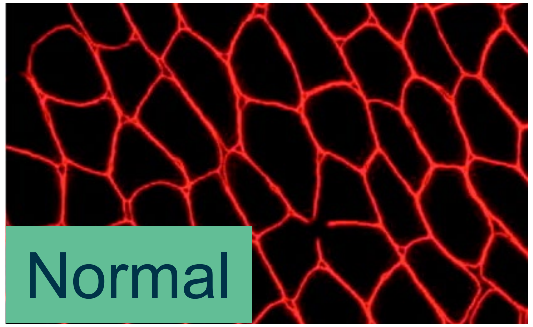
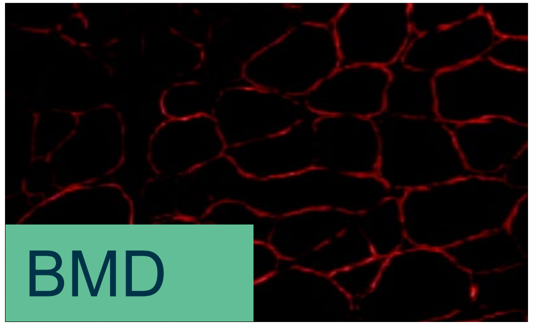
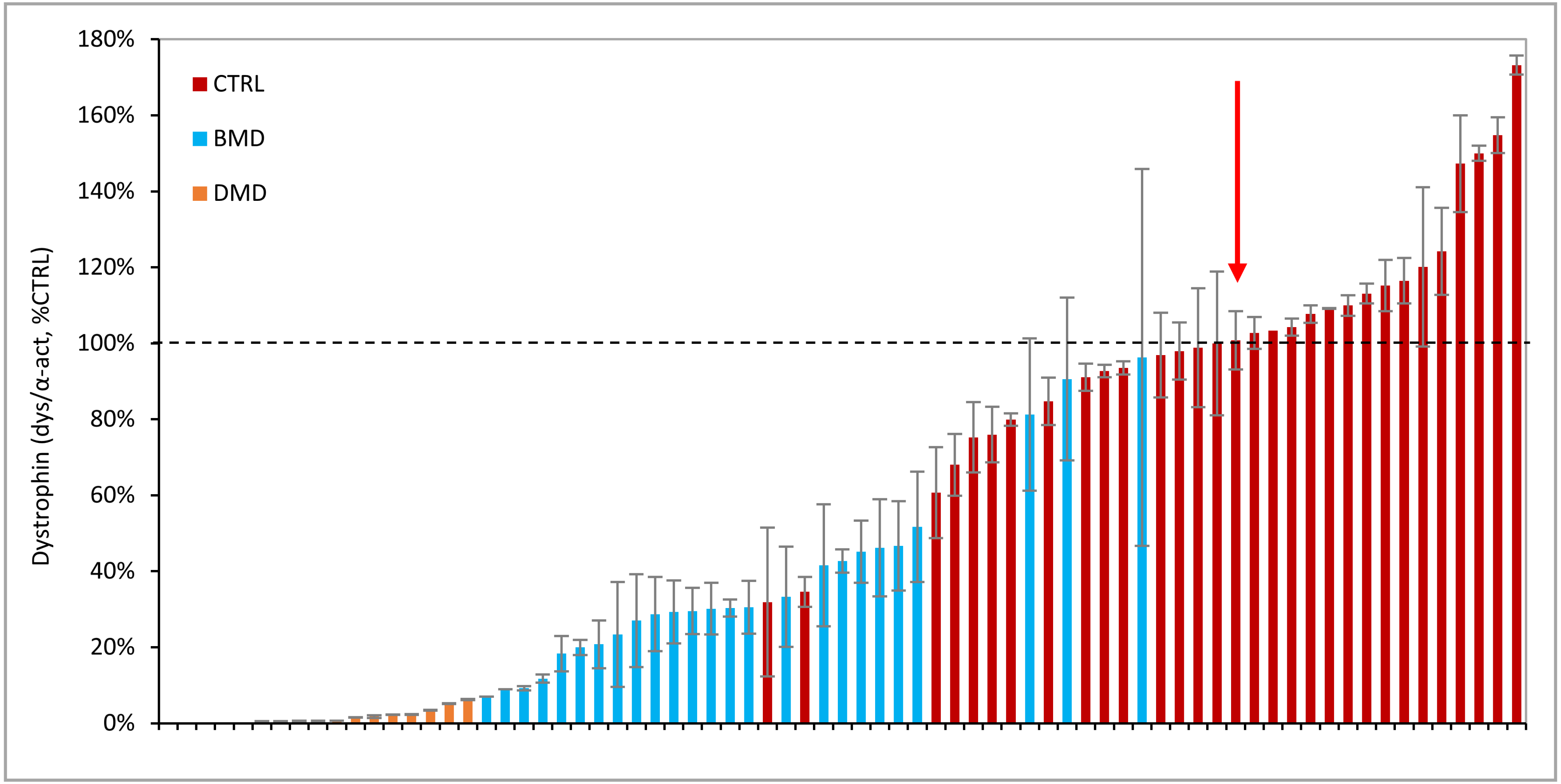


Abb. 6. Neue x-chromosomale Muskeldystrophie. Altersaufbau der Kranken. ▨ krank, ■ gehunfähig krank, ← ungenaue Angaben über die Zeit der Erkrankung. (Die Grenze, an der der Pfeil ansetzt, bezeichnet das Alter, in dem die Muskeldystrophie mit Sicherheit vorhanden war.) + verstorben.

Partial and Variable Expression of Dystrophin in Muscle Fibers







BMD, Becker muscular dystrophy; CTRL, control; DMD, Duchenne muscular dystrophy.
Beekman et al. PloS One. 2018; 13(4):e0195850.

North Star Ambulatory Assessment: a Validated Measure of Ambulatory Function that is Clinically Meaningful in a Real-World Context

The NSAA Test Items

Hop left leg	Hop right leg
Stand on heels	
Rise from floor	
Run	
Jump	
Lift head	
Descend box step (L)	Descend box step (R)
Climb box step (L)	Climb box step (R)
Stand one leg (L)	Stand one leg (R)
Get to sitting	
Rise from chair	
Walk	
Stand	

Each activity is scored on whether it can be completed

+2 pts	Perform normally
+1 pts	Perform with compensation due to weakness
0 pts	Cannot perform

Real-world implications for individuals with BMD

Measure	Activity
Jump, hop, run	Playing sports
Stand on heels	Walking on uneven ground, cycling, difficulty getting out of a chair, striding, cycling
Rise from floor	Getting up after falling, playing on the floor with children
Climb box steps	Independent outdoor mobility particularly easy tasks like stairs and sidewalk curbs
Stand on one leg	Dressing oneself, putting on shoes/socks while standing, reaching high shelves
Gets to sitting	Sitting up in bed, adjust to falls
Rise from chair	Using a toilet independently, getting out of bed, using public transportation to get around
Walk	Walking to mailbox to pick up mail, hiking, everyday mobility
Stand	Grooming, preparing meals, adapting to mobility device, transferring to chair

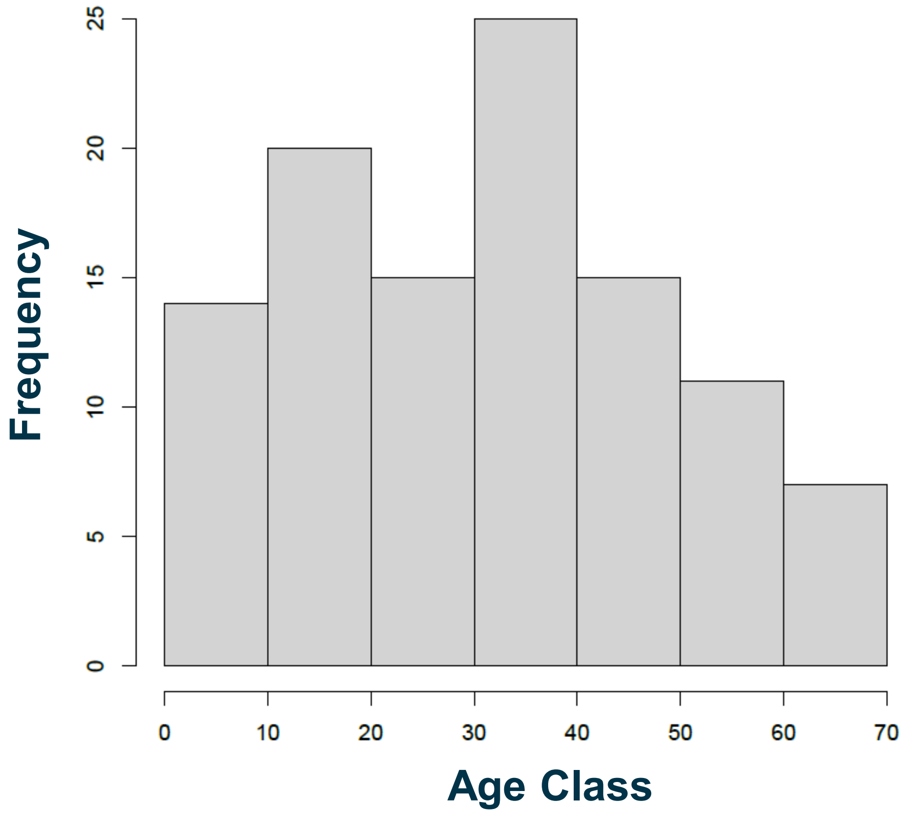
BMD, Becker muscular dystrophy; NSAA, the North Star Ambulatory Assessment

1. Scott E, et al. Physiother Res Int. 2012;17(2):101-109. 2. Mercuri E, et al. PLoS One. 2016;11(8);e0160195.

NSAA Trajectories in a Recent 6-year Natural History Study

- **Sample size**: 107 BMD participants
  - Ambulatory
  - Includes patients already on corticosteroids or initiated during observation period
- **Ages**: 31.4 ± 17.3 years old (range 3-69 years old)
- **Follow up**: 6.1 ± 3.6 years

Overall Age Distribution of Patients at Baseline



RESEARCH ARTICLE OPEN ACCESS

Longitudinal Changes of Motor Function in Becker Muscular Dystrophy

Luca Bello,[1] Pietro Riguzzi,[1] Giuliana Capece,[1] Martina Penzo,[1] Angela Petrosino,[1] Elena Sogus,[1] Sara Mastellaro,[1] Michela Caroli,[1] Matteo Villa,[1] Daniele Sabbatini,[1,2] Domenico Gorgoglione,[1] Sara Vianello,[1] Gianni Sorarù,[1] and Elena Pegoraro[1]

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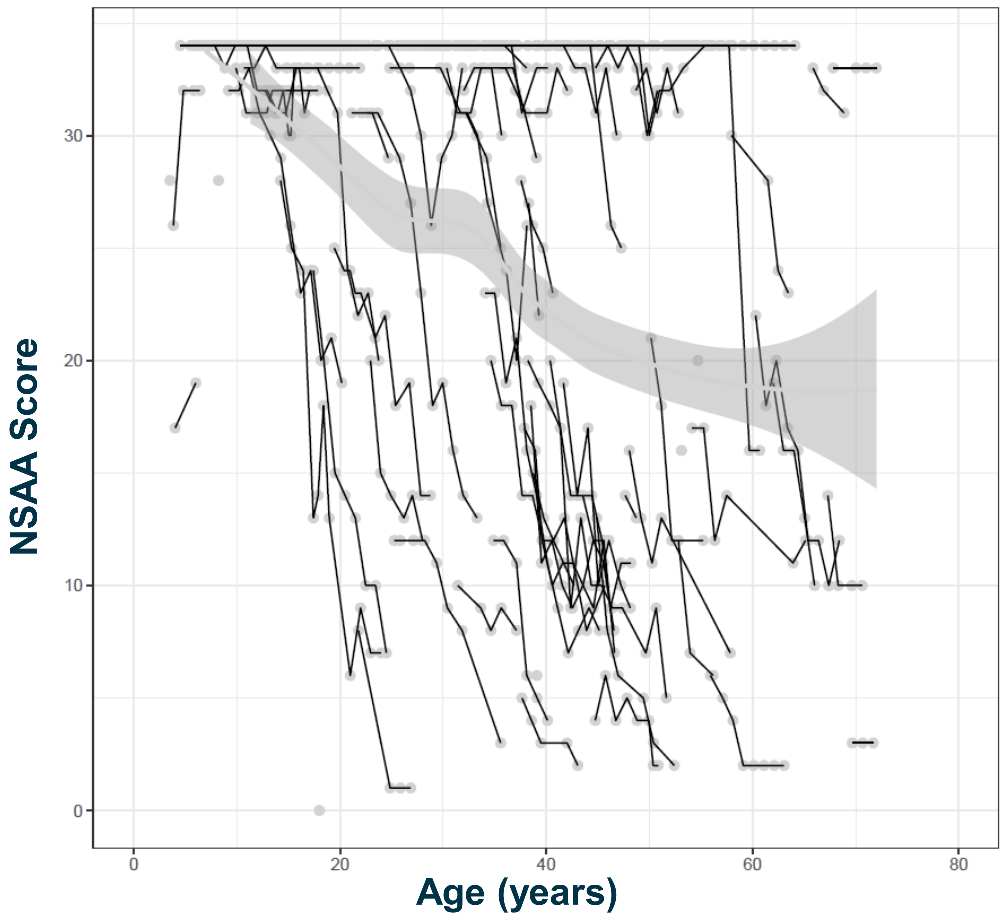
Neurol Genet 2025;11:e200285. doi:10.1212/NXG.0000000000200285

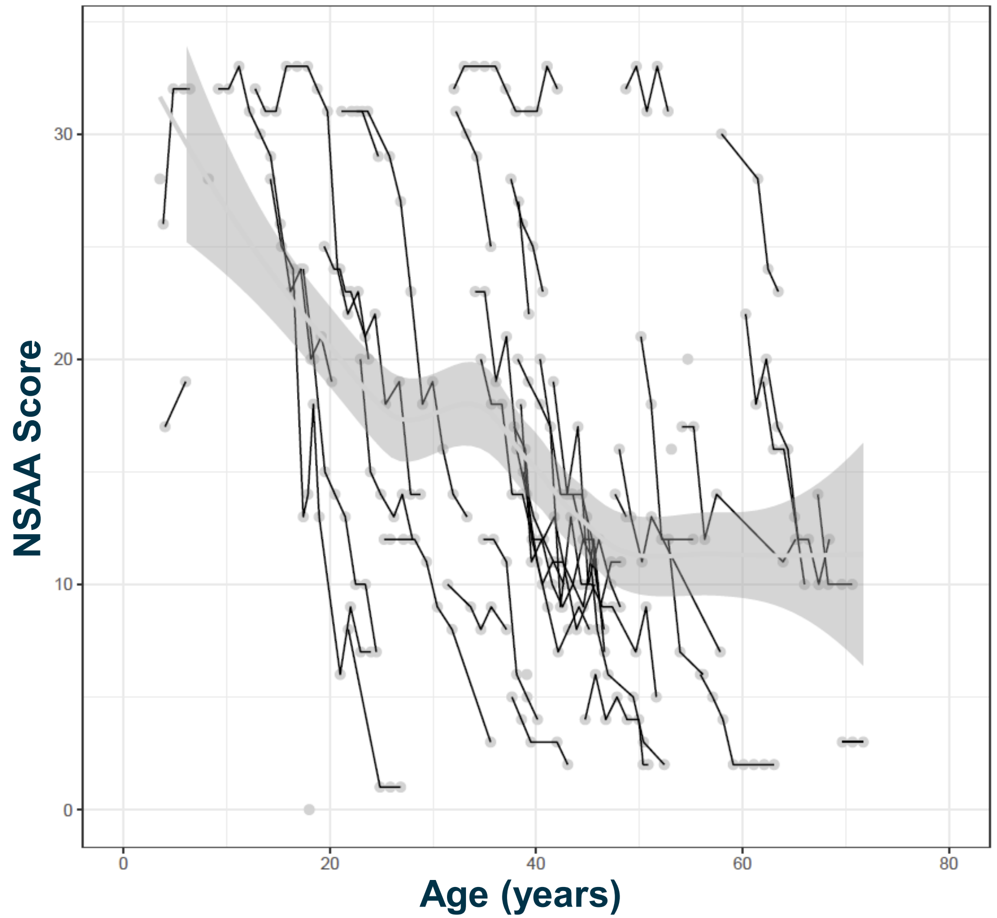
BMD, Becker Muscular Dystrophy; NSAA, North Star Ambulatory Assessment

NSAA Decline More Evident in Participants with Baseline Values ≤32

All BMD
(n=100)



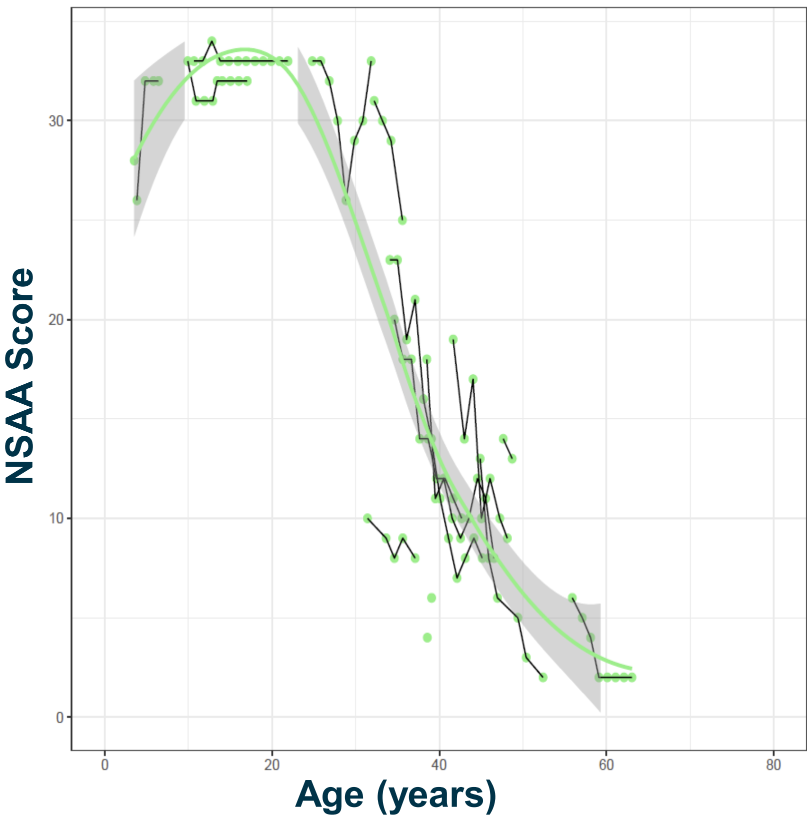
BMD with Baseline NSAA ≤32
(n=45)



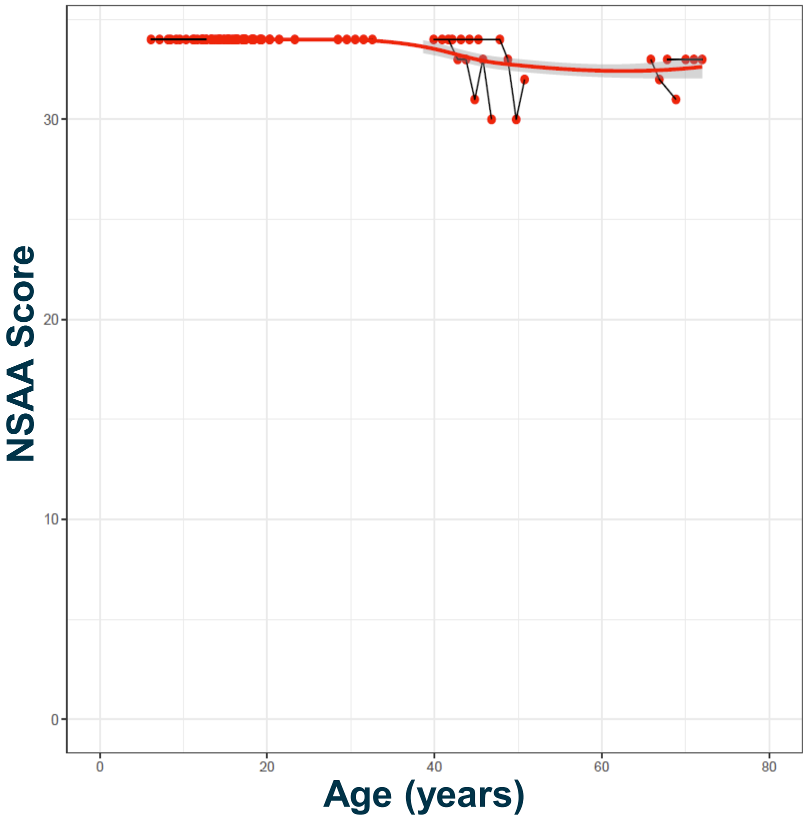
BMD, Becker muscular dystrophy; NSAA, North Star Ambulatory Assessment
Bello L, et al. Neurol Genet. 2025;11(4):e200285.

NSAA Decline Highly Variable Across Genotypes

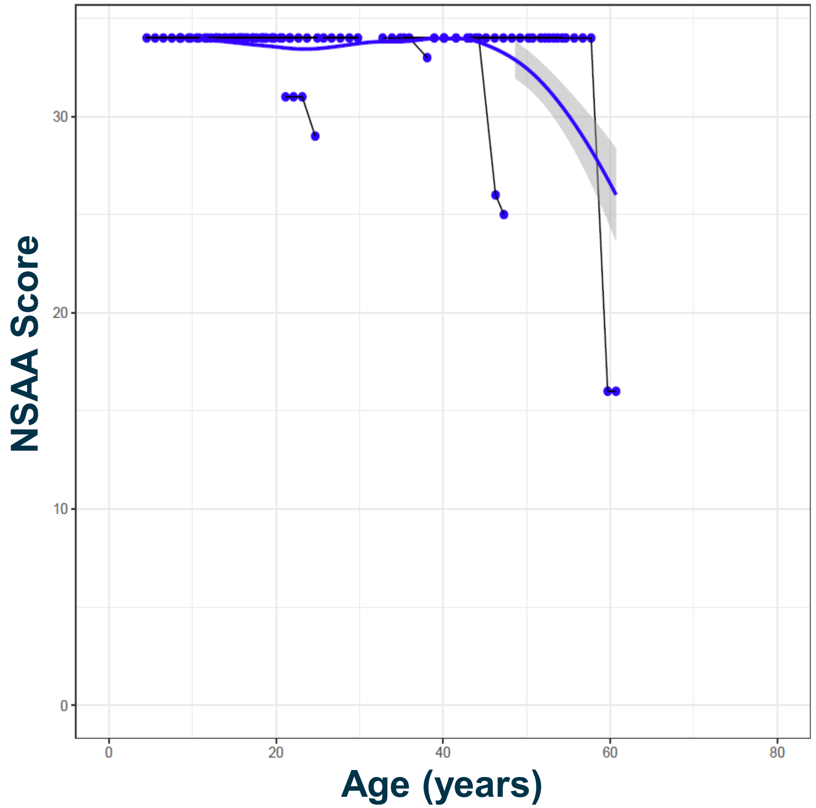
Deletions 45-47
(n=14)



Deletions 48
(n=12)



Deletions x-51
(n=15)



NSAA, North Star Ambulatory Assessment
Bello L, et al. Neurol Genet. 2025;11(4):e200285.

NSAA Trajectories in a Recent 3-year Natural History Study

- **Sample size**: 36 BMD participants
  - Ambulatory and non-ambulatory patients
- **Mean age:** 41.8 years old (range 18.6-67.3)
- **Follow up**: yearly visits at baseline up to 3 years

Characteristics of the Study Population

		Del 45–47 subgroup analysis		nNOS subgroup analysis		Functional subgroup analysis	
	All participants (N = 36)	Del 45–47 (n = 11)	Other (n = 25)	nNOS– (n = 21)	Other (n = 15)	NSAA 10–32 at baseline (n = 15)	Other (n = 21)
Age at first visit, y, mean (SD)	41.8 (12.8)	41.2 (11.4)	42.1 (13.7)	44.4 (12.1)	38.1 (13.3)	40.1 (14.6)	43.1 (11.7)
Age at first symptoms[a], y, mean (SD)	9.0 (5.1)	8.5 (5.8)	9.3 (4.8)	8.8 (4.7)	9.4 (5.8)	8.4 (5.0)	9.5 (5.2)
Age at diagnosis, y, mean (SD)	20.1 (12.1)	20.2 (11.4)	20.1 (12.6)	21.0 (12.1)	19.0 (12.3)	20.7 (11.6)	19.8 (12.7)
Wheelchair use, n (%)							
Never	17 (47.2)	6 (54.5)	11 (44.0)	9 (42.9)	8 (53.3)	9 (60.0)	8 (38.1)
Intermittent	11 (30.6)	4 (36.4)	7 (28.0)	7 (33.3)	4 (26.7)	6 (40.0)	5 (23.8)
Permanent	8 (22.2)	1 (9.1)	7 (28.0)	5 (23.8)	3 (20.0)	0 (0.0)	8 (38.1)
Age at LoA[b], y, mean (SD)	36.2 (13.7)	33	36.5 (14.3)	40.6 (12.7)	28.5 (13.2)	30	36.8 (14.2)
Cardiomyopathy, n (%)	23 (69.9)	7 (63.6)	16 (64)	13 (61.9)	10 (66.7)	12 (80)	11 (52.4)
Ventilatory support, n (%)	2 (5.6)	0 (0)	2 (8)	0 (0)	2 (13.3)	0 (0)	2 (9.5)
BMI at first visit, mean (SD)	25.1 (4.3)	23.2 (3.6)	25.9 (4.4)	24.6 (4.9)	25.7 (3.4)	24.3 (3.3)	25.7 (4.9)

RESEARCH ARTICLE OPEN ACCESS

Sensitivity of Different Clinical Outcome Measures in Assessing Adults With Becker Muscular Dystrophy

A 3-Year Natural History Study

Esther J. Schrama,[1] Zaïda Koeks,[1] Nienke M. Van De Velde,[1] Iris Alleman,[2] Jules J. van Benthem,[3] Pieteke W. van Weperen,[4] Melissa T. Hooijmans,[5,6] Hermien E. Kan,[7,8] Pietro Spitali,[9] Nina Ajmone Marsan,[10] Douwe E. Atsma,[10] Hermine A. van Duyvenvoorde,[8,11] Jan J.G.M. Verschuuren,[1] and Erik H. Niks[1,8]

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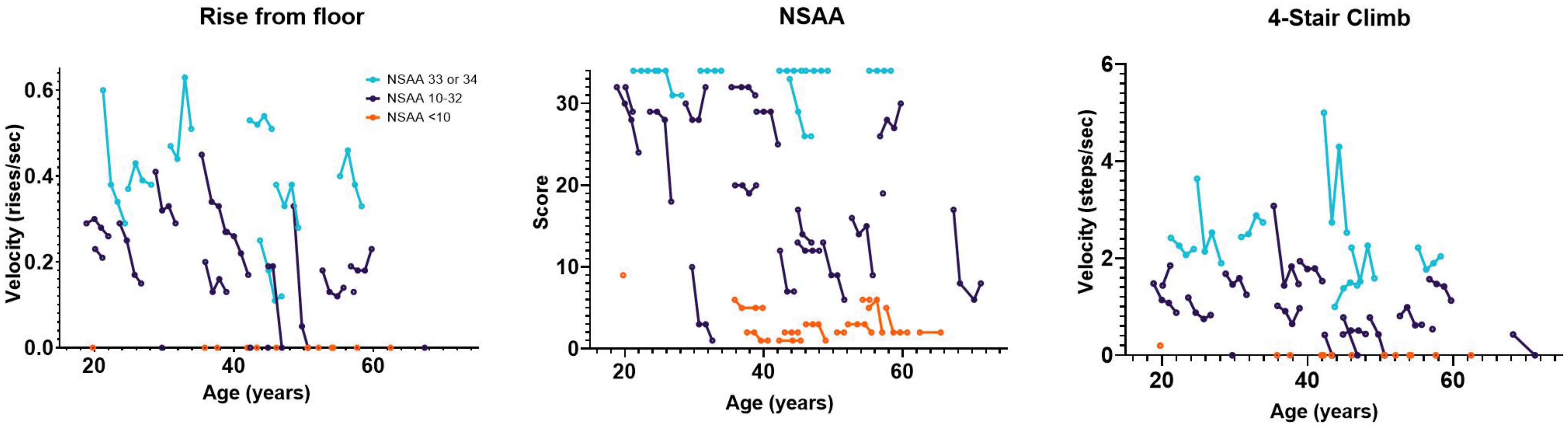
Neurology® 2025;105:e214071. doi:10.1212/WNL.0000000000214071

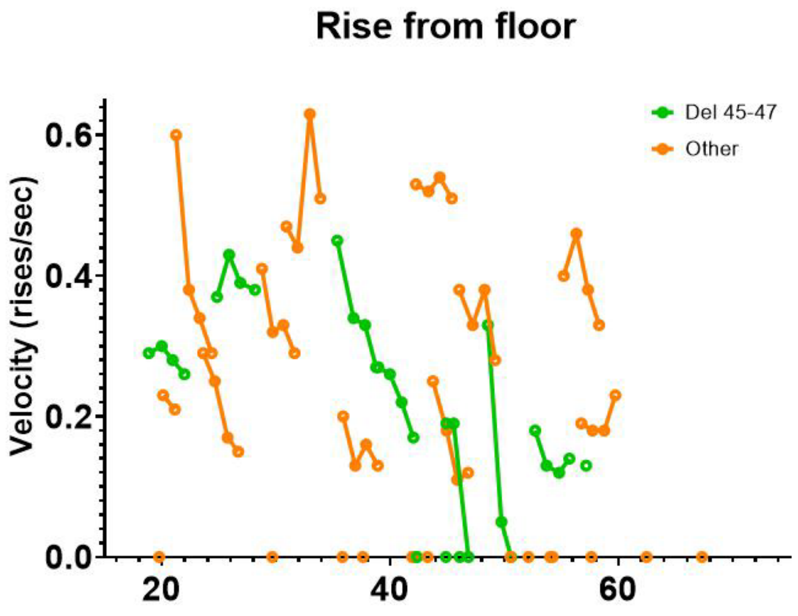
BMD, Becker Muscular Dystrophy; BMI, body mass index; LoA, loss of ambulation; NSAA, North Star Ambulatory Assessment; SD, standard deviation; nNOS, neuronal nitric oxide synthase

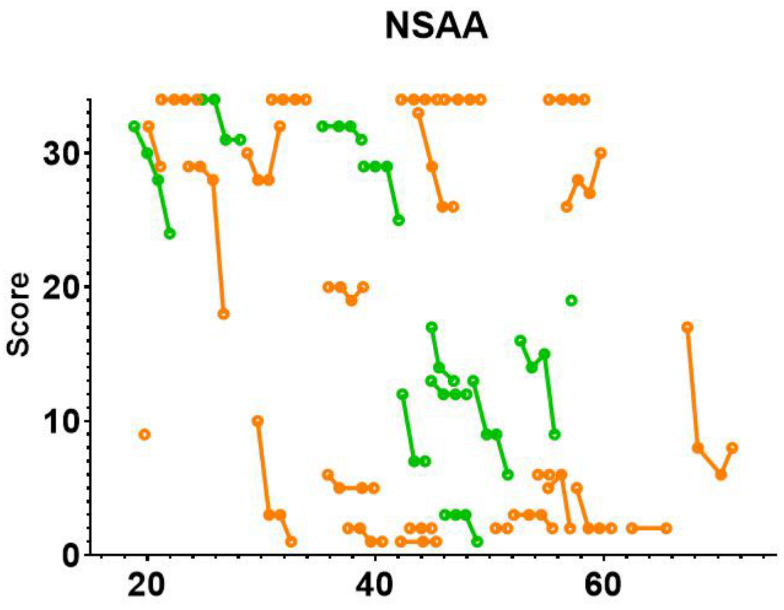
NSAA Decline More Linear in Subpopulation with Baseline Values 10-32

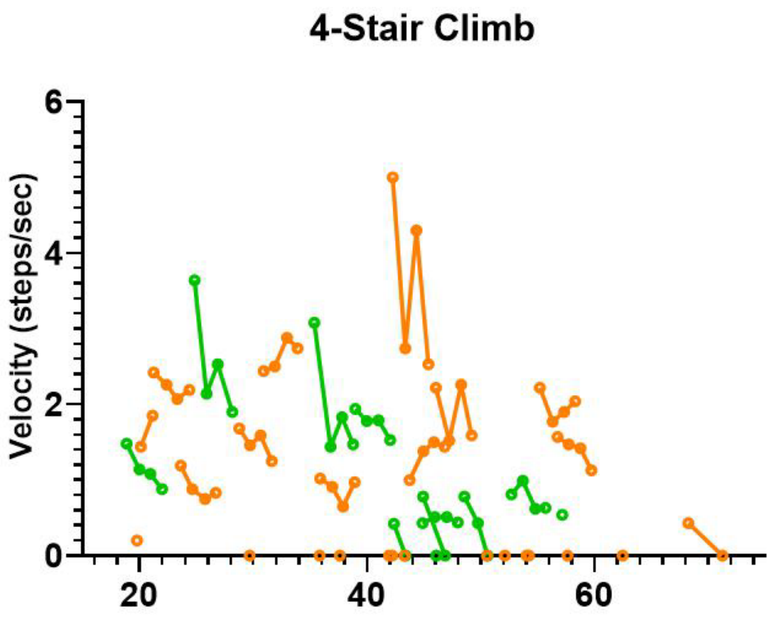


NSAA, North Star Ambulatory Assessment; Sec, second
Schrama E, et al. Neurology 2025;105(7):e214071

Phenotypical Variability within the del 45-47 Genotype



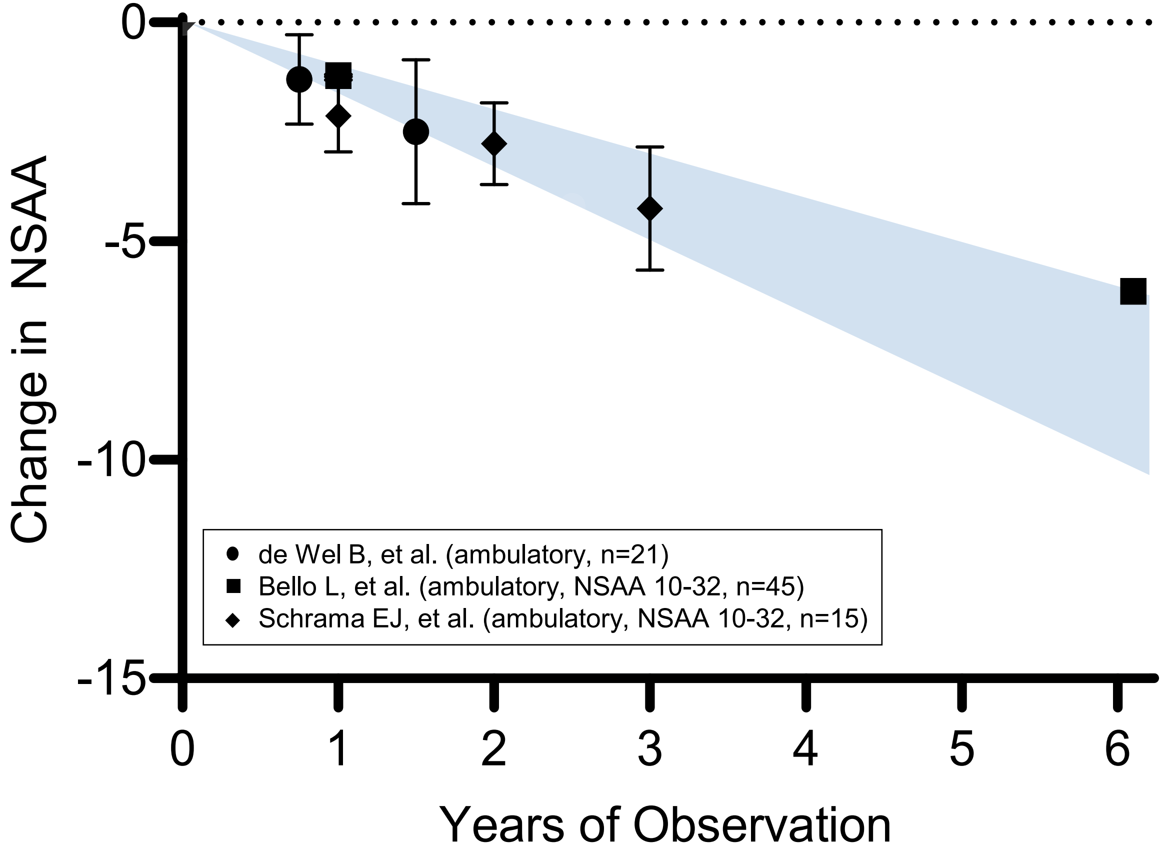




NSAA, North Star Ambulatory Assessment; Sec, second
Schrama E, et al. Neurology 2025;105(7):e214071

Combined Natural History Studies Show Mean Annual Rates of Decline in NSAA between 1.0 and 1.7 Points

Mean Annual Rates of NSAA Decline From Becker Natural History Studies



SCIENTIFIC REPORTS

OPEN

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Accepted: 05 August 2016
Published: 01 September 2016

Functional changes in Becker muscular dystrophy: implications for clinical trials in dystrophinopathies

Luca Bello[1], Paola Campadello[1], Andrea Barp[1], Marina Fanin[1], Claudio Semplicini[1], Gianni Sorarù[1], Luca Caumo[1], Chiara Calore[2], Corrado Angelini[1] & Elena Pegoraro[1]

OPEN ACCESS

Longitudinal Changes of Motor Function in Becker Muscular Dystrophy

Luca Bello,[1] Pietro Riguzzi,[1] Giuliana Capece,[1] Martina Penzo,[1] Angela Petrosino,[1] Elena Sogus,[1] Sara Mastellaro,[1] Michela Caroli,[1] Matteo Villa,[1] Daniele Sabbatini,[1,2] Domenico Gorgoglione,[1] Sara Vianello,[1] Gianni Sorarù,[1] and Elena Pegoraro[1]

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10.1212/NXG.0000000000200285

RESEARCH ARTICLE OPEN ACCESS

Selection Approach to Identify the Optimal Biomarker Using Quantitative Muscle MRI and Functional Assessments in Becker Muscular Dystrophy

Nienke M. van de Velde, MD, Melissa T. Hooijmans, PhD, Aashley S.D. Sardjoe Mishre, MSc, Kevin R. Keene, MD, Zaida Koeks, MD, Thom T.J. Veeger, MSc, Iris Alleman, Erik W. van Zwet, PhD, Jan-Willem M. Beenakker, PhD, Jan J.G.M. Verschuuren, MD PhD, Hermien E. Kan, PhD, and Erik H. Niks, MD PhD

Neurology® 2021;97:e513-e522. doi:10.1212/WNL.0000000000012233

RESEARCH ARTICLE OPEN ACCESS

Sensitivity of Different Clinical Outcome Measures in Assessing Adults With Becker Muscular Dystrophy

A 3-Year Natural History Study

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Neurology® 2025;105:e214071. doi:10.1212/WNL.0000000000214071

ORIGINAL ARTICLE

Lessons for future clinical trials in adults with Becker muscular dystrophy: Disease progression detected by muscle magnetic resonance imaging, clinical and patient-reported outcome measures

Bram De Wel[1,2] | Louise Iterbeke[2] | Lotte Huysmans[3,4] | Ronald Peeters[5] | Veerle Goosens[5] | Nicolas Dubuisson[6] | Peter van den Bergh[6] | Vinciane Van Parijs[6] | Gauthier Remiche[7] | Liesbeth De Waele[8,9] | Frederik Maes[3,4] | Patrick Dupont[10] | Kristl G. Claeys[1,2]

NSAA, North Star Ambulatory Assessment

1. Bello L, et al. Neurol Genet 2025. 2. Bello L et al. Sci Rep. 2016. 3. De Wel B, et al. Eur J Neurol. 2024. 4. Schrama EJ, et al. Neurology. 2025;105(7):e214071.

Edgewise THERAPEUTICS

Prediction Models

- Models to predict disease trajectories provide contextualization for clinical trial outcomes.
- This is especially valuable over multi-year periods in Becker muscular dystrophy for which placebo controls are not feasible.
- A prediction model for changes in the North Star Ambulatory Assessment (NSAA) total score in Becker patients was developed based on longitudinal natural history data from the Nertherlands.
- The model was then validated against published studies of independent BMD data from Italy and Belgium.

BMD, Becker muscular dystrophy
Niks E, et al. Poster presented at: WMS; October 7-11, 2025; Vienna, Austria. #629P.

A Predictive Model Based on Becker Natural History Data was Developed and Validated

Input Data Set

- **Source**: Leiden University Medical Center Becker natural history study
- **Data:** Changes from base in NSAA total score
- **Patient population**: Ambulatory adult males living with Becker muscular dystrophy
- **Data cut-off date**: Apr 2014 – Jul 2019
- **Median follow-up**: 37.0 months (range to 5 years)

Predictive Model

- **Baseline Predictors Applied**:
  – Age
  – 4 Stair climb velocity
  – 10m walk/run velocity
  – Time to rise from floor
- **Marginal R^2**: 0.53
- **Validated against mean values from two publications**:
- Bello et al. 2016
- De Wel et al. 2024

NSAA, Noth Star Ambulatory Assessment
Niks E, et al. Poster presented at: WMS; October 7-11, 2025; Vienna, Austria. #629P.

Participant Baseline Characteristics

Baseline Characteristics

Patient Characteristics, Mean ± SD	**LUMC Patients Ambulatory at Baseline** n = 24
Age, years	39.4 ± 12.6
NSAA total score	23.9 ± 10.6
10MWR velocity, meter/sec	2.0 ± 1.2
RFF velocity, 1/sec	0.2 ± 0.2
4SC velocity, tasks/sec	0.3 ± 0.3

- A total of 24 ambulatory male patients with Becker were included
- Median (range) follow-up: 37.0 months (11.7 – 60.7)

Baseline characteristics were summarized for the analytical sample (n=24) used in the final (best-fitting) prediction model including age, NSAA total score, 10MWR velocity, RFF velocity, and 4SC velocity with a linear time effect.
10MWR, 10-meter walk/run; Becker, Becker muscular dystrophy; RFF, rise from floor; 4SC, 4-stair climb; NSAA, North Star Ambulatory Assessment
Niks E, et al. Poster presented at: WMS; October 7-11, 2025; Vienna, Austria. #629P.

The Model was Validated Against Two Publications: Bello L, et al. 2016 and De Wel B, et al. 2024.

Baseline Functional Measures and Functional Changes at 1 year

Bello L, et al. Sci Rep. 2016

Functional Measures	n at baseline	Mean ± SD at Baseline	Median (range) at baseline	n with longitudinal data	Mean Change ± SD	Median Change (range)
6MWT distance, meters	68	391 ± 155	425 (0-721)	54	3 ± 66	− 2.5 (− 170-273)
NSAA total score	68	25.3 ± 10.8	32.5 (2-34)	57	**− 0.9 ± 1.6*** **	0 (− 6-1)
10MWR velocity, meter/sec	67	2.31 ± 1.49	3.00 (0-5)	54	− 0.03 ± 0.58	0 (− 1.67-2.5)
RFF velocity, 1/sec	68	0.32 ± 0.28	0.33 (0-1)	22	0.06 ± 0.25	0 (− 0.5-0.8)
Climb stairs velocity, steps/s	68	1.83 ± 1.46	1.33 (0.00-4.00)	51	− 0.13 ± 0.6	0 (− 2-0.67)

- **Study size**: 69 Becker patients, ages 6-69 years old
- **Follow up**: 12 ± 1 months

Baseline function measures and changes for all study participants are shown.
6MWT, 6 minute walk test; Becker, Becker muscular dystrophy; NSAA, North Star Ambulatory Assessment; SD, standard deviation; Sec, seconds; RFF, rise from floor
***p<0.001 (Friedman Rank Sum test)
Bello L et al. Sci Rep. 2016.

The Model was Validated Against Two Publications: Bello L, et al. 2016 and De Wel B, et al. 2024.

Baseline Characteristics and Changes at 9 and 18 Months of Follow-Up

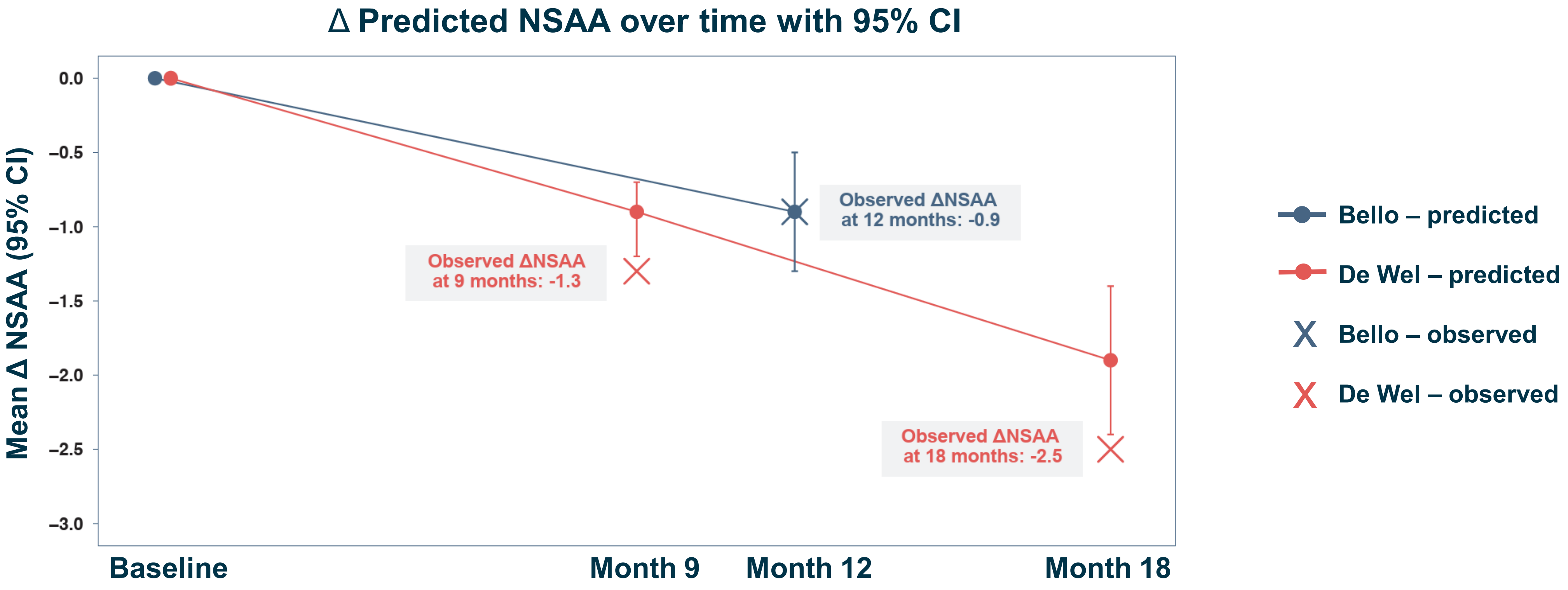
De Wel B, et al. 2024

Functional Measures	Baseline Mean ± SD	Month 9	p-value	Month 18	p-value
6MWT distance, meters	433.2 ± 178.8	−15.1 ± 34.8	0.083	−28.7 ± 57.3	0.042*
NSAA total score	22.1 ± 10.5	**−1.3 ± 2.0**	**0.010***	**−2.5 ± 3.2**	**0.006***
10MWR velocity, meter/sec	1.7 ± 0.8	−0.1 ± 0.1	0.097	−0.1 ± 0.3	0.032*
RFF velocity, 1/sec	0.2 ± 0.2	0.0 ± 0.1	0.294	0.0 ± 0.1	0.351
4SC velocity, meters/s	0.3 ± 0.3	0.0 ± 0.1	0.870	0.0 ± 0.1**	0.028*

- **Study size**: 21 adult Becker participants
- **Follow up:** 9 and 18 months

9- and 18-month columns both show the changes over this time compared to baseline.
*marks p-values that were significant before Holm's correction for multiple testing
**4SC velocity decreased by 0.03 m/s
6MWT, 6 minute walk test; Becker, Becker muscular dystrophy; NSAA, North Star Ambulatory Assessment; RFF, rise from floor; 4SC, 4-stair climb; SD, standard deviation; Sec, second
De Wel B, et al. Eur J Neurol. 2024

The Model Performed Well, With Predicted Means Closely Matching Observed Values



- Compared to Bello et al. 2016, the predicted mean ΔNSAA at 12 months (-0.9 [95% CI: -1.3 to -0.5]) closely matched the observed value (-0.9)
- Compared to De Wel et al. 2024, the predicted mean ΔNSAA showed slightly smaller declines of -0.9 [95%CI: -1.2 to -0.7] vs. -1.3 at 9 months, and -1.9 [95% CI: -2.4 to -1.4] vs. -2.5 at 18 months; however, absolute differences were within 1 unit.

NSAA, North Star Ambulatory Assessment; CI, confident interval
Niks E, et al. Poster presented at: WMS; October 7-11, 2025; Vienna, Austria. #629P.

Key Takeaways

- Natural history is essential for understanding disease progression and severity.
- Recent Becker muscular dystrophy natural history data helps to identify subpopulations in decline.
- Prediction models for natural history trajectories can provide important benchmarks for the outcomes of patients receiving novel therapies.
- This is especially valuable over multi-year periods in Becker and other muscular dystrophies for which placebo controls are not feasible.
- A predictive model was developed to examine NSAA trajectories and changes in individuals living with Becker.
- This model was validated using recent Becker natural history studies. Application of this model is going to be discussed in the next section!

NSAA, North Star Ambulatory Assessment;.

Advancements with an Investigational Agent: Sevasemten Clinical Program Update

Craig McDonald, MD

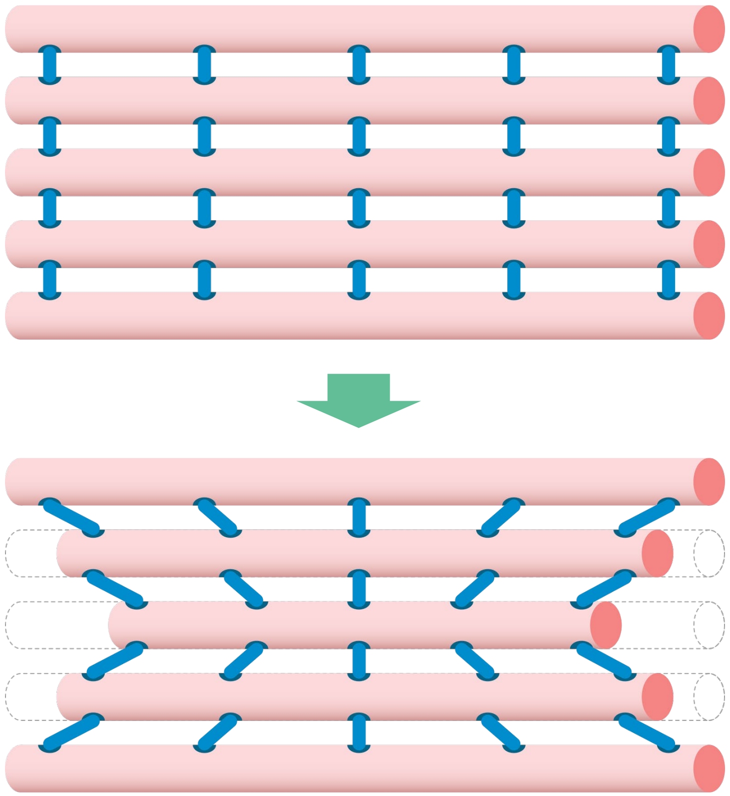
Edgewise THERAPEUTICS

Disclaimers

Dr. Craig McDonald has served on advisory boards, done consulting work on Becker and Duchenne muscular dystrophy clinical trials for Edgewise Therapeutics, and has received research funding for the conduct of clinical trials from Edgewise Therapeutics.

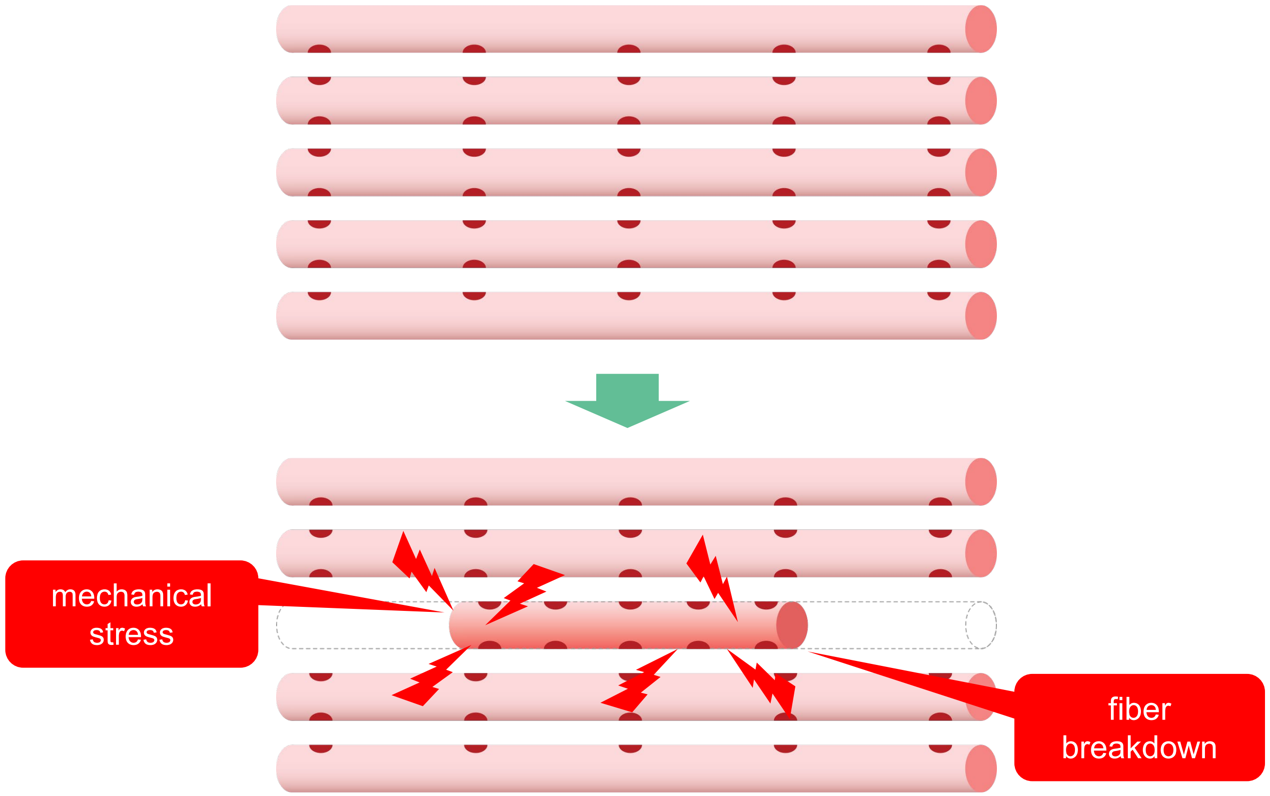
In Dystrophinopathy, Fast Muscle Fibers Are Disproportionately Injured By Contraction

Healthy muscle contraction



Dystrophin connects contractile proteins to the membrane and surrounding matrix to protect against contraction-induced injury.

Dystrophic muscle contraction



Contraction-induced muscle injuries occur in the absence of full-length dystrophin.

Becker Muscular Dystrophy Research at Edgewise Therapeutics

Edgewise Approach: Protect Susceptible Muscle Fibers

In Becker, fast skeletal muscle fibers are more susceptible to damage due to the lack of functional dystrophin.[1]

Edgewise has made an investigational therapy, **sevasemten** designed to protect these susceptible muscle fibers from damage, regardless of mutation.[2]

Clinical trials in Becker are ongoing to assess sevasemten's ability to protect susceptible muscle fibers from injury caused by contraction using biomarkers of muscle damage and functional assessments.

Edgewise Becker Research Program

Study	Trial	Focus	Extension	Status
ARCH	Phase 1 Becker	*Open-label, safety, PK, function*	*OLE*	***Completed***
DUNE	Phase 2 Becker, LGMD2i, & McArdle	*Exercise challenge study*	*OLE*	***Completed***
CANYON	Phase 2 Becker	*Biomarkers, safety, function*	*OLE*	***Completed***
GRAND CANYON	Pivotal Cohort Becker	*Function, biomarkers , safety*	*OLE*	***Active not recruiting***
MESA	Becker Open Label Extension Study	*Long-term safety, biomarkers, function*		***Enrolling by invitation***

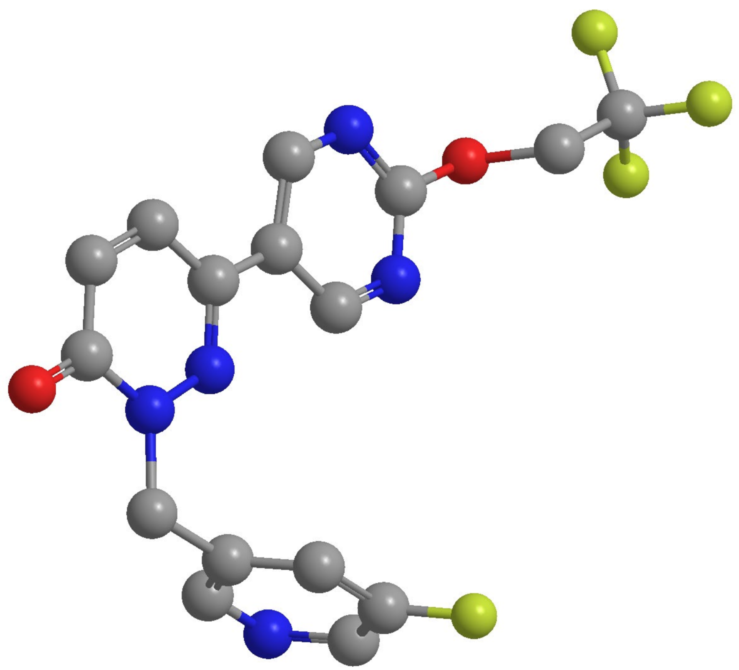
Sevasemten is an investigational agent and is not approved in any territory.

Becker, Becker muscular dystrophy; LGMD2i, Limb-girdle muscular dystrophy 2I; McArdle, McArdle disease; OLE, open-label extension; PK, pharmacokinetics;
Sevasemten is an investigational agent that is not currently approved in any territory.

1. Moens P, et al. J Muscle Res Cell Motil. 1993;14(4):446-451. 2. Russell A, et al. J Clin Invest. 2023;133(10):e153837.

Sevasemten Overview

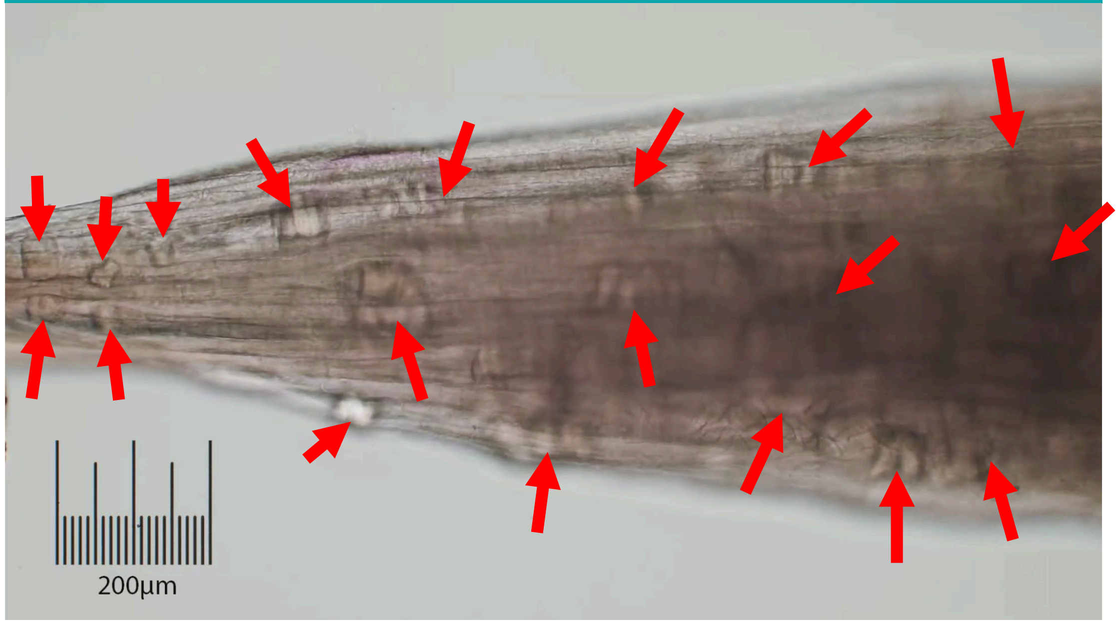
- **A novel, first-in-class, oral, fast myofiber (type II) myosin inhibitor** that is designed to limit contraction of fast muscle fibers
- Inactive against slow skeletal and cardiac myofiber (type I) myosin and so **does not directly affect cardiac function**
- In pre-clinical models, limits but does not prevent fast fiber contraction, allowing muscles to function normally and **protecting them from contraction-induced injury**
- Developed as a **single agent therapy**, and currently being studied in combination with available therapies
- **Mutation-agnostic**



Sevasemten is an investigational therapy that is not currently approved in any territory.

Sevasemten Targets Fast Myosin To Protect Dystrophic Muscle Against Contraction-Induced Injury In *mdx* Mice

Contracting at 100% without sevasemten



In *mdx* mouse muscle, even a few contractions cause visible injury

Contracting at 85% with sevasemten

By minimally decreasing contraction, while preserving function, visible contraction-induced injury is prevented

Sevasemten is an investigational therapy that is not currently approved in any territory.
Russell AJ, et al. J Clin Invest. 2023;133(10):e153837.

ARCH

An open-label, single-center study to assess sevasemten safety and pharmacokinetics in adults with Becker

NCT05160415

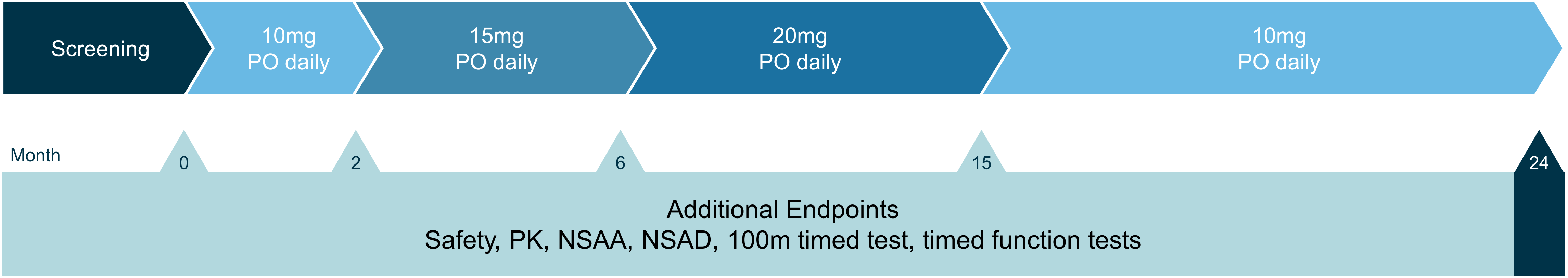
Edgewise THERAPEUTICS

ARCH

An Open-Label, Single-Center Study To Assess Sevasemten Safety and Pharmacokinetics In Adults With Becker

- **Primary objective:** Safety and tolerability at 24 months
- **Key inclusion criteria:** Ambulatory males aged 18 to 55 years with a dystrophin mutation and a Becker phenotype, not on corticosteroids, who could complete 100-m timed test
- **Patients enrolled:** 12

Study design - 24 months



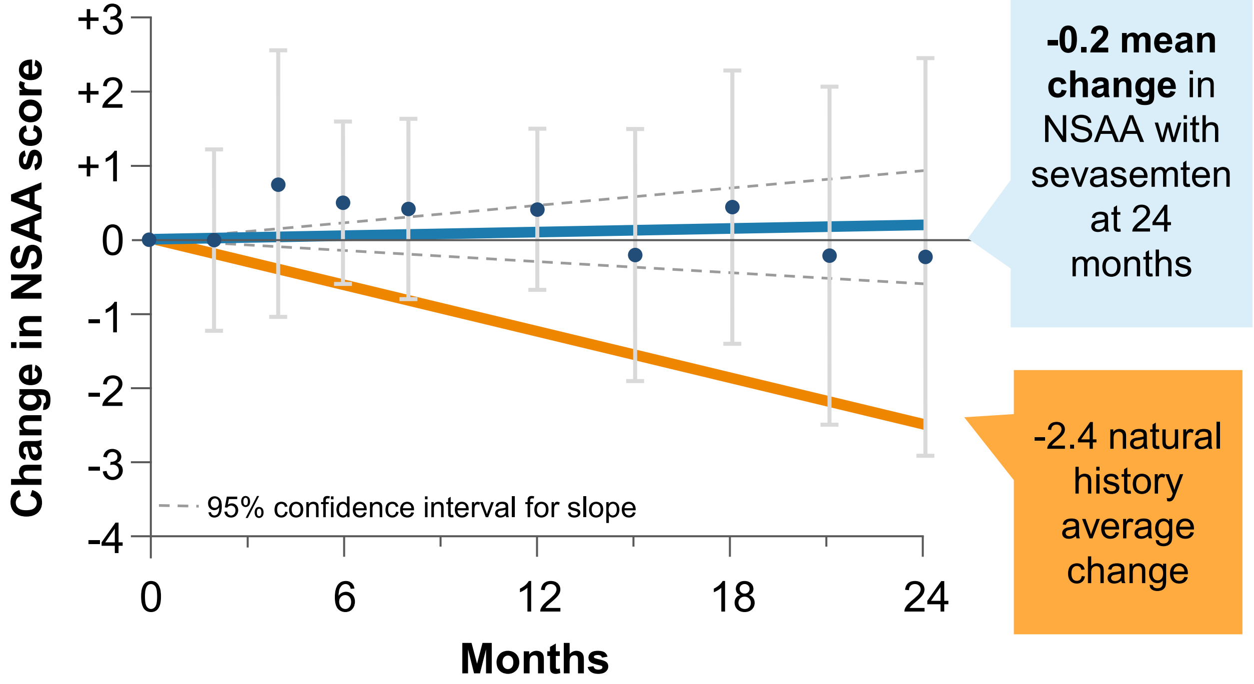
Becker, Becker muscular dystrophy; PK, pharmacokinetics; NSAA, North Star Ambulatory Assessment; NSAD, North Star Assessment for Limb Girdle Muscular Dystrophy;
Sevasemten is an investigational therapy that is not currently approved in any territory.
Phan H, et al. Oral presentation presented at: American Academy of Neurology; April 13-18, 2024; Denver, CO.

ARCH An Open-Label, Single-Center Study To Assess Sevasemten Safety and PK In Adults With Becker

ARCH is a 24-month open-label study in 12 ambulatory adults with Becker muscular dystrophy

- Sevasemten was well-tolerated.
- Early and rapid reductions in CK and TNNI2, biomarkers of muscle damage, were sustained to 24 months.
- Stabilization of functional assessments was seen.
  - NSAA diverged from natural history.
  - No statistically significant change in 100-meter timed test velocity and max grip strength.

NSAA change



Becker, Becker muscular dystrophy; CK, creatine kinase; TNNI2, fast skeletal muscle troponin I; NSAA North Star Ambulatory Assessment; PK, pharmacokinetics
Sevasemten is an investigational therapy that is not currently approved in any territory.
Phan H, et al. Oral presentation presented at: American Academy of Neurology; April 13-18, 2024; Denver, CO.

CANYON

A multi-center, randomized, double-blind, placebo-controlled, Phase 2 study to evaluate the safety, pharmacokinetics, biomarkers, and functional measures of sevasemten

NCT05291091

Edgewise THERAPEUTICS

CANYON

A Phase 2 Multi-Center Study to Assess Sevasemten Safety and Effects on Biomarkers in Adults with Becker

ADULT PRIMARY EFFICACY ENDPOINT

Change from baseline in CK averaged across Months 6, 9 and 12

KEY INCLUSION CRITERIA

Ambulatory males aged 12 to 50 years with a dystrophin mutation and a Becker phenotype, not on corticosteroids, with a **NSAA between 5-32***

PATIENTS ENROLLED

Adults: **40**

Adolescents: **29**

Study design - 12 months

ADULTS
- **10 mg** PO daily
- Placebo

ADOLESCENTS (ages 12-17)
- **5 mg or 12.5 mg** PO daily
- Placebo

Month: 0, 1, 3, 6, 9, 12

Key Secondary: North Star Ambulatory Assessment (NSAA); change from baseline at month 12
Additional Endpoints: Safety, PK, biomarkers, timed function tests, MRI

*Adolescents were not selected based on NSAA
Becker, Becker muscular dystrophy; CK, creatine kinase; NSAA, North Star Ambulatory Assessment; PK, pharmacokinetics
Sevasemten is an investigational therapy that is not currently approved in any territory.
McDonald C, et al. Poster presentation presented at: WMS; October 7-11, 2025. #614P

CANYON

Adult Participants Had Significant Functionally Impairment at Baseline

Functional test	Adults Sevasemten (n=28)	Adults Placebo (n=12)	Adolescents Sevasemten (n=20)	Adolescents Placebo (n=9)
Mean total NSAA score, points (SD)	18.4 (7.66)	24.2 (8.19)	31.3 (2.53)	29.3 (6.34)
Mean 4SC velocity, 1/seconds (SD)	0.22 (0.128)	0.34 (0.173)	0.497 (0.113)	0.429 (0.161)
Mean RFF velocity, 1/seconds (SD)*	0.14 (0.114)	0.21 (0.128)	0.362 (0.122)	0.310 (0.157)
Mean 10MWR velocity, meters/second (SD)	1.52 (0.731)	2.00 (0.884)	2.863 (0.506)	2.612 (0.692)
Mean 100MTT velocity, meters/second (SD)	1.50 (0.856)	1.78 (0.782)	3.011 (0.680)	2.568 (0.892)

*At baseline, 1 placebo and 9 sevasemten treated participants were unable to rise from floor
100MTT, 100-meter timed test; 10MWR, 10-meter walk/run; 4SC, 4-stair climb; NSAA, North Star Ambulatory Assessment; SD, standard deviation
Sevasemten is an investigational therapy that is not currently approved in any territory.
McDonald C, et al. Poster presentation presented at: WMS; October 7-11, 2025. #614P

CANYON Sevasemten was Well Tolerated in Adults and Adolescents

	Adults Sevasemten (n=28) n (%)	Adults Placebo (n=12) n (%)	Adolescents Sevasemten (n=20) n (%)	Adolescents Placebo (n=9) n (%)
Any TEAE in ≥5% of participants	**26 (92.9%)**	**10 (83.3%)**	**19 (95%)**	**9 (100%)**
Eye disorders				
Vision blurred	1 (3.6%)	2 (17%)	0 (0%)	0 (0%)
General disorders and administration site conditions				
Fatigue	5 (18%)	3 (25%)	3 (15%)	1 (11%)
Pyrexia	0 (0%)	0 (0%)	2 (10%)	2 (22%)
Infections and infestations				
COVID-19	6 (21%)	2 (17%)	0 (0%)	0 (0%)
Nasopharyngitis	6 (21%)	2 (17%)	5 (25%)	2 (22%)
Upper respiratory tract infection	5 (18%)	2 (17%)	4 (20%)	2 (22%)
Influenza	4 (14%)	1 (8%)	0 (0%)	0 (0%)
Sinusitis	0 (0%)	0 (0%)	4 (20%)	0 (0%)
Injury, poisoning and procedural complications				
Fall	8 (29%)	2 (17%)	4 (20%)	0 (0%)
Investigations				
Ejection fraction decreased	0 (0%)	2 (17%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders				
Back pain	3 (11%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders				
Headache	9 (32%)	2 (17%)	0 (0%)	0 (0%)
Dizziness	9 (32%)	0 (0%)	1 (5%)	2 (22%)
Somnolence	5 (18%)	1 (8%)	3 (15%)	0 (0%)
Migraine	3 (11%)	1 (8%)	0 (0%)	0 (0%)
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	4 (14%)	0 (0%)	0 (0%)	0 (0%)
Cough	3 (11%)	0 (0%)	0 (0%)	0 (0%)
Sinus congestion	0 (0%)	0 (0%)	2 (10%)	2 (22%)
Upper respiratory tract congestion	0 (0%)	0 (0%)	1 (5%)	2 (22%)
Gastrointestinal disorders				
Diarrhea	0 (0%)	0 (0%)	2 (10%)	1 (11%)
Nausea	0 (0%)	0 (0%)	2 (10%)	1 (11%)
Vomiting	0 (0%)	0 (0%)	2 (10%)	1 (11%)

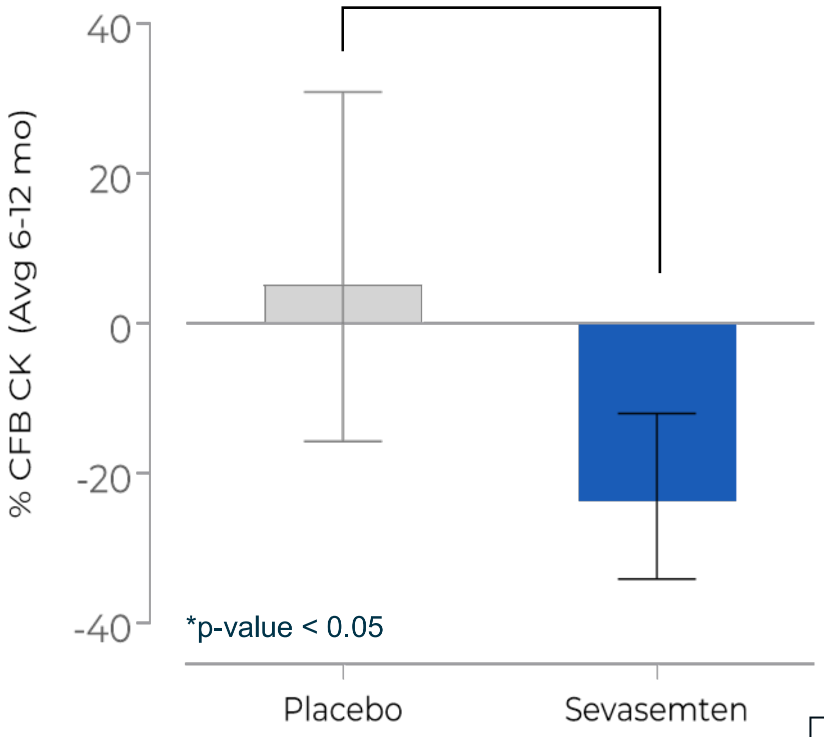
Most common adverse events: headache, dizziness, nasopharyngitis

TEAE, treatment emergent adverse event
Sevasemten is an investigational therapy that is not currently approved in any territory.
McDonald C, et al. Poster presentation presented at: WMS; October 7-11, 2025. #614P

CANYON Biomarkers of Muscle Damage Decreased Significantly

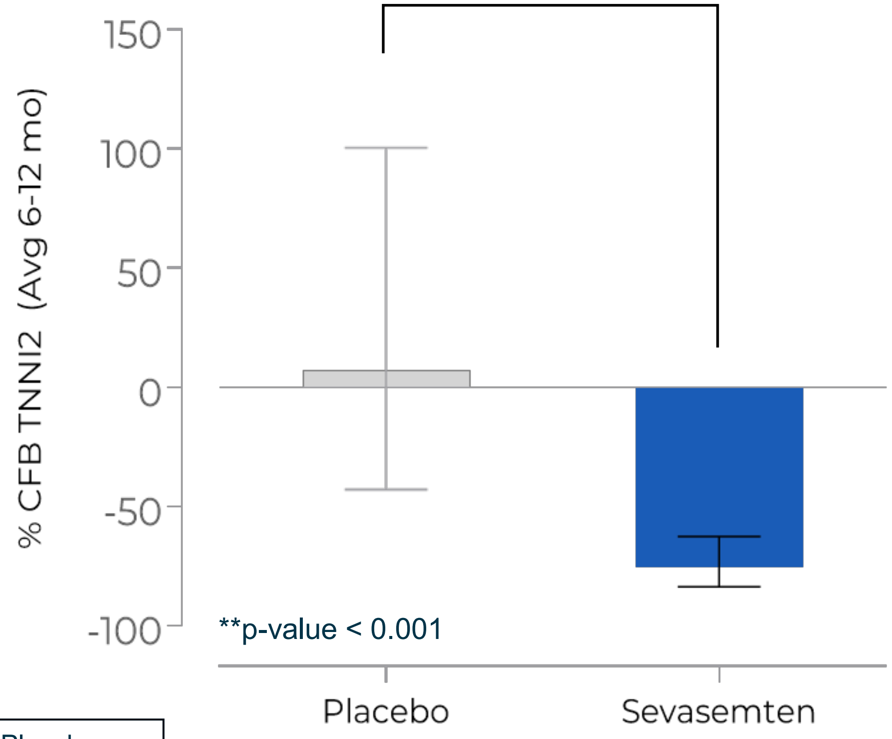
Primary Endpoint:
CK % Change from Baseline

-28% *



TNNI2 % Change from Baseline

-77% **

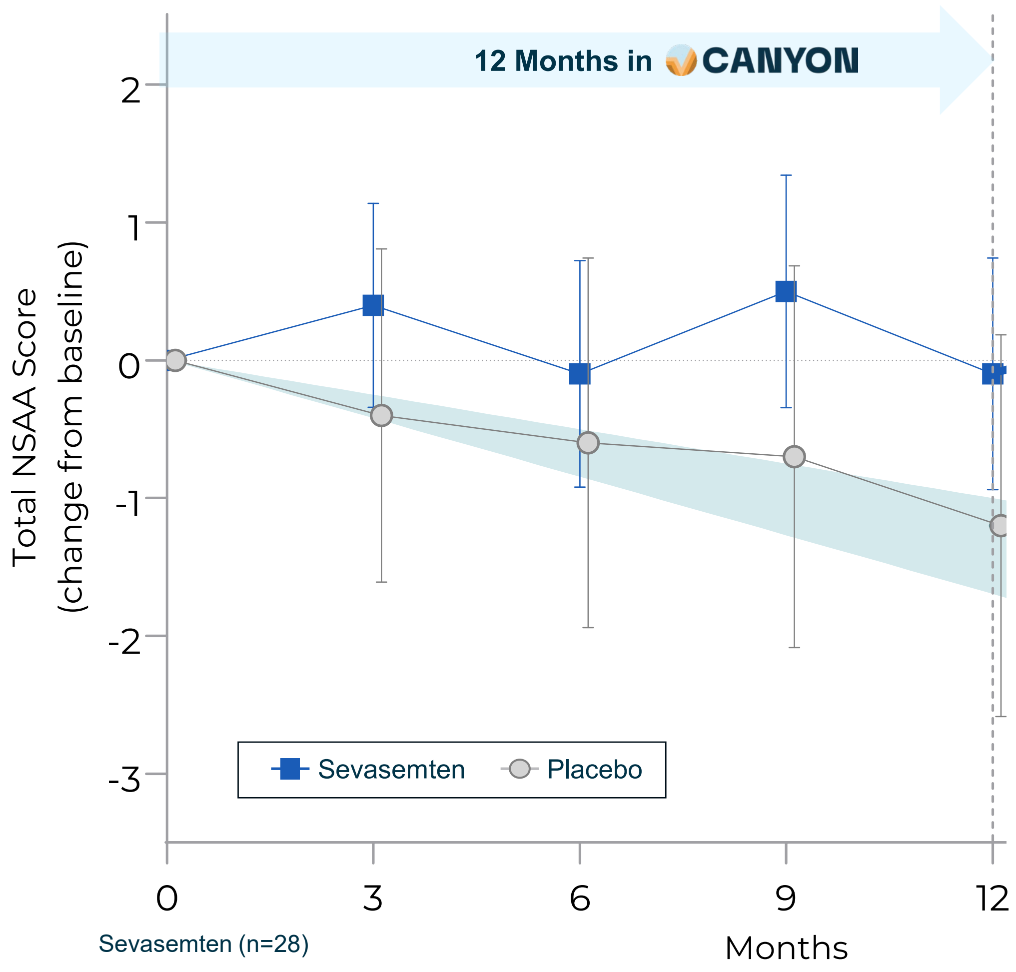


Sevasemten Placebo

LS Means, LS Mean differences and 95% CI shown for Safety Population. CK and TNNI2 values were log-transformed. LS (least squares) means, LS mean differences and Cis were back-transformed to percent scale; CFB, change from baseline; CK, creatine kinase; TNNI2, fast skeletal troponin I
Sevasemten is an investigational agent that is not currently approved in any territory.
McDonald C, et al. Poster presentation presented at: WMS; October 7-11, 2025. #614P

NSAA Trajectory on Sevasemten Diverged from Natural History

NSAA Score Change from Baseline



Sevasemten (n=28)

Initial Placebo (n=12)

+1.12*

NSAA vs placebo at month 12

Range from Natural History Studies

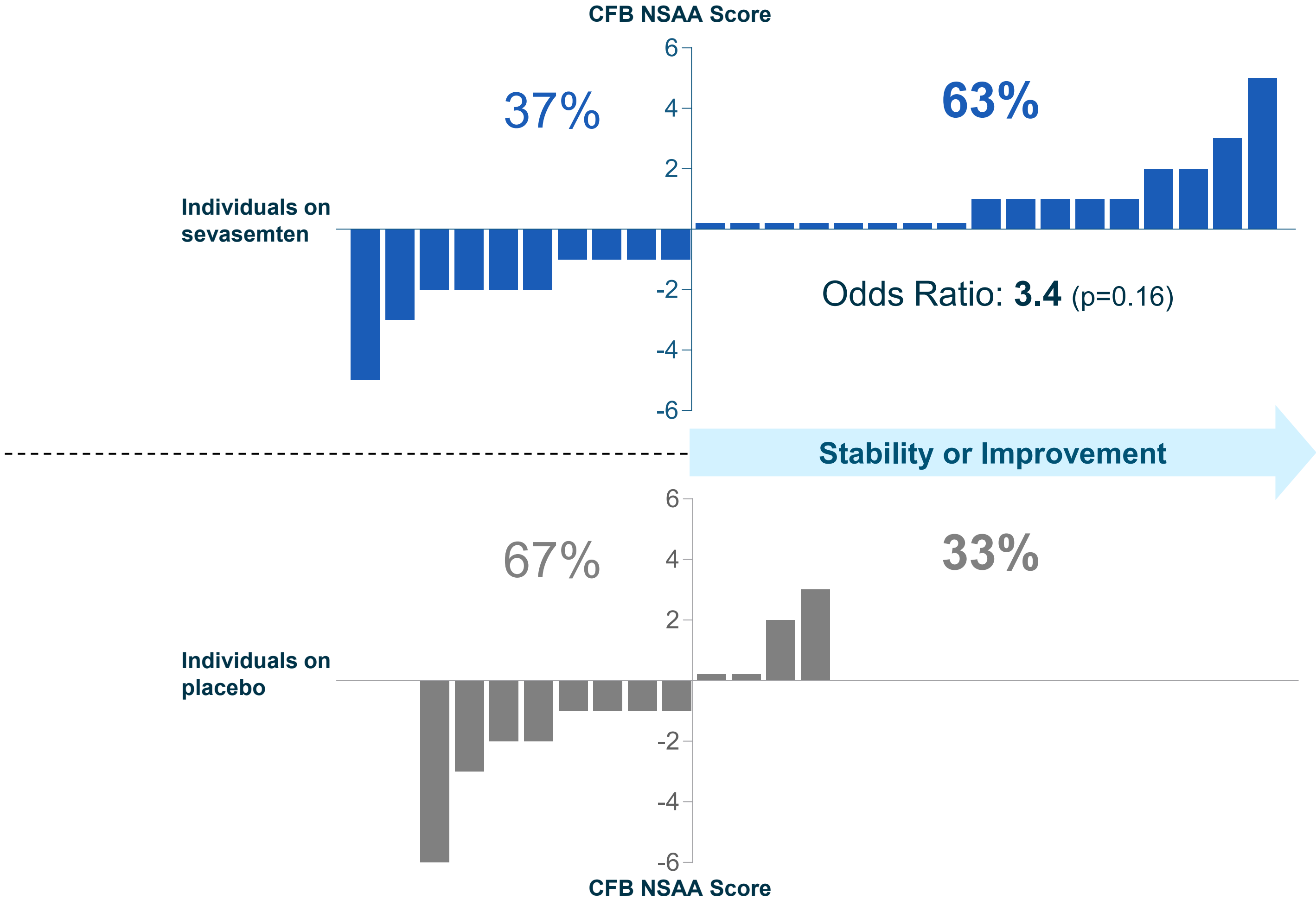
Natural history studies have shown that NSAA decreased between an average of **1 to 1.7 points per year**.

*p-value = 0.16; Through Month 12, LS Means and 95% CI shown for Safety Population. Post-Month 12 timepoints, observed means and 95% CI are presented.
NSAA, North Star Ambulatory Assessment
Sevasemten is an investigational agent that is not currently approved in any territory.
McDonald C, et al. Poster presentation presented at: WMS; October 7-11, 2025. #614P

CANYON

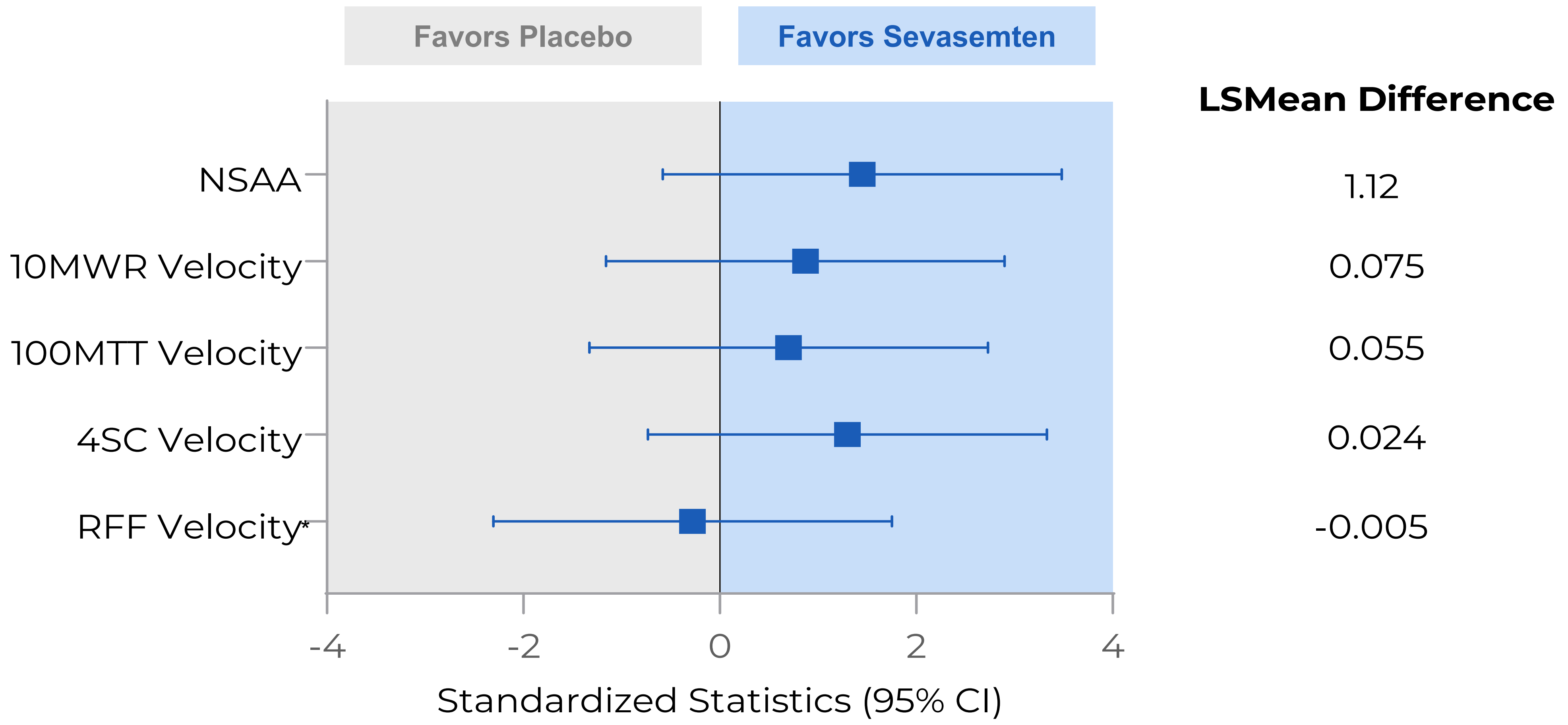
63% of Patients Treated with Sevasemten Showed Stable or Improved Function After 12 Months

Sevasemten NSAA Responder Analysis



CFB, Change from baseline; CI, confidence interval; NSAA, North Star Ambulatory Assessment
Sevasemten is an investigational therapy that is not currently approved in any territory.
McDonald C, et al. Poster presentation presented at: WMS; October 7-11, 2025. #614P

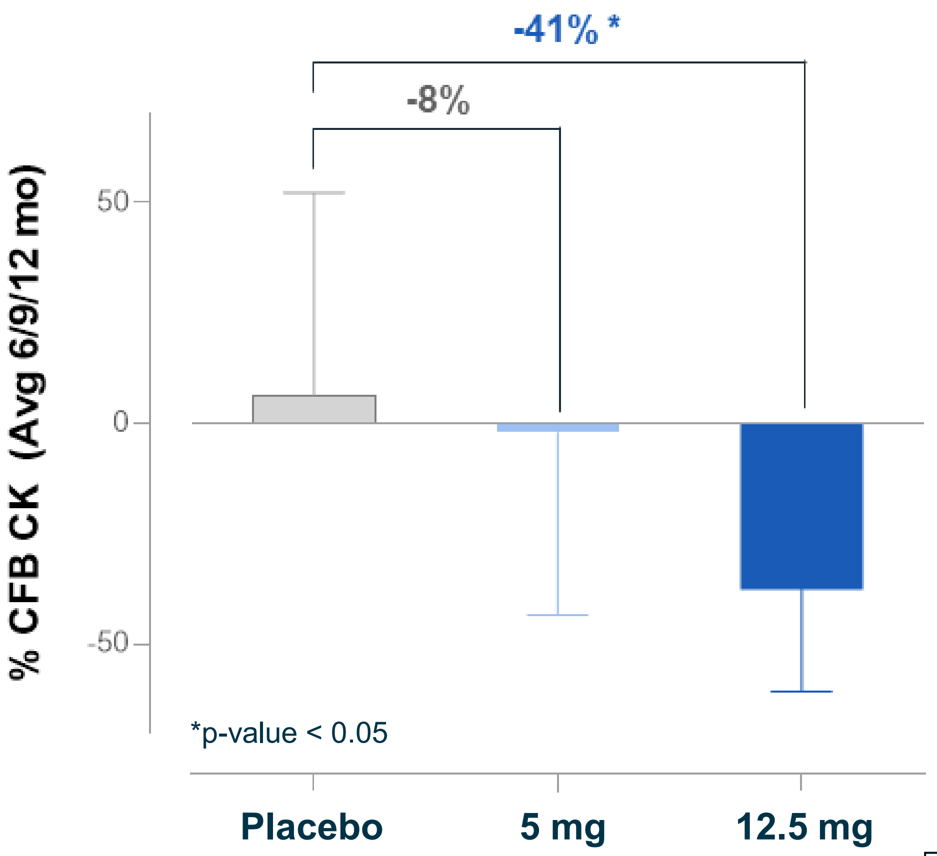
CANYON Trends in Other Functional Measures Favor Sevasemten Treatment Arm

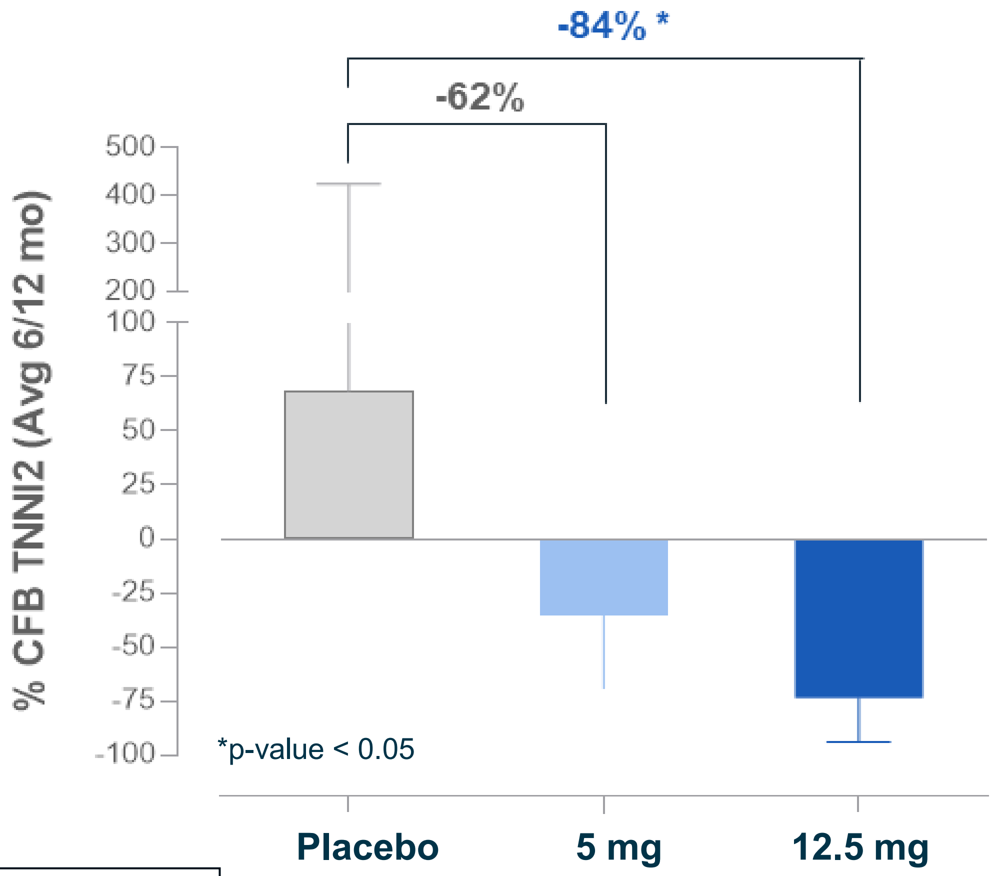


*At baseline, 9 sevasemten and 1 placebo treated participants were unable to rise from floor. At Month 12, 9 sevasemten and 2 placebo treated participants were unable to rise from floor. Note: For the figures, LSM differences and Cis were standardized by dividing by the SE. LSM differences presented on the right of the figure are on original scale (without SE adjustment).
CI, confidence interval; NSAA, North Star Ambulatory Assessment
Sevasemten is an investigational therapy that is not currently approved in any territory
McDonald C, et al. Poster presentation presented at: WMS; October 7-11, 2025. #614P

CANYON

Adolescents Treated with 12.5 mg Sevasemten had Significant Decreases in CK and TNNI2, Similar to Changes in Adults





Sevasemten Placebo

LS Means, LS Mean differences and 95% CI shown for Safety Population. CK and TNNI2 values were log-transformed. LS (least squares) means, LS mean differences and Cis were back-transformed to percent scale;
CFB, change from baseline; CK, creatine kinase; TNNI2, fast skeletal troponin I
Sevasemten is an investigational agent that is not currently approved in any territory.
McDonald C, et al. Poster presentation presented at: WMS; October 7-11, 2025. #614P

Edgewise THERAPEUTICS

CANYON Summary of Trial Results

For more information on CANYON, please see **Poster #614P**

Safety

- **Well-tolerated at all doses**, in adults and adolescents
- No safety concerns identified

Biomarkers

- Primary endpoint achieved: **28% decrease in CK** vs. placebo ($p<0.05$) in adults
- **TNNI2 decreased 77%** from baseline vs. placebo ($p<0.001$) in adults
- In adolescents treated with 12.5 mg sevasemten, **41% decrease in CK** ($p<0.05$) and **84% TNNI2 decrease** ($p<0.05$) vs. placebo

Function

- Sevasemten treated patients showed **stabilization of NSAA with trends toward improvement**
- Placebo group (n=12) **declined in line with natural history**

Secondary & Exploratory

- Other functional endpoints, such as 4SC, 10MWR, 10mTT, **trended favorably**

CK, creatine kinase; NSAA, North Star Ambulatory Assessment
Sevasemten is an investigational therapy that is not currently approved in any territory.
McDonald C, et al. Poster presentation presented at: WMS; October 7-11, 2025. #614P

MESA

An Open-Label Extension of Sevasemten in Participants with Becker Muscular Dystrophy

NCT06066580

MESA Sevasemten Efficacy in Becker Continues to be Assessed in the MESA Open-Label Study

ARCH — **Phase 1**: 24-month Open Label Study (N=12)
COMPLETE

DUNE — **Phase 2**: 16-weeks Placebo Controlled Exercise Challenge Study (N=9)
COMPLETE

CANYON — **Phase 2**: 12-month Placebo Controlled Study (N=40 Adults)
COMPLETE

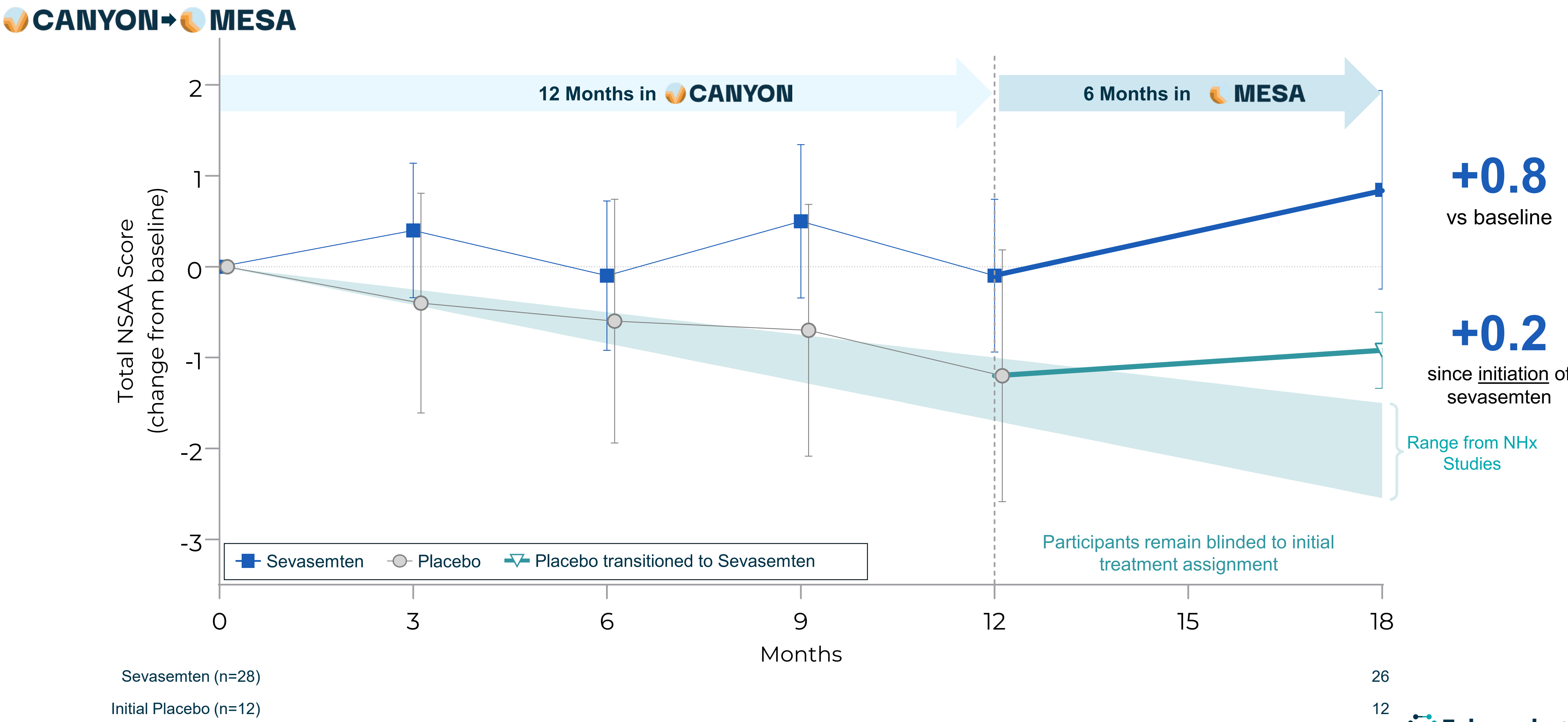
GRAND CANYON — **Pivotal Cohort**: 18-month Placebo Controlled Study (N=175 Adults)
ACTIVE, Not Recruiting

MESA (NCT06066580)

Open-label extension study in adults and adolescents with Becker
As of March 2025, **85 participants** enrolled in MESA (99% of eligible)

Becker, Becker Muscular Dystrophy
Sevasemten is an investigational therapy that is not currently approved in any territory

After Transitioning To MESA, CANYON Participants Showed an Increase in NSAA After 18 Months



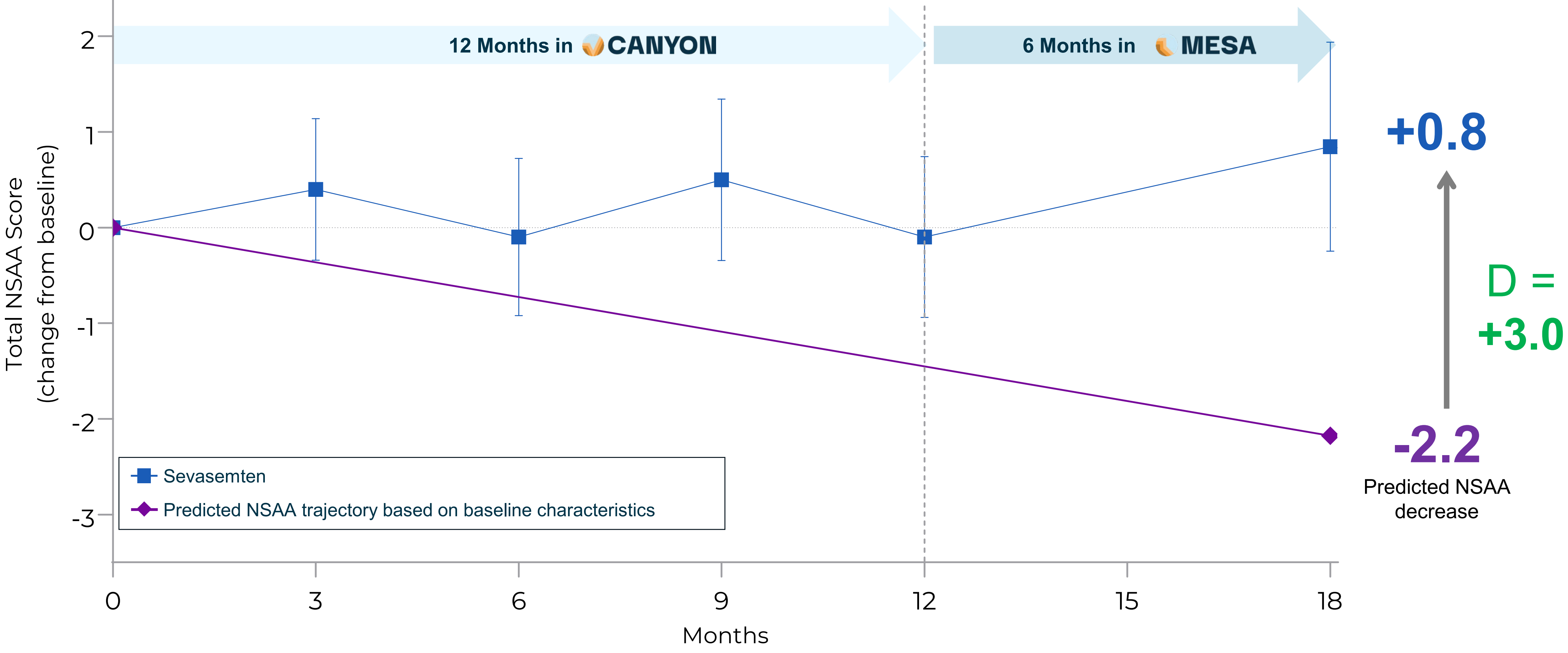
Through Month 12, LS Means and 95% CI shown for Safety Population. Post-Month 12 timepoints, observed means and 95% CI are presented.
Data on File. Sevasemten is an investigational therapy that is not currently approved in any territory

CANYON Participants' NSAA Scores Diverge from Predicted Natural History; 92% Improved vs their Predicted Scores

MESA

CANYON ➔ MESA

NSAA Score Change from Baseline



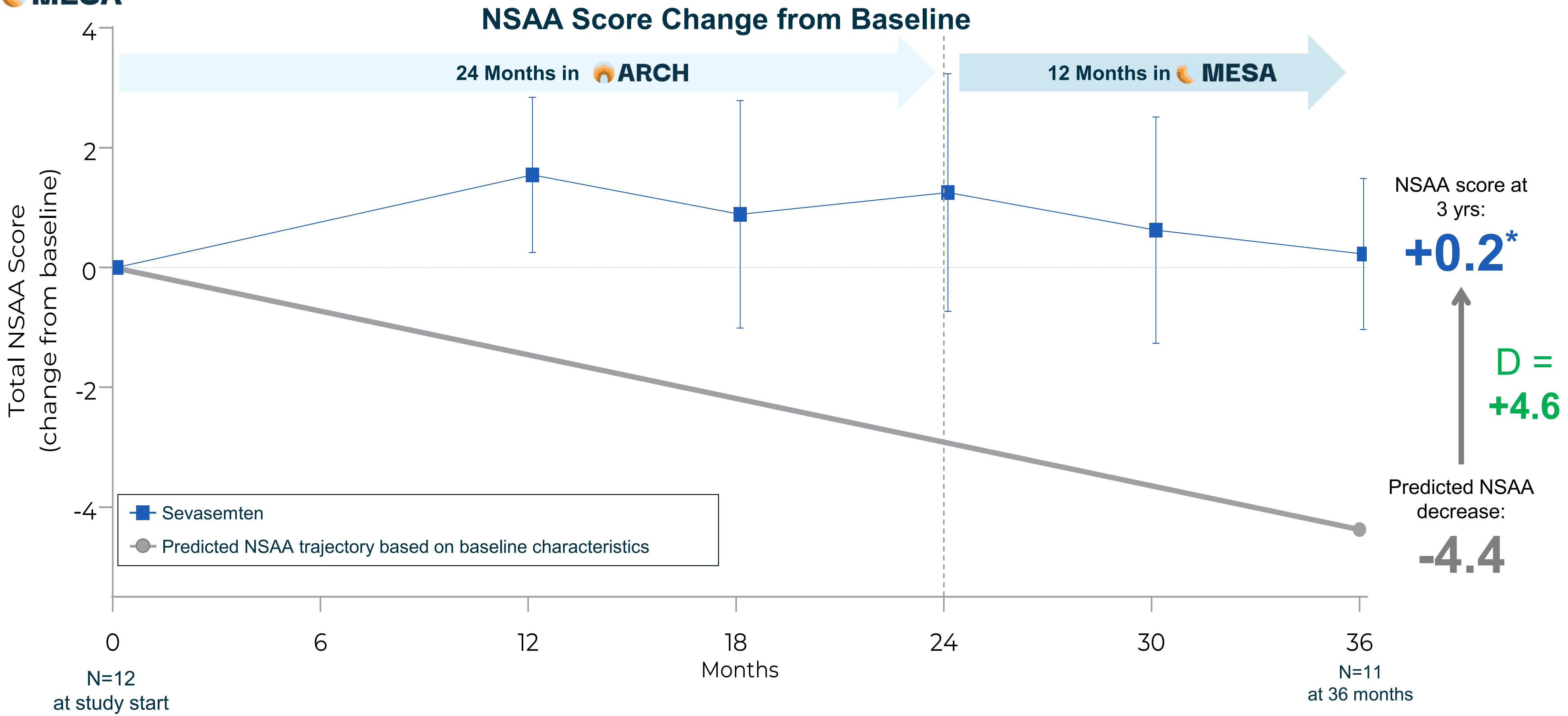
NSAA, North Star Ambulatory Assessment
Through Month 12, LS Means and 95% CI shown for Safety Population; Post-Month 12 timepoints, observed means and 95% CI are presented
Data on File. Sevasemten is an investigational therapy that is not currently approved in any territory

ARCH Participants Remained Stable After 3 Years vs a Predicted -4.4 Point NSAA Decline; 89% Achieved Higher NSAA Scores vs Predicted

MESA

For more information on the application of the model to ARCH & CANYON, please see **poster #629P**

ARCH➔MESA



NSAA, North Star Ambulatory Assessment
*Subject with meniscal tear at month 15 excluded from subsequent NSAA measures
Means and 95% CI shown for Safety Population; Natural history comparators not available for time points earlier than 12 months
Data on File. Sevasemten is an investigational therapy that is not currently approved in any territory.

Sevasemten Continues to be Investigated in Becker; GRAND CANYON is Fully Enrolled and Ongoing

GRAND CANYON

An 18-month pivotal placebo-controlled trial to evaluate the effect of sevasemten on biomarkers of muscle damage and functional measures in individuals living with Becker

Primary Endpoint is **NSAA at 18 months** (powered at >90% to demonstrate a statistically significant difference)

Enrolled participants were adult individuals with Becker with **NSAA 5-32**, **not taking corticosteroids**

GRAND CANYON enrolled **175 participants** at sites across the US, Europe, Israel, and Australia

What's Next?

GRAND CANYON is on track for **topline data by the end of 2026**

Becker, Becker muscular dystrophy; NSAA, North Star Ambulatory Assessment.
Sevasemten is an investigational agent that is not currently approved in any territory.

Duchenne Muscular Dystrophy

Duchenne Clinical Program at Edgewise Therapeutics

LYNX

Phase 2 trial of sevasemten in children with Duchenne

Status: Active, not recruiting

FOX

Phase 2 trial of sevasemten in children and adolescents with Duchenne previously treated with gene therapy

Status: Active, not recruiting

Duchenne Study Goals: Explore a Range of Doses to Assess Safety and Identify a Potentially Beneficial Dose for Phase 3

- Determine the target patient population, background therapy and primary endpoints for Phase 3 design.
- Dose escalation paradigm: 3-month placebo-controlled period to evaluate biomarkers for dose selection, followed by open-label period.
- After safety review, participants were transitioned to the highest tolerated dose.

Sevasemten is an investigational therapy that is not currently approved in any territory.

Sevasemten is Positioned as a Foundational Therapy and Continues to be Investigated in Duchenne

For more information on LYNX, please see **Poster #730LBP**

LYNX

Phase 2 trial of sevasemten in children with Duchenne

FOX

Phase 2 trial of sevasemten in children and adolescents with Duchenne previously treated with gene therapy

Functional observations support **the 10 mg dose** of sevasemten as the dose to move forward with to a pivotal-stage program.

With a dose of 10 mg, sevasemten was found to be **well-tolerated**, with no new safety concerns identified.

Trials will continue with an **open-label extension** to collect longer term data**.**

Meetings are planned with regulatory agencies to receive input on **Phase 3** design, including target patient population and endpoints.

Sevasemten is an investigational agent that is not currently approved in any territory

Sevasemten is Currently Being Investigated in Becker, Duchenne, and Other Muscular Dystrophies

	Study	Description	Design	Extension	Status
Becker	ARCH	Phase 1 Becker	*Open-label, safety, PK, function*	*OLE*	***Completed***
Becker	DUNE	Phase 2 Becker, LGMD2i, & McArdle	*Exercise challenge study*	*OLE*	***Completed***
Becker	CANYON	Phase 2 Becker	*Biomarkers, safety, function*	*OLE*	***Completed***
Becker	GRAND CANYON	Pivotal Cohort Becker	*Function, biomarkers , safety*	*OLE*	***Active, not recruiting***
Becker	MESA	Becker Open Label Extension Study	*Open-label long-term safety, biomarkers, function*		***Enrolling by invitation***
Duchenne	LYNX	Ph 2 Duchenne Dose-Ranging	*PK, biomarkers, safety*	*OLE*	***Active, not recruiting***
Duchenne	FOX	Ph 2 Duchenne Boys on Gene Tx	*PK, biomarkers, safety*	*OLE*	***Active, not recruiting***

Up to date as of 01Oct2025. Sevasemten is an investigational agent that is not currently approved in any territory.
Becker, Becker muscular dystrophy; Duchenne, Duchenne muscular dystrophy; LGMD2i, Limb-girdle muscular dystrophy 2i; McArdle, McArdle disease; Gene Tx, gene therapy
1. ARCH. ClinicalTrials.gov identifier: NCT05160415. 2. Stemmerick MG, et al. Poster presented at WMS; Oct 8-12, 2024; Prague, Czechia. #732LBP. 3. CANYON. ClinicalTrials.gov identifier: NCT05291091. 4. MESA ClinicalTrials.gov identifier: NCT06066580. 5. LYNX. ClinicalTrials.gov identifier: NCT05540860. 6. FOX. ClinicalTrials.gov identifier: NCT06100887.

Thank You For Your Attendance!

We wish to thank the patients, investigators, study site personnel, and all of those who are helping to facilitate clinical trials and to improve care!

For questions about our clinical trials, please email:
studies@edgewisetx.com
or visit clinicaltrials.gov

Talk to Edgewise at **Booth #16**

Learn more at posters **614P, 629P,** and **730LBP**

Visit the first site dedicated to Becker muscular dystrophy disease education at **beckermusculardystrophy.com/**

Panel Discussion

We now welcome both virtual and in person questions from the audience.

For virtual viewers, please utilize the WMS app to ask your questions.

For the in person audience, please use the microphone to ask your question.

Thank you!