CANYON trial results: Sevasemten, an investigational fast skeletal myosin inhibitor, reduced muscle damage biomarkers and stabilized function in Becker muscular dystrophy (BMD)

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Disclosures

Sevasemten is an investigational agent that is not approved for use by any regulatory authority in any territory.

Professor McDonald has served on Advisory Boards, done consulting work on Becker and Duchenne muscular dystrophy clinical trials, and has received research funding for the conduct of clinical trials from Edgewise Therapeutics.

Our Goal is to Positively Impact the Course of Becker Muscular Dystrophy

- Becker muscular dystrophy (Becker) is a rare, genetic, life-shortening, debilitating and degenerative neuromuscular disorder.
- The disease predominately affects males and imposes significant physical, emotional, financial and social impacts on the individuals and their caregivers.
- Individuals with Becker lose mobility, function and independence in the prime of their lives.
- There is currently no treatment for Becker.

Reference: NIH Genetics Home Reference - Duchenne and Becker muscular dystrophy; Romitti PA et. al., Pediatrics, 2015; Bushby KM, et. al., Lancet, 1991; Salari N, et. al., J Orthop Surg Res, 2022; : J Med Genet 2016;53:145–151; Lancet, 337 (8748), 1022–1024; J Orthop Surg Res 17, 96 (2022)

NSAA: A Well-Established and Validated Measure of Global Function that is Clinically Meaningful in a Real-World Context

Composite evaluation of motor function across 17 tests with increasing difficulty

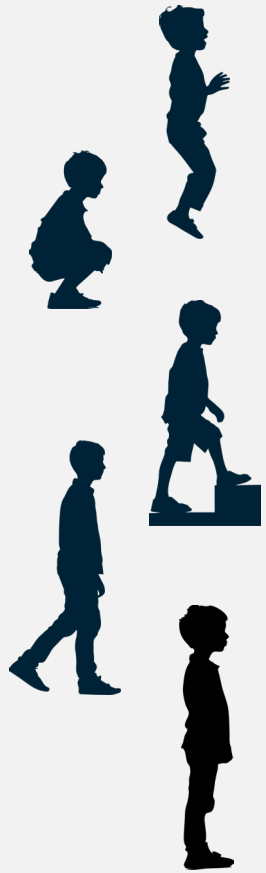
Hop left leg
Hop right leg
Stand on heels
Rise from floor
Run
Jump
Lift head
Descend box step (L)
Descend box step (R)
Climb box step (L)
Climb box step (R)
Stand one leg (L)
Stand one leg (R)
Get to sitting
Rise from chair
Walk
Stand

Hardest

Easiest

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



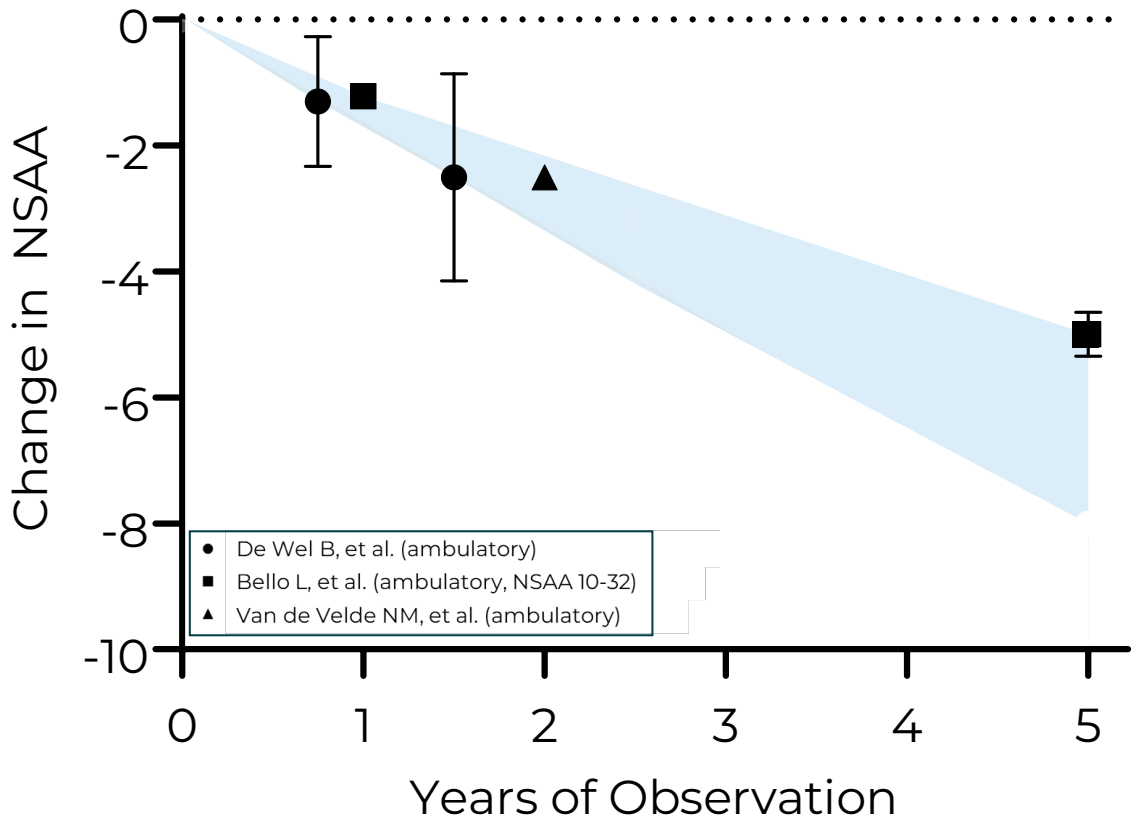
Real-world implications for Becker individuals

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

Natural History Data in Becker Supports that Functional Decline, Measured by NSAA, is Consistent and Predictable

Natural history of Becker muscular dystrophy

- The North Star Ambulatory Assessment NSAA) is utilized in muscular dystrophy natural history studies to longitudinally assess function.
- Multiple natural history studies in individuals with Becker demonstrate a **NSAA average score decline of 1.0 to 1.7 points annually**.[1,2,3,4]
- Becker Natural history studies support that NSAA decline is consistent in Becker patients who are already progressing

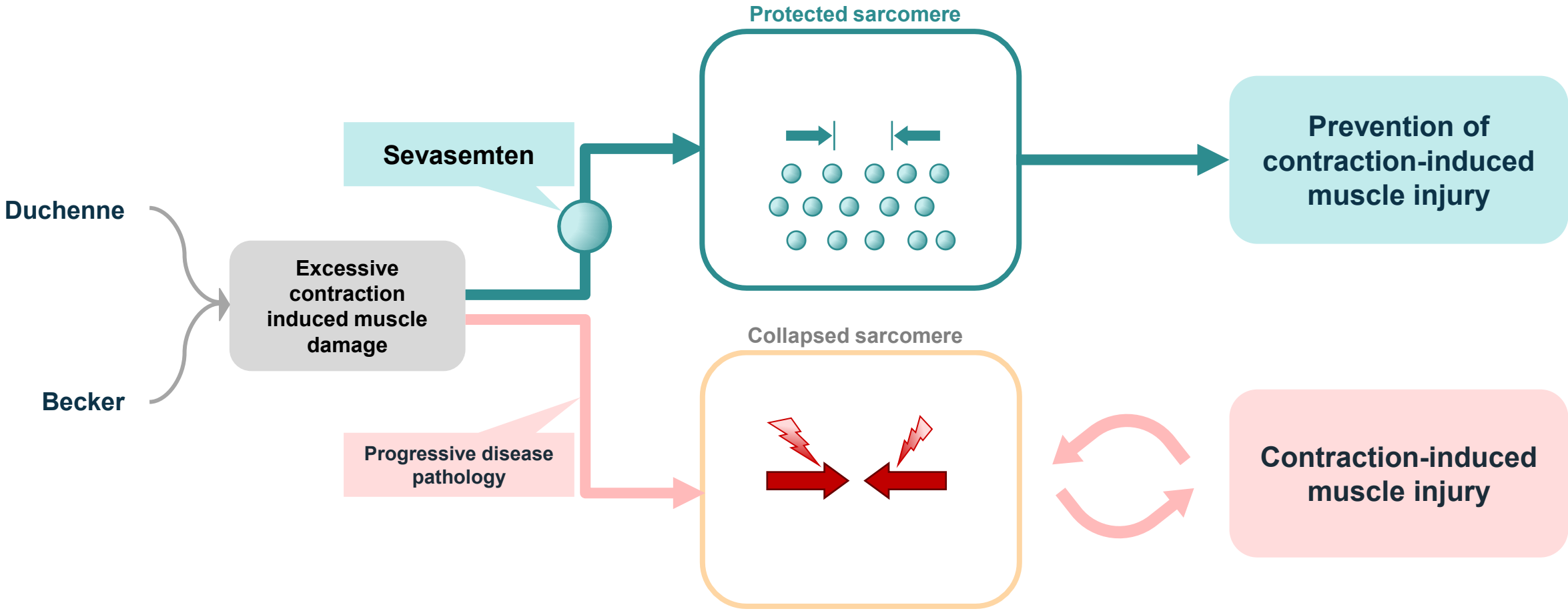


1. Bello L, et al. 2016. 2. De Wel B, et al. Eur J Neurol. 2024. 3. Van de Velde NM, et al. Neurology. 2021.;4. Bello L et al 2024 WMS; 95% CI shown

Edgewise THERAPEUTICS

Sevasemten: A First-in-Class Fast Myofiber (Type II) Myosin Inhibitor Designed to Protect Against Contraction-Induced Muscle Injury

Sevasemten Therapeutic Hypothesis



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

Overview of the Sevasemten Clinical Program in Becker

ARCH	**Phase 1 Becker**	*Open-label, safety, PK, function* → *OLE*	***Complete***
DUNE	**Phase 2 Becker, LGMD2i, & McArdle**	*Exercise challenge study* → *OLE*	***Complete***
CANYON	**Phase 2 Becker**	*PK, biomarkers and longer-term safety* → *OLE*	***Complete***
GRAND CANYON	**Pivotal Cohort Becker** *(NCT05291091)*	*Function (NSAA), PK, biomarkers and longer-term safety* → *OLE*	***Active, currently not enrolling***
MESA	**Becker Open Label Extension Study** *(NCT06066580)*	*Open-label long-term safety, biomarkers and functional measures*	***Enrolling by invitation***

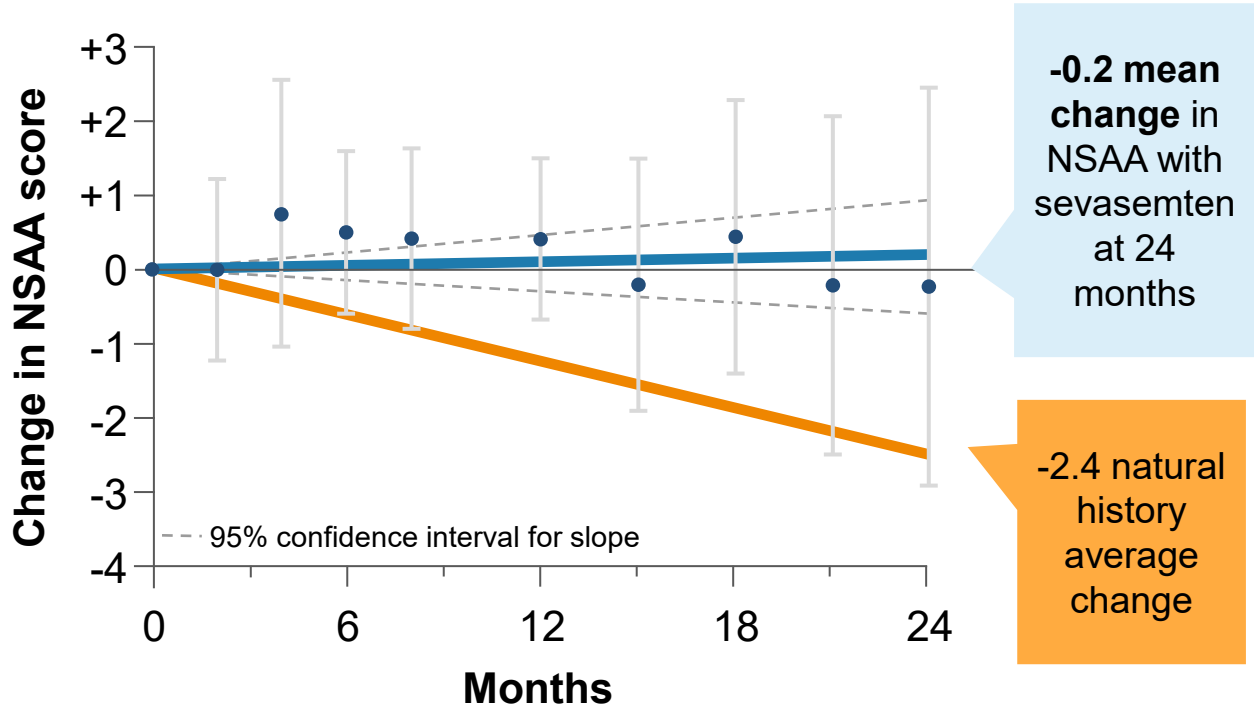
Becker, Becker Muscular Dystrophy; LGMD, Limb-Girdle Muscular Dystrophy; NSAA, North Star Ambulatory Assessment; PK, pharmacokinetics

ARCH A Single-Center Study to Assess Sevasemten Safety and Pharmacokinetics 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



CK, creatine kinase; TNNI2, fast skeletal troponin I; NSAA, The North Star Ambulatory Assessment; PK, pharmacokinetics

Phan H, et al. Oral presentation presented at: American Academy of Neurology; April 13-18, 2024; Denver, CO.

Edgewise THERAPEUTICS

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 Effect 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

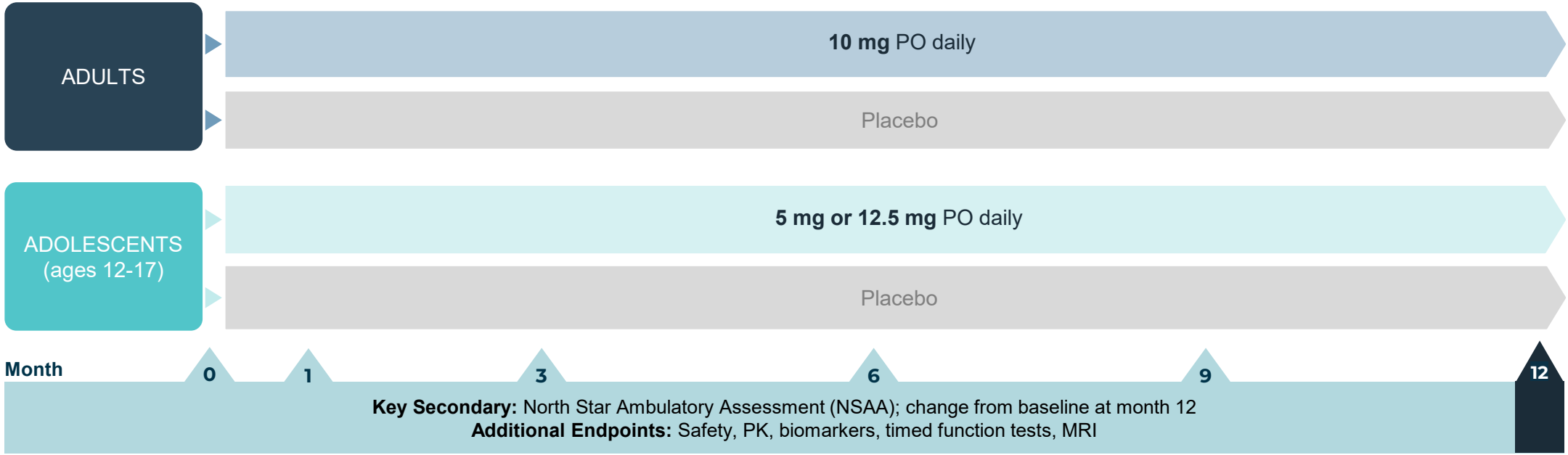
Ambulatory males aged 12 to 50 years with a dystrophin mutation and a Becker phenotype, not on corticosteroids, with a **NSAA between 5-32***

PATIENTS ENROLLED

Adults: **40**

Adolescents: **29**

Study design - 12 months



*Adolescents were not selected based on NSAA

CK, creatine kinase; NSAA, North Star Ambulatory Assessment; PK, pharmacokinetics

Edgewise THERAPEUTICS

CANYON Functional Measures Not Well Matched at Baseline; Patients in Sevasemten Group had Lower Baseline NSAA

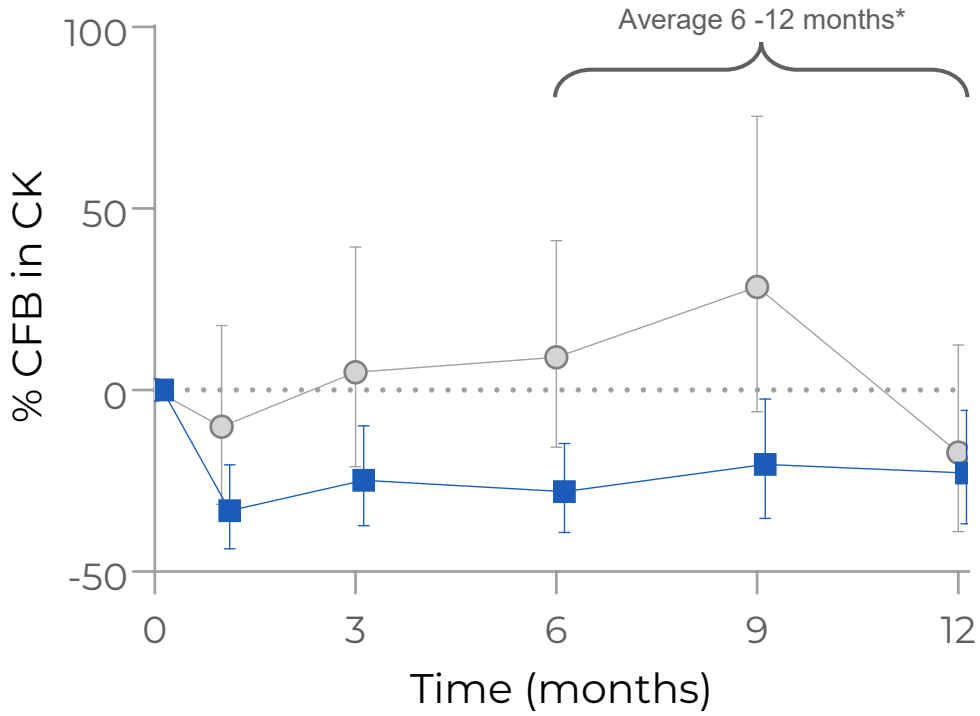
Functional test	Adults Sevasemten (n=28)	Adults Placebo (n=12)	Difference (from placebo)	P-value vs. Placebo
Mean total NSAA score, points (SD)	18.4 (7.66)	24.2 (8.19)	**-5.8**	**0.04**
Mean 4SC velocity, 1/seconds (SD)	0.22 (0.128)	0.34 (0.173)	**-0.12**	**0.02**
Mean RFF velocity, 1/seconds (SD)*	0.14 (0.114)	0.21 (0.128)	**-0.07**	**0.09**
Mean 10MWR velocity, meters/second (SD)	1.52 (0.731)	2.00 (0.884)	**-0.48**	**0.08**
Mean 100MTT velocity, meters/second (SD)	1.50 (0.856)	1.78 (0.782)	**-0.28**	**0.32**

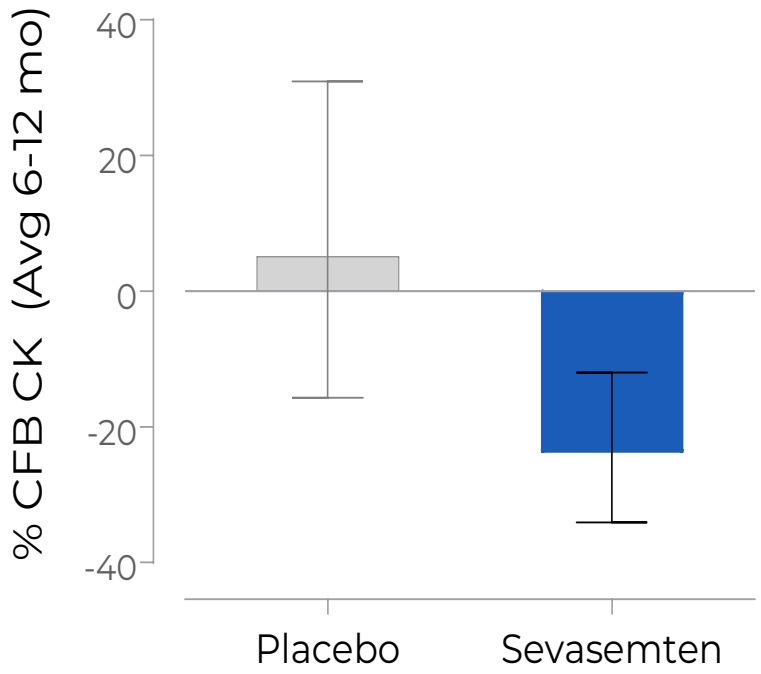
The baseline imbalance observed is a direct consequence of a small study and should resolve in the larger GRAND CANYON cohort (n=120)

*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

Statistically Significant Decrease in the Primary Endpoint of CK: 28% Reduction vs. Placebo

CK between-group difference LSMean: **-28%**
(95% CI -44% to -6%); **p-value = 0.02**



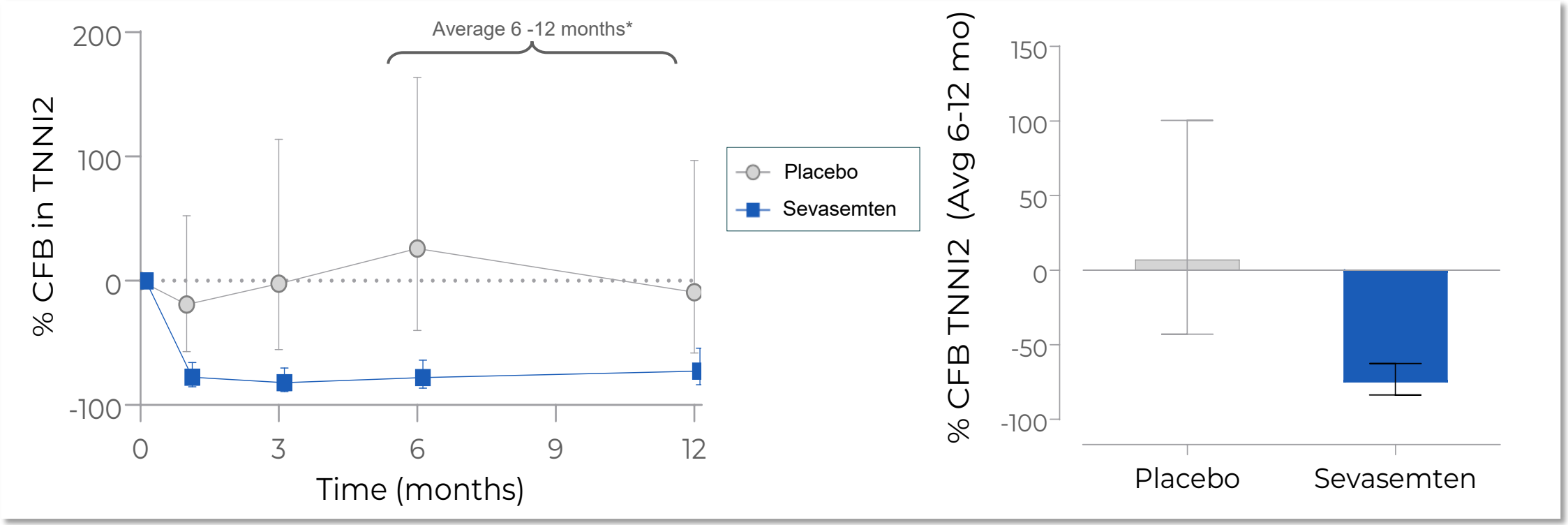


CK showed rapid and sustained decreases with sevasemten treatment

*p<0.05; CK values are log-transformed. LS (least squares) means, LS mean differences and CIs were back-transformed to percent scale
CFB, change from baseline; CI, confidence interval; CK, creatine kinase

TNNI2 Decreased 77% from Baseline in the Sevasemten Treatment Group vs. Placebo

Fast skeletal troponin I (TNNI2) between-group difference LSMean: **-77%**
(95% CI -89% to -51%); **p-value < 0.001**

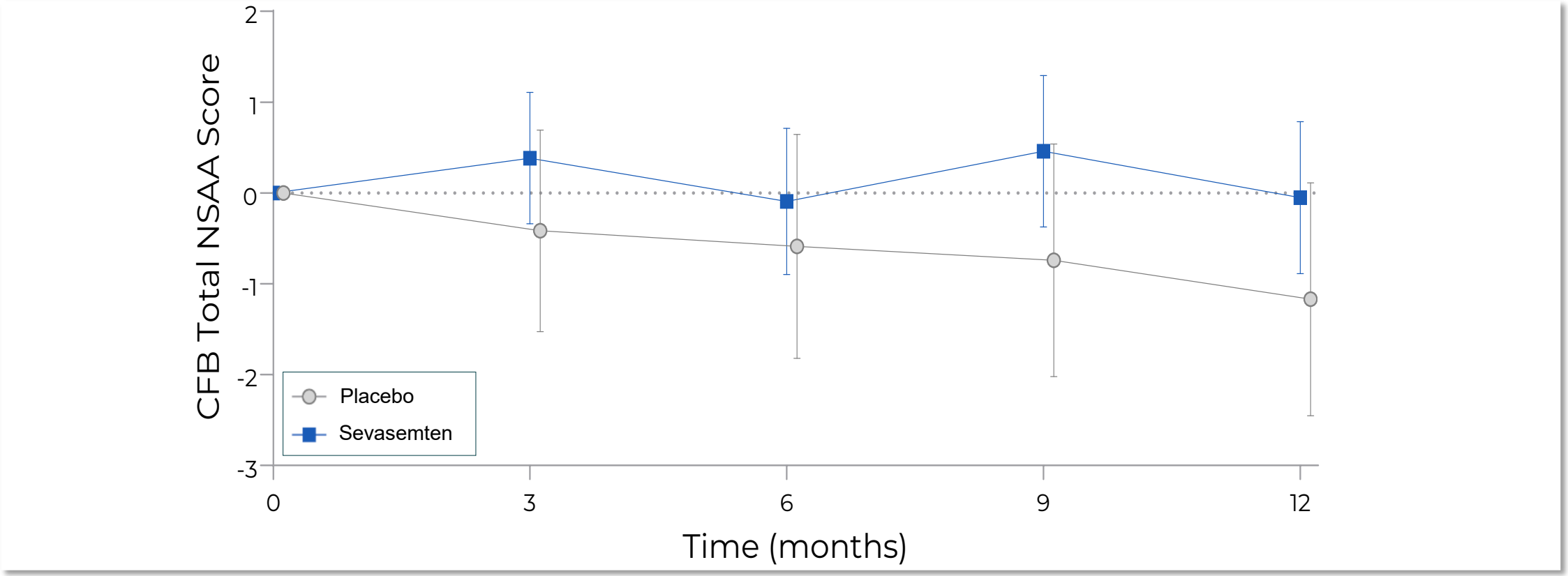


TNNI2, an on-target biomarker of fast muscle fiber damage, also demonstrated rapid and sustained decreases with sevasemten treatment

*p<0.05; TNNI2 values are log-transformed. LS (least squares) means, LS mean differences and CIs were back-transformed to percent scale
CFB, change from baseline; CI, confidence interval; TNNI2, fast skeletal troponin I

Key Secondary Endpoint: NSAA Remained Stable Over Time in Sevasemten Group

NSAA between-group difference LSMean: **1.12**
(95% CI -0.4 to 2.7); **p-value = 0.16**

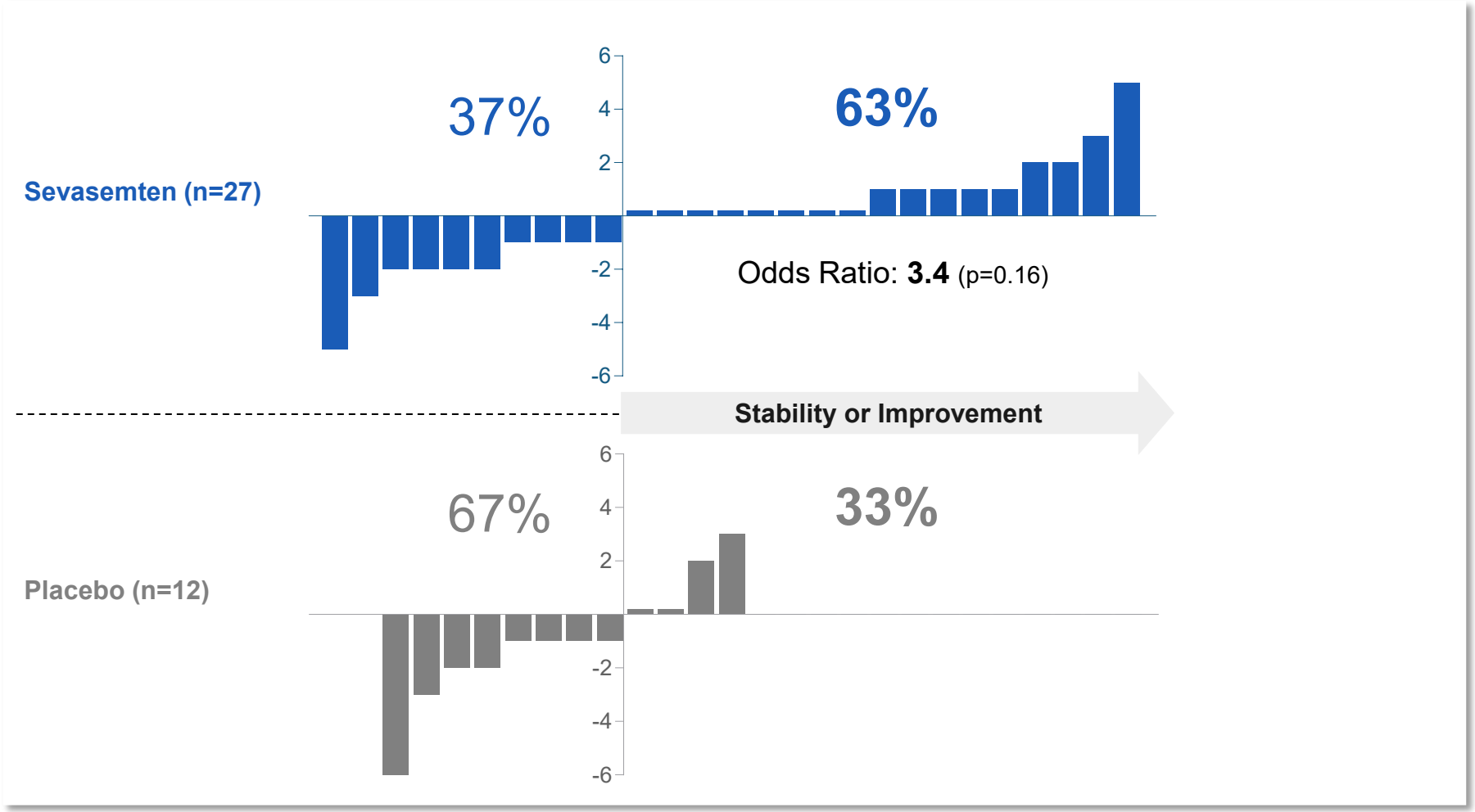


Positive trends in NSAA favoring sevasemten with placebo declining in line with natural history

CI, confidence interval; NSAA, North Star Ambulatory Assessment

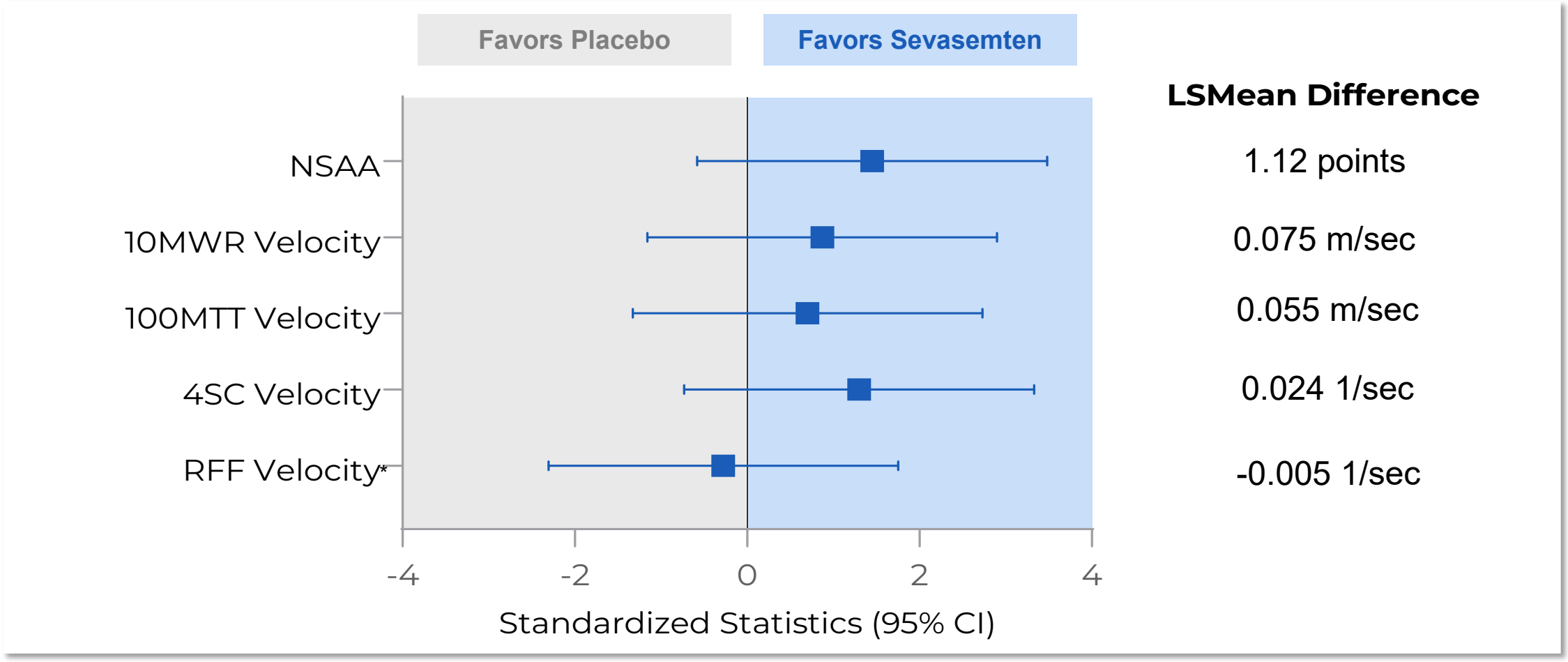
CANYON 63% of Patients Treated with Sevasemten Showed Stable or Improved Function After 12 Months

Sevasemten NSAA Responder Analysis



CI, confidence interval; NSAA, North Star Ambulatory Assessment

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 was Well Tolerated: Overview of Treatment Emergent Adverse Events (TEAE)

	Sevasemten (n=28) n (%)	Placebo (n=12) n (%)	Total (N=40) n (%)
Any TEAE	26 (92.9)	10 (83.3)	36 (90)
Severe TEAE	0 (0)	0 (0)	0 (0)
Serious Adverse Events	1 (3.6)	0 (0)	1 (2.5)
Any drug related TEAE	16 (57.1)	5 (41.7)	21 (52.5)
Discontinuation due to TEAE	1 (3.6)	0 (0)	1 (2.5)
Deaths	0 (0)	0 (0)	0 (0)

TEAE, treatment emergent adverse event

CANYON Sevasemten was Well Tolerated: TEAEs Occurring in ≥5% of Total

System Organ Class/Preferred Term	Sevasemten (n=28) n (%)	Placebo (n=12) n (%)	Total (N=40) n (%)
Any TEAE	**26 (92.9%)**	**10 (83.3%)**	**36 (90%)**
Eye disorders			
Vision blurred	1 (3.6%)	2 (17%)	3 (8%)
General disorders and administration site conditions			
Fatigue	5 (18%)	3 (25%)	8 (20%)
Infections and infestations			
COVID-19	6 (21%)	2 (17%)	8 (20%)
Nasopharyngitis	6 (21%)	2 (17%)	8 (20%)
Upper respiratory tract infection	5 (18%)	2 (17%)	7 (18%)
Influenza	4 (14%)	1 (8%)	5 (13%)
Injury, poisoning and procedural complications			
Fall	8 (29%)	2 (17%)	10 (25%)
Investigations			
Ejection fraction decreased	0 (0%)	2 (17%)	2 (5%)
Musculoskeletal and connective tissue disorders			
Back pain	3 (11%)	0 (0%)	3 (8%)
Nervous system disorders			
Headache	9 (32%)	2 (17%)	11 (28%)
Dizziness	9 (32%)	0 (0%)	9 (23%)
Somnolence	5 (18%)	1 (8%)	6 (15%)
Migraine	3 (11%)	1 (8%)	4 (10%)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	4 (14%)	0 (0%)	4 (10%)
Cough	3 (11%)	0 (0%)	3 (8%)

CANYON Summary of Trial Results

Safety

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

Biomarkers

- Primary endpoint achieved: 28% average decrease in CK versus placebo (p=0.02)
- Plasma TNNI2 decreased 77% from baseline versus placebo (p<0.001)

Function

- Sevasemten treated patients (n=28) showed stabilization of NSAA with trends toward improvement
- Placebo group (n=12) declined in line with natural history

Secondary & Exploratory

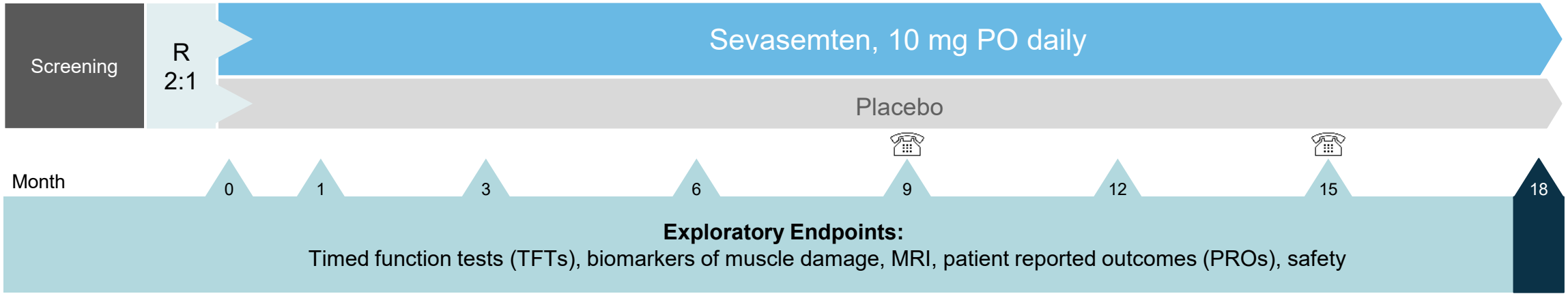
- The imbalance between groups confounded interpretation of a few endpoints (e.g., MRI); evaluation of the full data set ongoing

CK, creatine kinase; NSAA, North Star Ambulatory Assessment

Global, Multi-Center, Placebo-Controlled Study of Sevasemten; Pivotal Cohort and Potentially Registrational

- **Population:** Adults with Becker with NSAA 5-32, not on corticosteroids
- **Enrollment:** 175 patients (powered to show a difference in NSAA at 18 months)
- **Primary endpoint:** NSAA at 18 months
- **Secondary Endpoints:** 100 m timed test, biomarkers of muscle damage, MRI

Study design - 18 months



R, randomization; NSAA, North Star Ambulatory Assessment.

1. ClinicalTrials.gov. NCT05291091. https://clinicaltrials.gov/ct2/show/NCT05291091. 2. Data on file.

Acknowledgements

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