Understanding disease progression of Becker muscular dystrophy and a potential novel agent to protect muscle

Symposium at the 29th Annual Congress of the World Muscle Society

Prague, Czech Republic

Tuesday 08 October 2024, 16:30-17:30, South Hall 2

Presentation is intended for healthcare providers only

Disclosures for Joanne Donovan

Joanne is an employee of Edgewise Therapeutics and holds stock.

Program overview

Introduction
Joanne Donovan, MD, PhD

Natural history of Becker muscular dystrophy
Luca Bello, MD, PhD

Outcome measures in Becker muscular dystrophy and an overview of the sevasemten clinical program
Craig McDonald, MD

Panel Discussion
Joanne Donovan, MD, PhD

Joanne Donovan, MD, PhD
CMO, Edgewise Therapeutics, US

Craig McDonald, MD
Professor and Chair, PM&R
U of California Davis, CA, US

Luca Bello, MD, PhD
Associate Professor,
University of Padova, IT

Note: Sevasemten (EDG-5506) is an investigational agent that is not approved for use by any regulatory authority in any territory.

Session Objectives

- Expand awareness of current Becker natural history studies.
- Understand how the latest data supports the severity of Becker and the predictable trajectory towards irreversible muscle loss once functional decline begins.
- Increase understanding of measures, such as NSAA and 6MWT, and their clinical meaningfulness in Becker.
- Share updates from the sevasemten clinical program, which is an example of utilizing these outcomes to measure disease progression in clinical research.

Natural history of Becker muscular dystrophy

Luca Bello, MD, PhD

Associate Professor of Neurology
Department of Neurosciences
University of Padova, Italy

Disclosures

- Speaker honoraria from PTC Therapeutics and Edgewise Therapeutics
- Advisory boards and consultation fees for PTC Therapeutics, Sarepta Therapeutics, Edgewise Therapeutics, Roche, Pfizer, Italfarmaco, and Epirium Bio
- Participation in research sponsored by Santhera Pharmaceuticals, Pfizer, Edgewise Therapeutics, and PTC Therapeutics

Natural history is important to our understanding of disease progression, patient care, and clinical trial development

Disease Progression

Provides the communities with an increased understanding of the disease progression

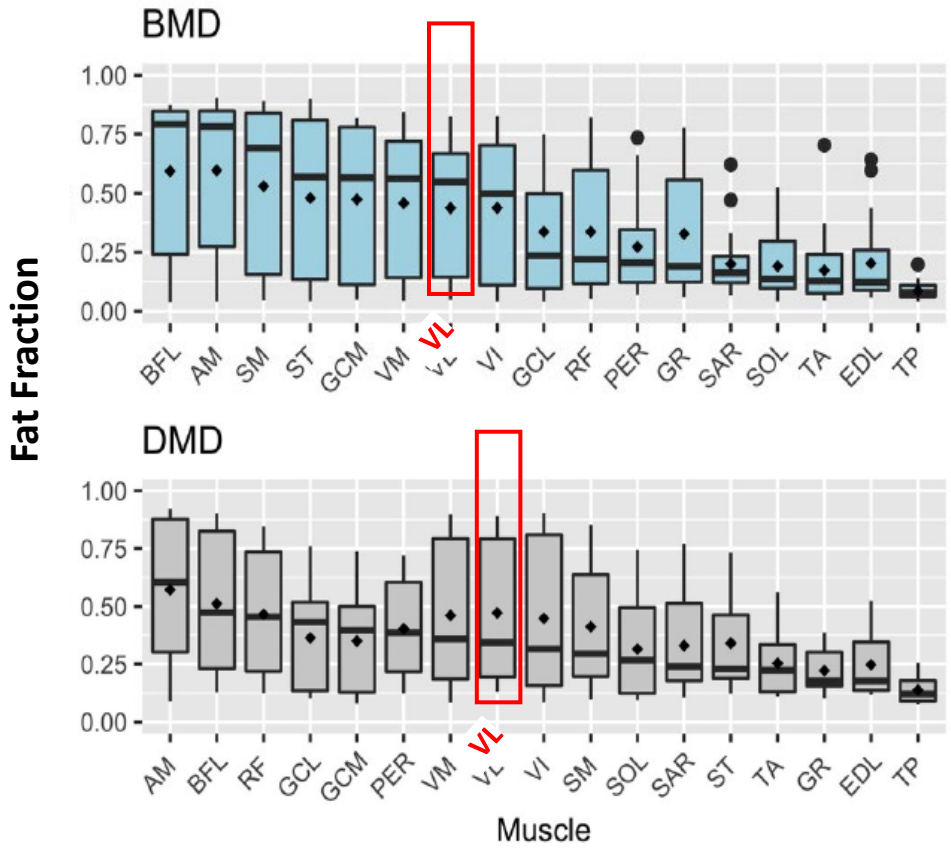
Prognostic Purposes

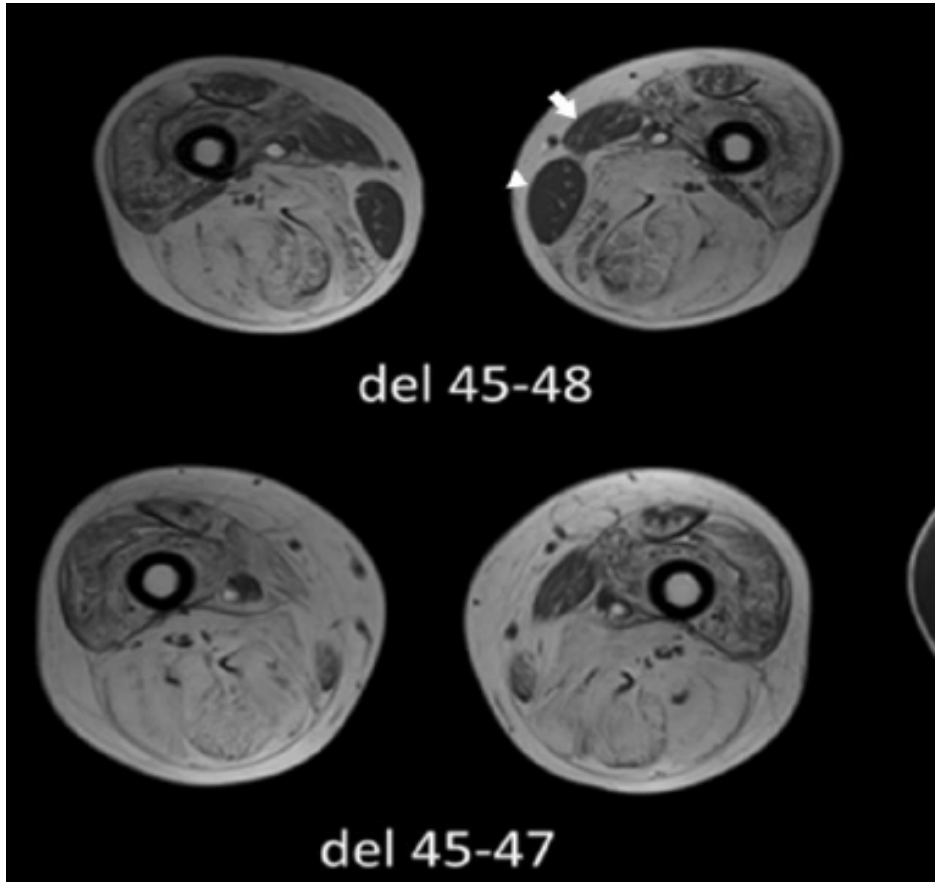
- Clinical and genetic counseling
- Identification of prognostic markers (inclusion criteria)
- Insights about pathology (therapeutic targets)

Functional Change Measures

- Insightful for powering and designing clinical trials

In Becker, much like in Duchenne, diminished function develops as a result of muscle loss and fat replacement



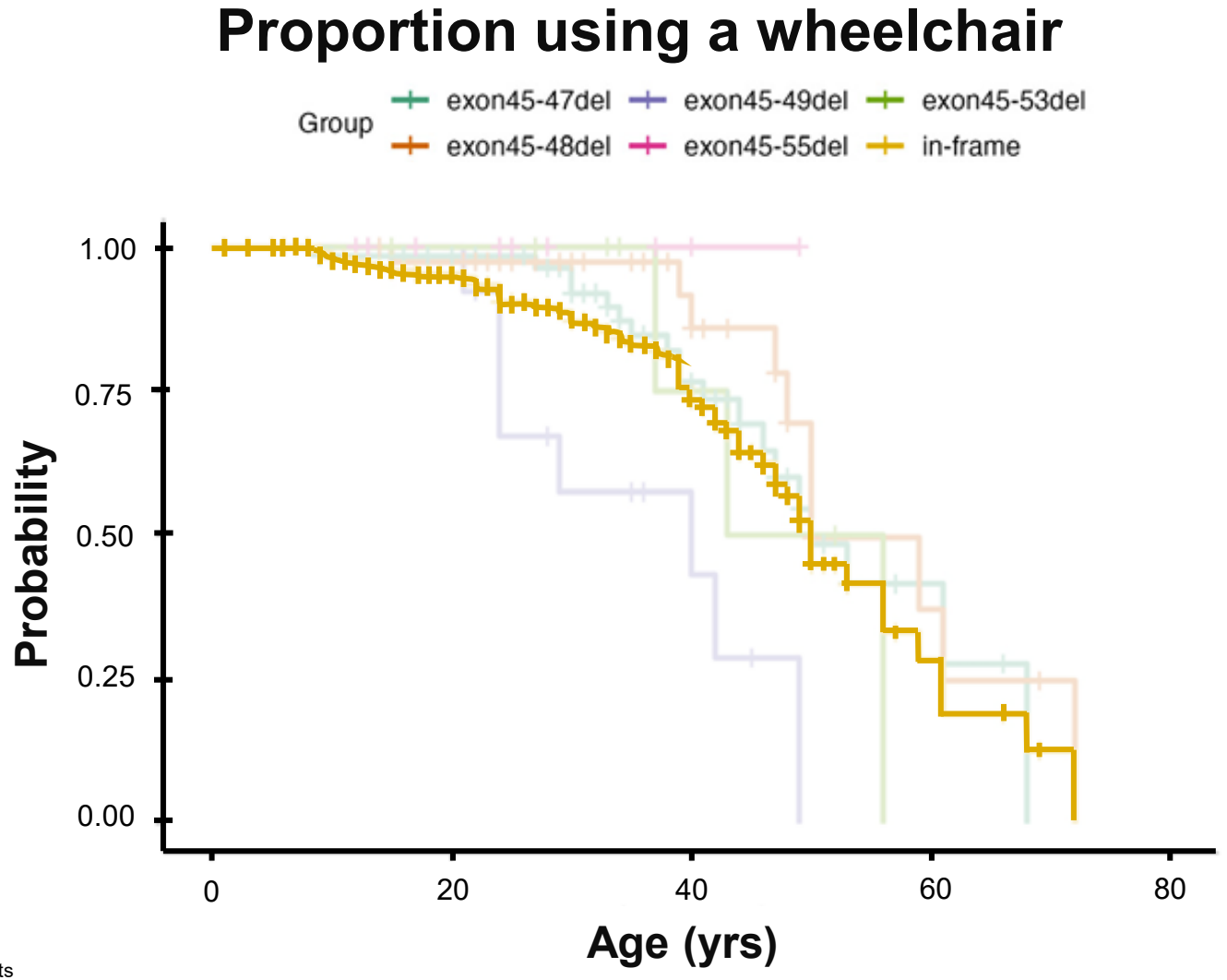


- Average fat fraction in Becker individuals similar to Duchenne
- Greater fat accumulation in select muscles compared to Duchenne for a given functional status

Reference: Veeger TTJ, et al. Muscle Nerve. 2021;64(5):576-84.

Natural history study of 225 Becker patients found that loss of ambulation can occur early on in disease progression

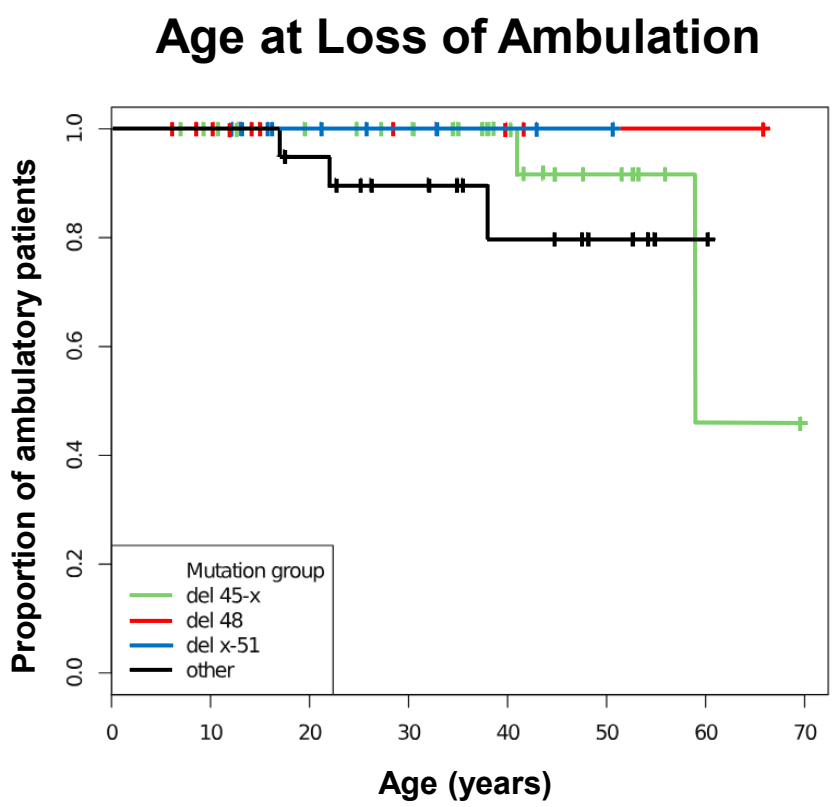
- 2017 Japanese cohort study of Becker natural history that used patient data extracted from medical records
- The age of wheelchair introduction in patients with exon 45-49del was significantly younger than other groups.
- The median age of initial wheelchair use was ~48 years old.

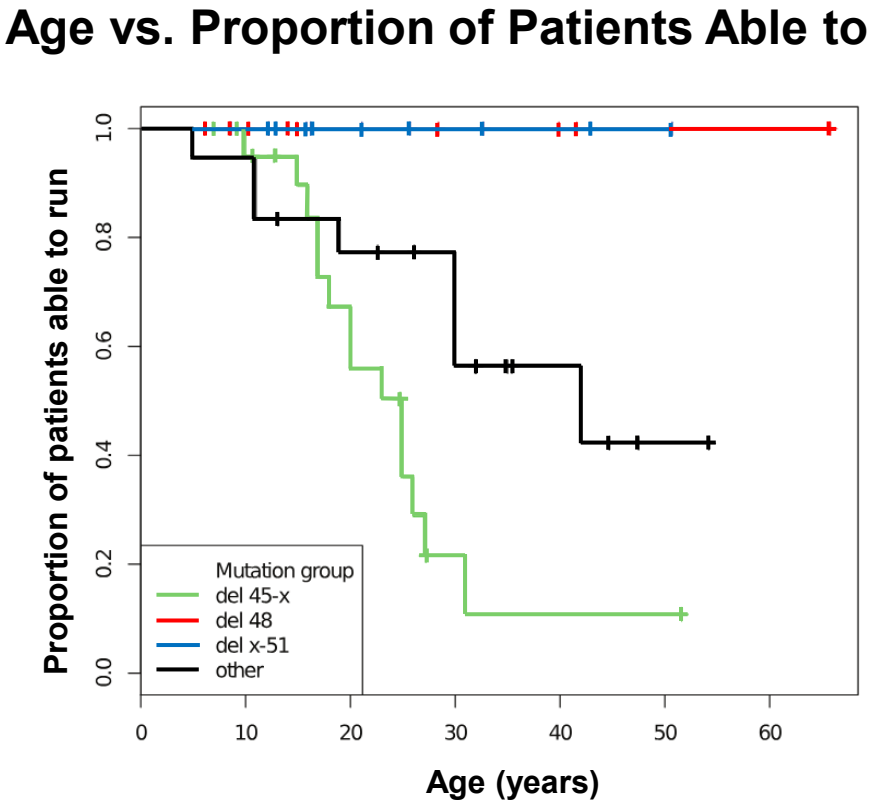


6MWT, 6 minute walk test; NSAA, North Star Ambulatory Assessment; TFT, timed function tests

Reference: Nakamura A, et al. Ann Clin Transl Neurol. 2023;19(12):2360-2372.

1-Year longitudinal Becker natural history shows that patients experience early functional decline and ambulation loss

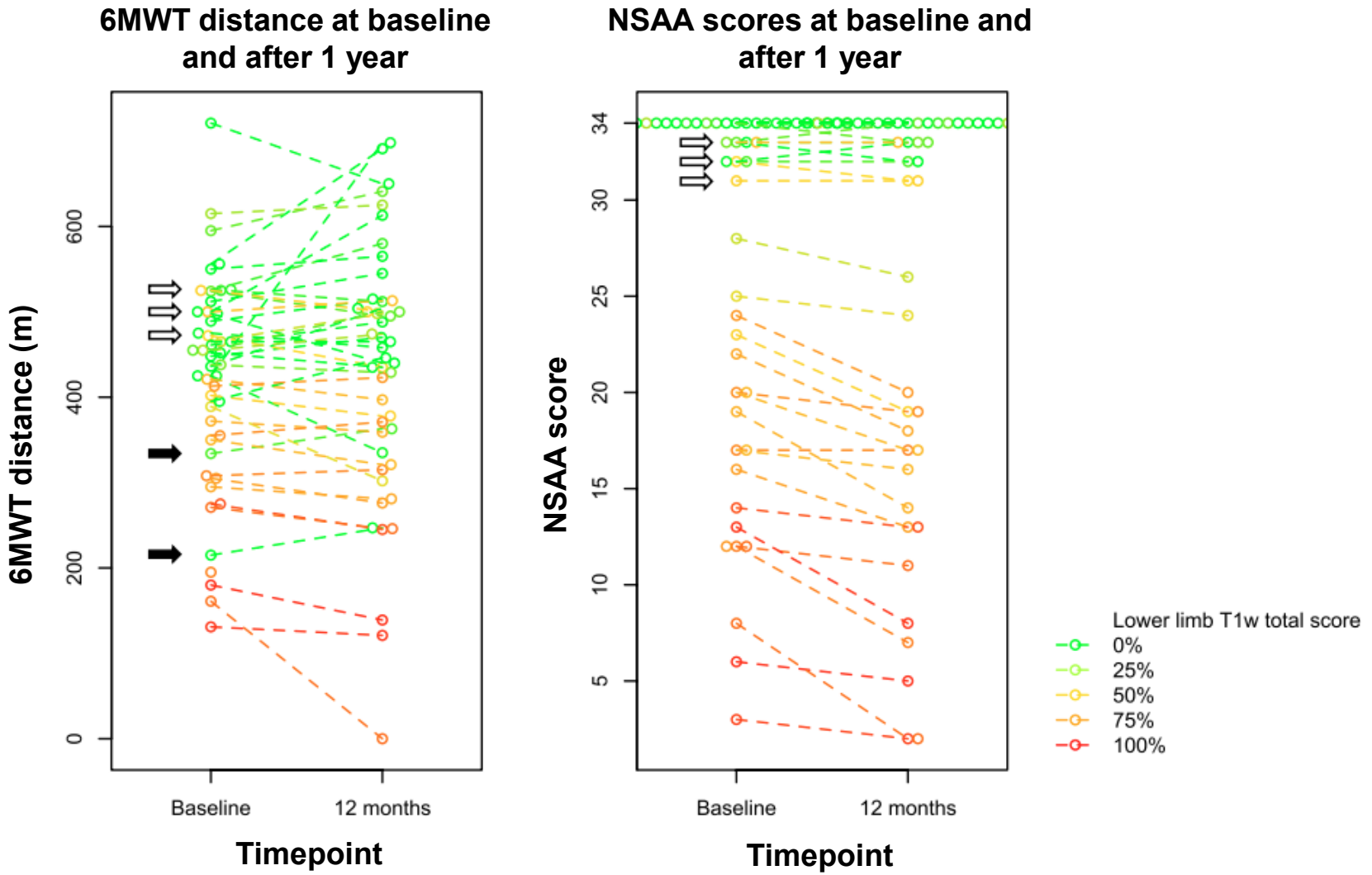




- A 1-year longitudinal study of 69 Becker patients with various mutation statuses looked at 6MWT, NSAA, and TFTs.
- Significant changes were seen, with a decline in function and loss of ambulation occurring early in disease progression.

6MWT, 6 minute walk test; NSAA, North Star Ambulatory Assessment; TFT, timed function tests
Reference: Bello L, et al. Sci Rep. 2016:6:32439.

Functional measures, such as 6MWT and NSAA, show that Becker patients experience rapid functional decline



6MWT, 6 minute walk test; NSAA, North Star Ambulatory Assessment

Reference: Barp A, et al. Sci Rep. 2017;7(1):16060.

Becker patients with an NSAA score ≤32 at baseline were associated with a mean change of ~1.3 points per year

Baseline NSAA and Changes at 1 year

Mutation group	N at baseline	Mean ± SD at baseline	Median (range) at baseline	N with longitudinal data	Mean change ± SD	Median change (range)
del 48	10	33.9 ± 0.32	34 (33-34)	9	-0.3 ± 0.5	0 (-1-0)
del x-51	10	33.7 ± 0.95	34 (31-34)	10	0 ± 0	0 (0-0)
del 45-x	27	20.9 ± 11.1	20 (2-34)	20	-1.3 ± 1.7*	-1 (-5-1)
Other	21	23.0 ± 11.2	24 (2-34)	18	-1.3 ± 2.2	0 (-6-1)
All BMD	68	25.3 ± 10.8	32.5 (2-34)	57	-0.9 ± 1.6**	0 (-6~1)

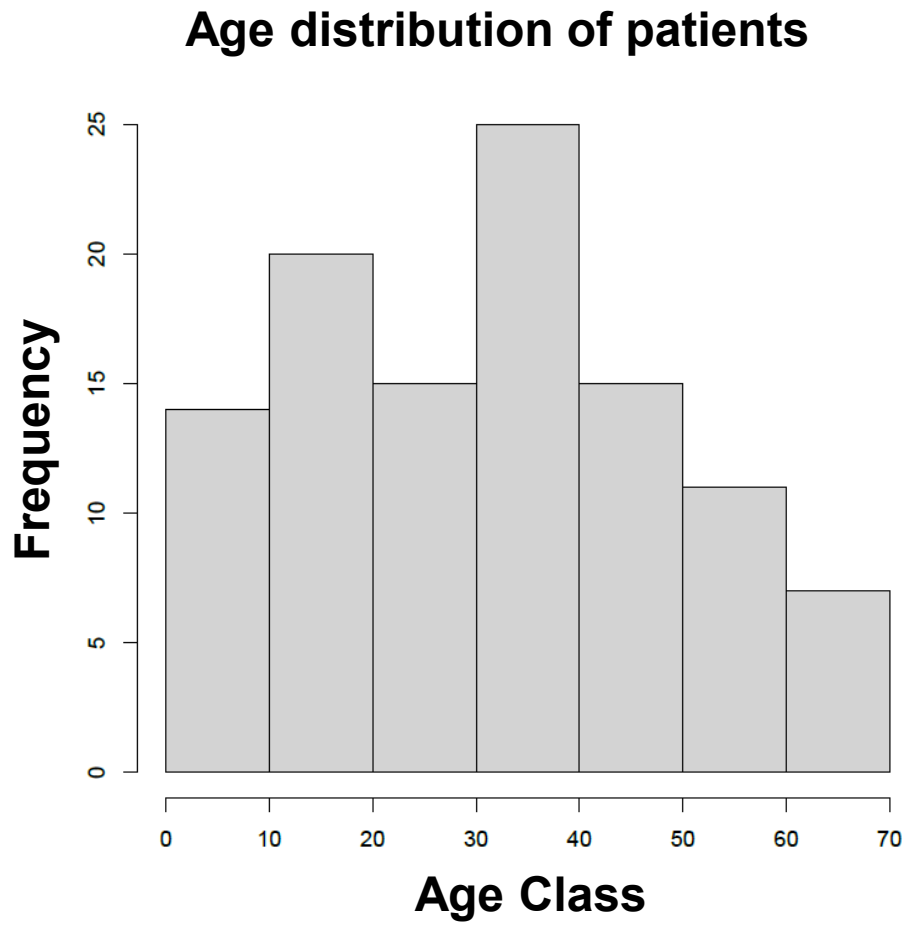
- Becker patients experience an average of -0.9 points per year decline in NSAA score
- Those with an NSAA score of higher than 32 were associated with minimal changes.
- This supports that once functional decline begins, individuals with Becker continue on a consistent trajectory towards irreversible muscle loss.

*p=0.001, **p<0.001
6MWT, 6 minute walk test; NSAA, North Star Ambulatory Assessment; SD, standard deviation; m, meter
Reference: Bello L, et al. Sci Rep. 2016:6:32439.

Longitudinal observation of functional measures: The Padova Cohort

- A 5-year follow up of the Padova Cohort was conducted.
  - **Sample size**: 107 Becker patients
  - **Ages**: 31.4 ± 17.3 years old (range 3-69 years old)
  - **Evaluations**: 6.4 ± 3.5 per patient
  - **Follow up**: 6.1 ± 3.6 years

For more information on this study, please see WMS poster #358P



Reference: Data on File

Padova Cohort: Genotype

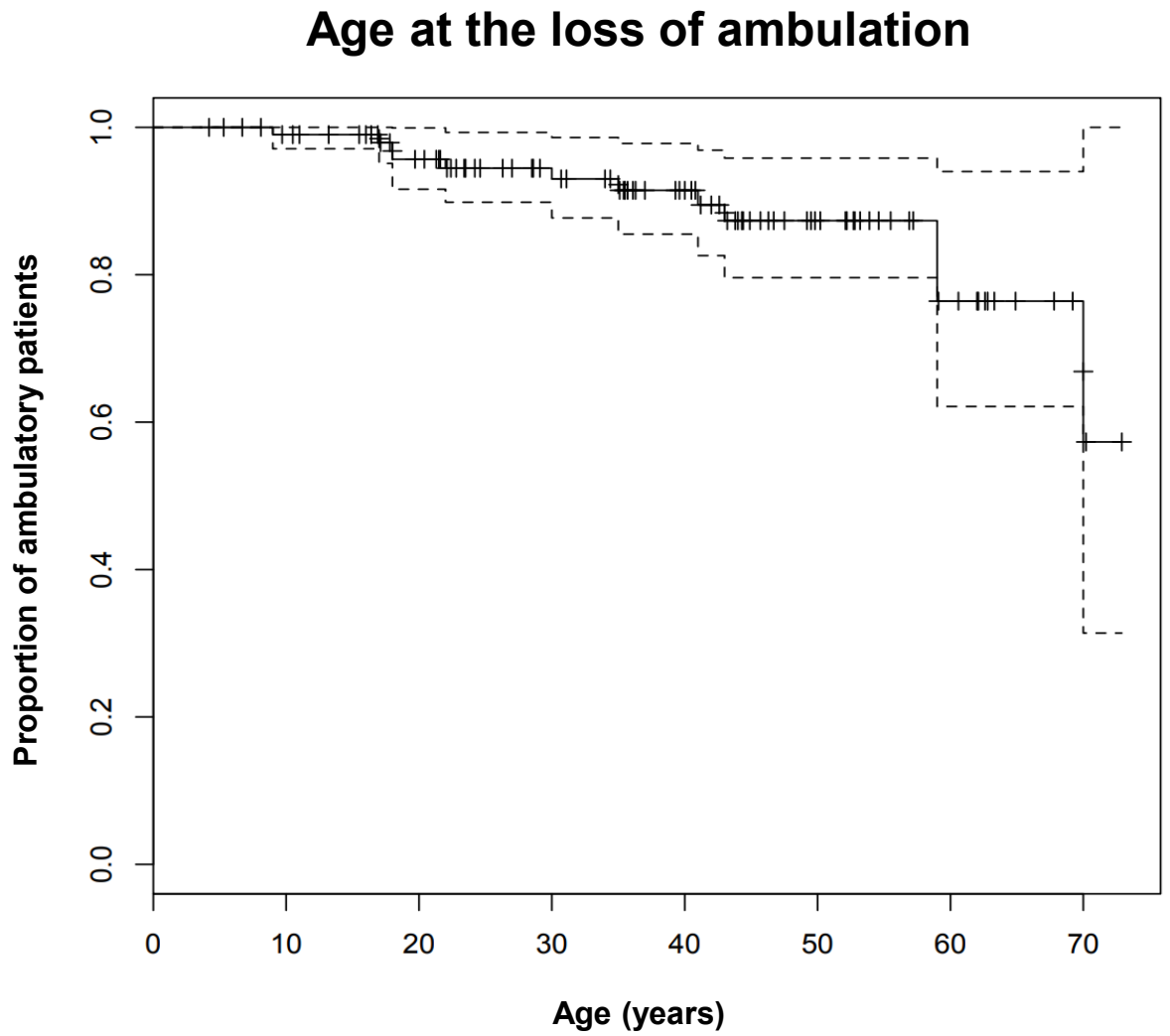
Genotype Breakdown of Cohort

Mutational groups	Specific mutation	n	Age (years)	
			Mean ± SD	Median (range min ~ max)
del 45-48		17	39.1 ± 15.7	38.3 (9.2 ~ 69.7)
del 45-47		17	31.7 ± 16.0	34.6 (3.5 ~ 55.9)
del x-51	del 45-51, 48-51, 50-51, 34-51	15	24.7 ± 15.0	21.1 (4.5 ~ 50.7)
del 48		12	26.8 ± 22.1	14.5 (6.1 ~ 67.8)
del 45-55		5	40.6 ± 26.1	51.6 (6.9 ~ 67.3)
del 48-49		4	38.6 ± 25.4	45.1 (4.0 ~ 60.3)
Nonsense		4	19.1 ± 11.4	18.1 (8.2 ~ 32.0)
Other	Duplications, other deletions, small deletions, missense mutations, synonymous mutations	32		

Reference: Data on File

Padova Cohort: Loss of ambulation

- 12 of the 107 lost ambulation (11.2%)
  - “del 45-47” group: 2 of 17 patients
  - “del 45-48” group: 2 of 17 patients
  - “other” group: 8 of 31 patients
- 10% of patients lost ambulation by age 40
- 25% of patients lost ambulation by age 60
- None of the “del x-51” or “del 48” patients lost ambulation.



Reference: Data on File

Padova Cohort: Baseline NSAA Scores

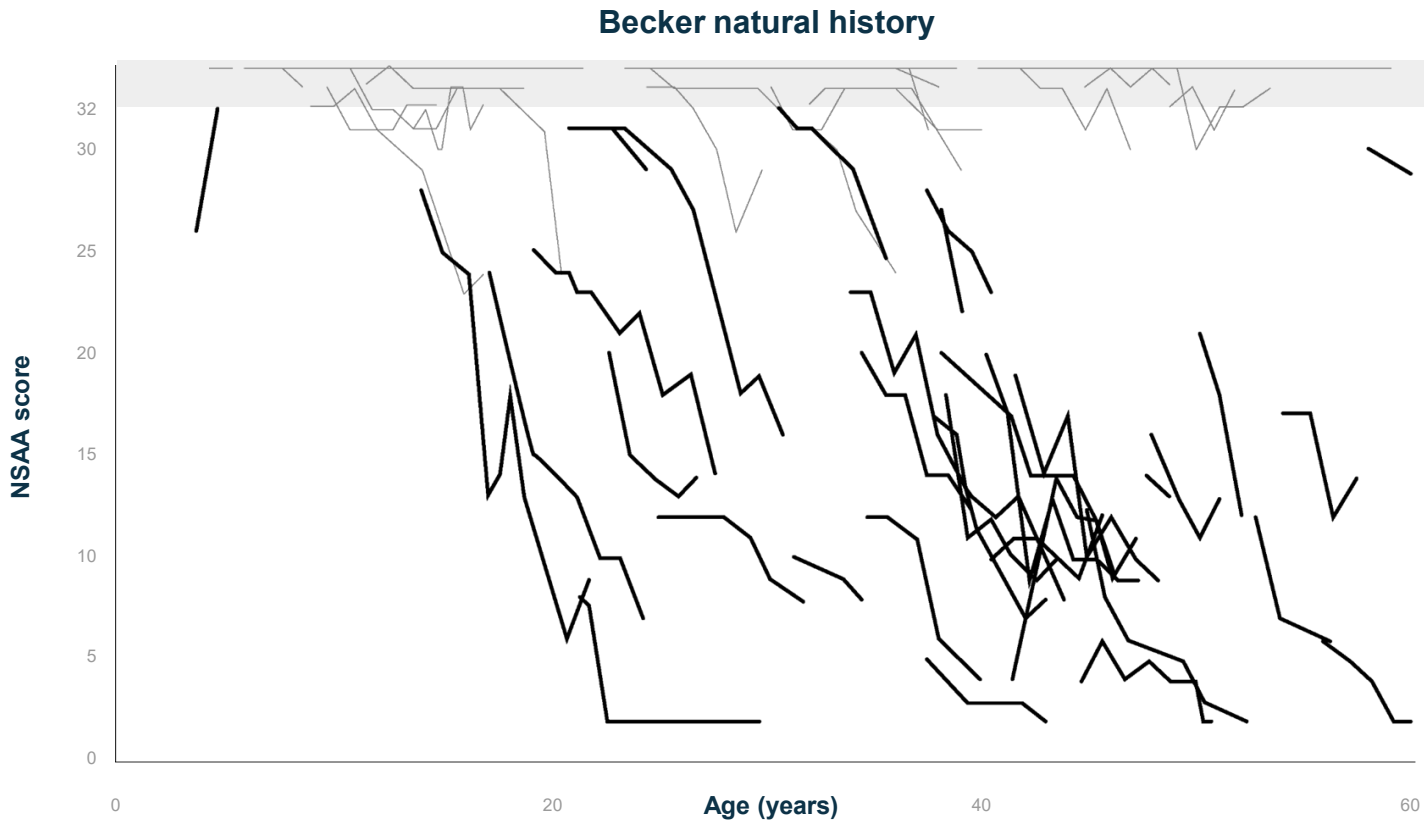
- **Whole cohort average**: 26.4 ± 10.0
- **“del x-51” and “del 48”**: higher scores
- **“del 45-47” and “del 45-48”**: lower scores

Baseline NSAA Scores

Measure	Group	n	Mean ± SD	Median (range min ~ max)
NSAA	del 45-48	15	22.4 ± 10.2	21 (3 ~ 34)
	del 45-47	16	19.8 ± 10.2	19.5 (4 ~ 33)
	del x-51	15	33.8 ± 0.77	34 (31 ~ 34)
	del 48	12	33.8 ± 0.39	34 (33 ~ 34
	del 45-55	5	29.2 ± 8.7	34 (14 ~ 34)
	del 48-49	4	23.0 ± 7.0	21 (17 ~ 33)
	nonsense	4	26.5 ± 10	30 (12 ~ 34)

Includes only patients who had baseline NSAA evaluations
Reference: Data on File

Padova Cohort: Longitudinal NSAA Scores

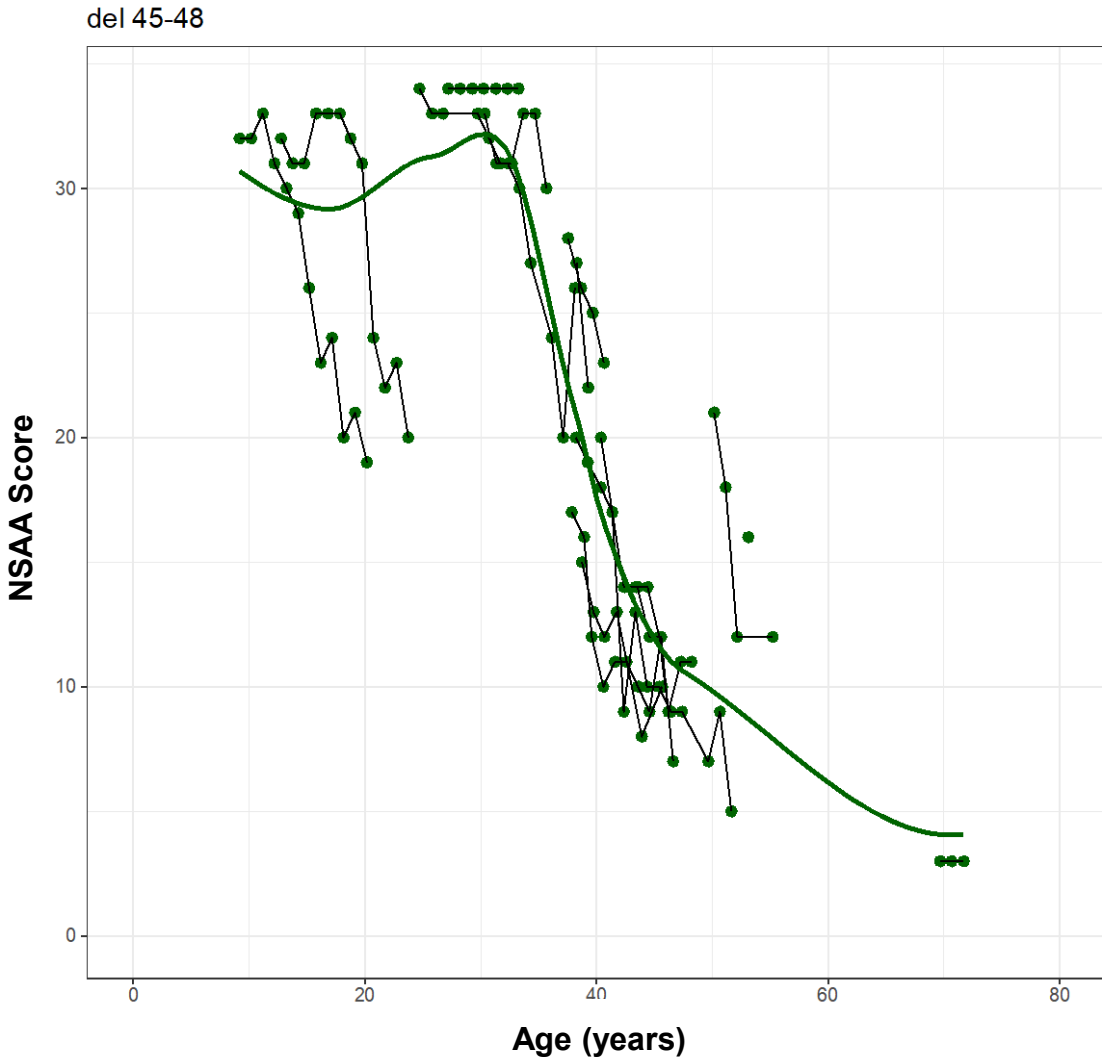


- Becker individuals with a baseline NSAA score of 10-32 exhibit an estimated yearly NSAA decline of -1.0 points

Baseline NSAA Score	Estimated Yearly Change	Standard Error	P-value
33-34	-0.03	0.01	NS
10-32	**-0.99**	**0.07**	**<0.0001**

Reference: Bello et al, submitted manuscript;

Padova Cohort: Longitudinal NSAA - del 45-48

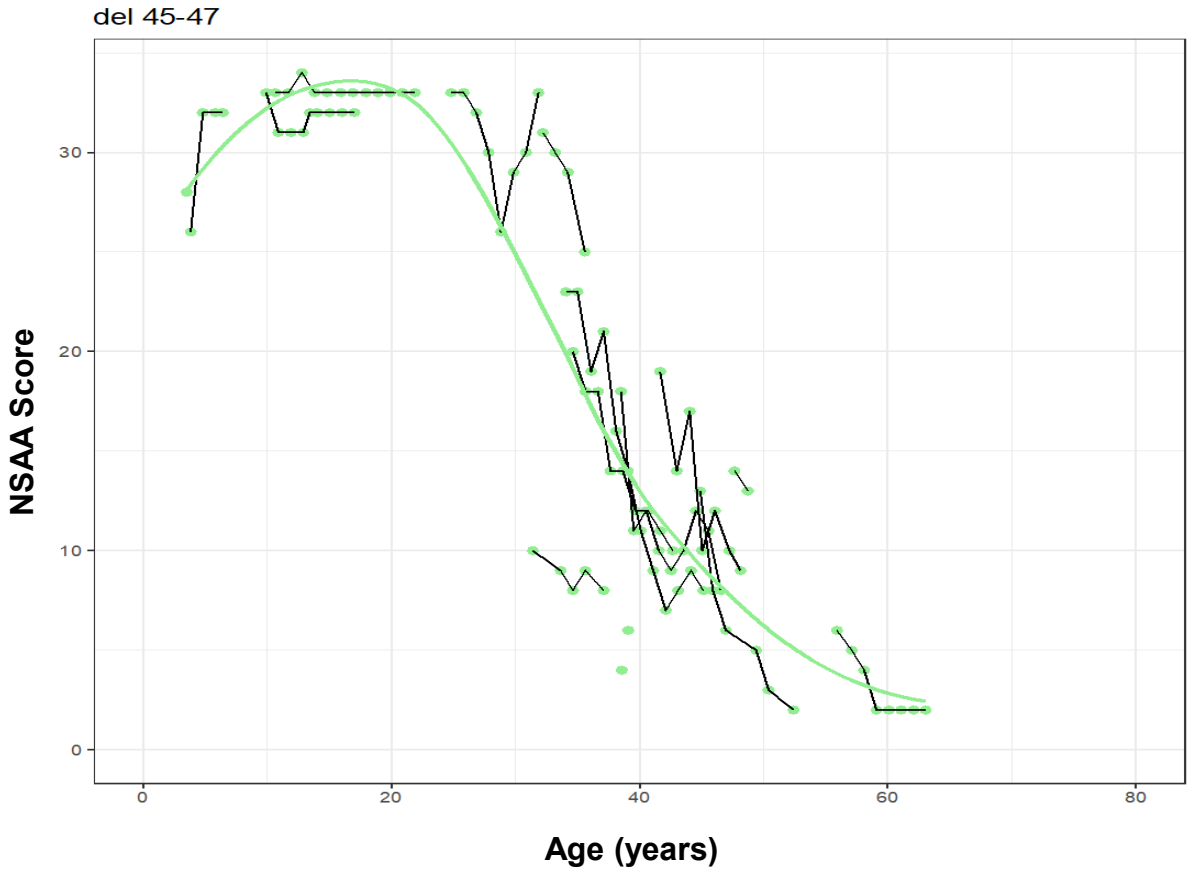


5-Year NSAA Changes

Measure	Group	n (pts)	n (evals)	Estimate of yearly change	SE	p-value
NSAA	All	89	504	-0.63	0.04	< 0.0001
	del 45-48	15	94	-0.74	0.08	< 0.0001
	del 45-47	14	80	-1.00	0.08	< 0.0001
	del x-51	11	50	-0.03	0.01	0.0007
	del 48	12	63	-0.08	0.04	n.s.
	del 45-55	5	12	-0.47	0.16	n.s.
	del 48-49	3	14	-1.35	0.16	< 0.0001
	nonsense	2	24	-0.38	0.10	0.002

Reference: Data on File

Padova Cohort: Longitudinal NSAA - del 45-47



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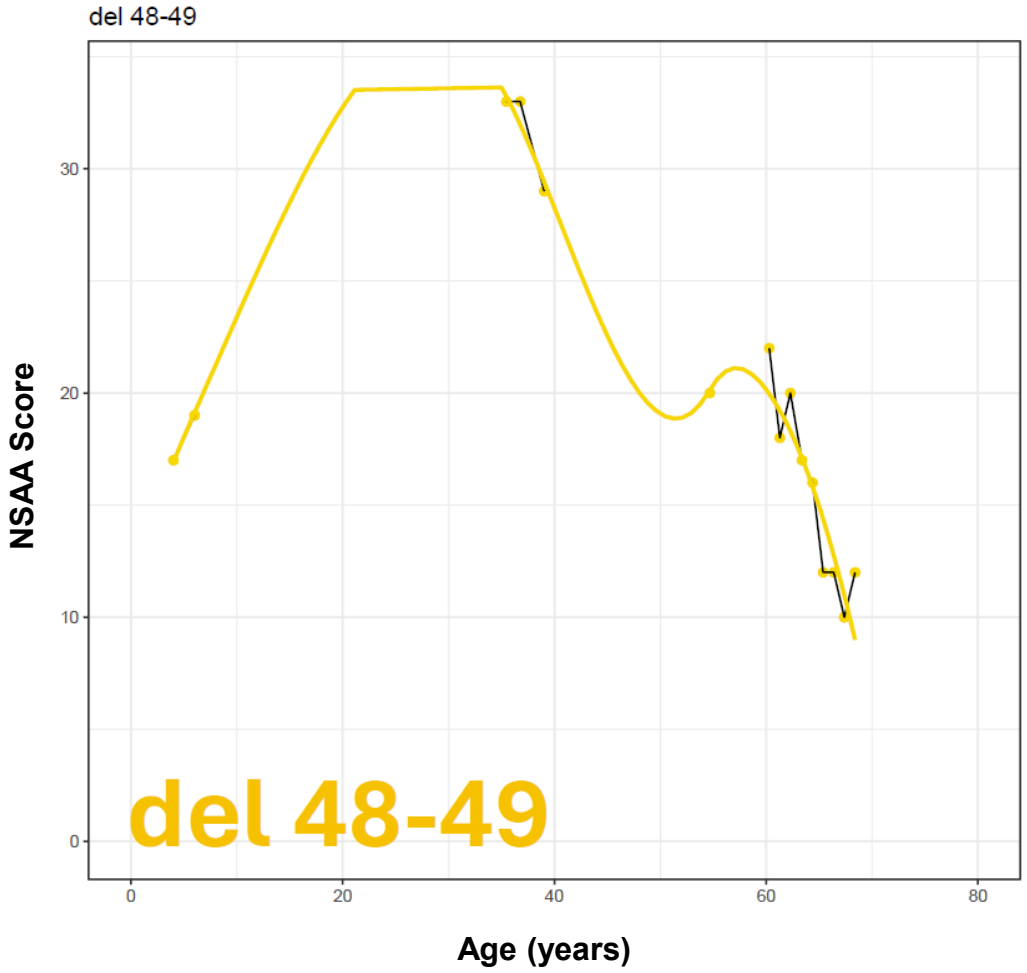
Reference: Data on File

Padova Cohort: Longitudinal NSAA - del 48-49



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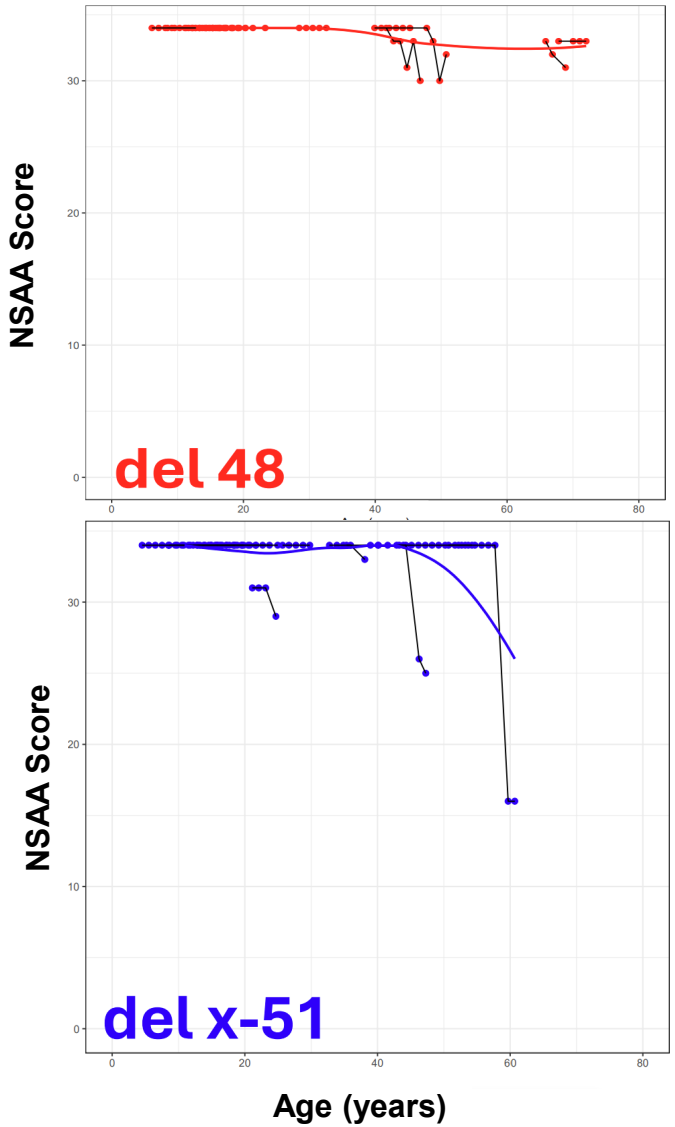
	del 48	12	63	-0.08	0.04	n.s.
	del 45-55	5	12	-0.47	0.16	n.s.
	del 48-49	3	14	-1.35	0.16	< 0.0001
	nonsense	2	24	-0.38	0.10	0.002

Reference: Data on File

Padova Cohort: Longitudinal NSAA - del 48 and del x-51



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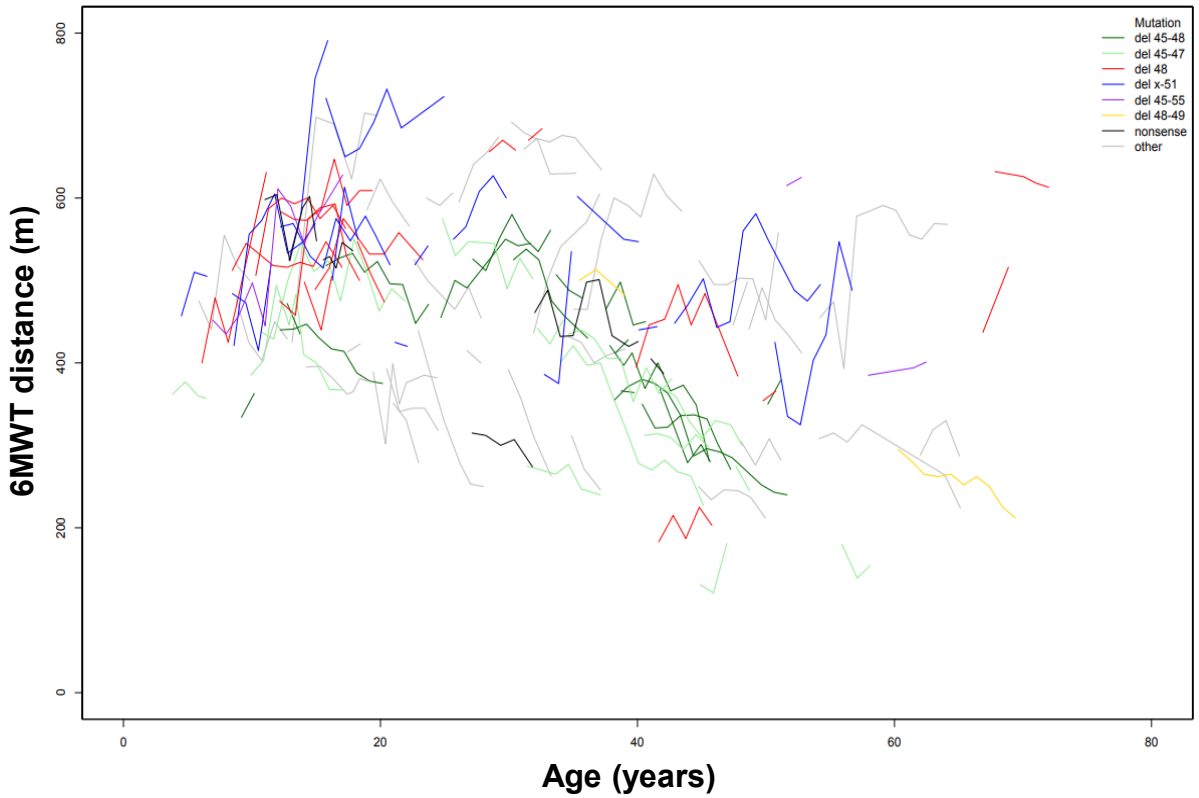
	del 48	12	63	-0.08	0.04	n.s.
	del 45-55	5	12	-0.47	0.16	n.s.
	del 48-49	3	14	-1.35	0.16	< 0.0001
	nonsense	2	24	-0.38	0.10	0.002

Reference: Data on File

Padova Cohort: Longitudinal 6MWT

The average change in 6MWT for the entire cohort was **-4.81m annually (p<0.0001).**



5-Year 6MWT Changes

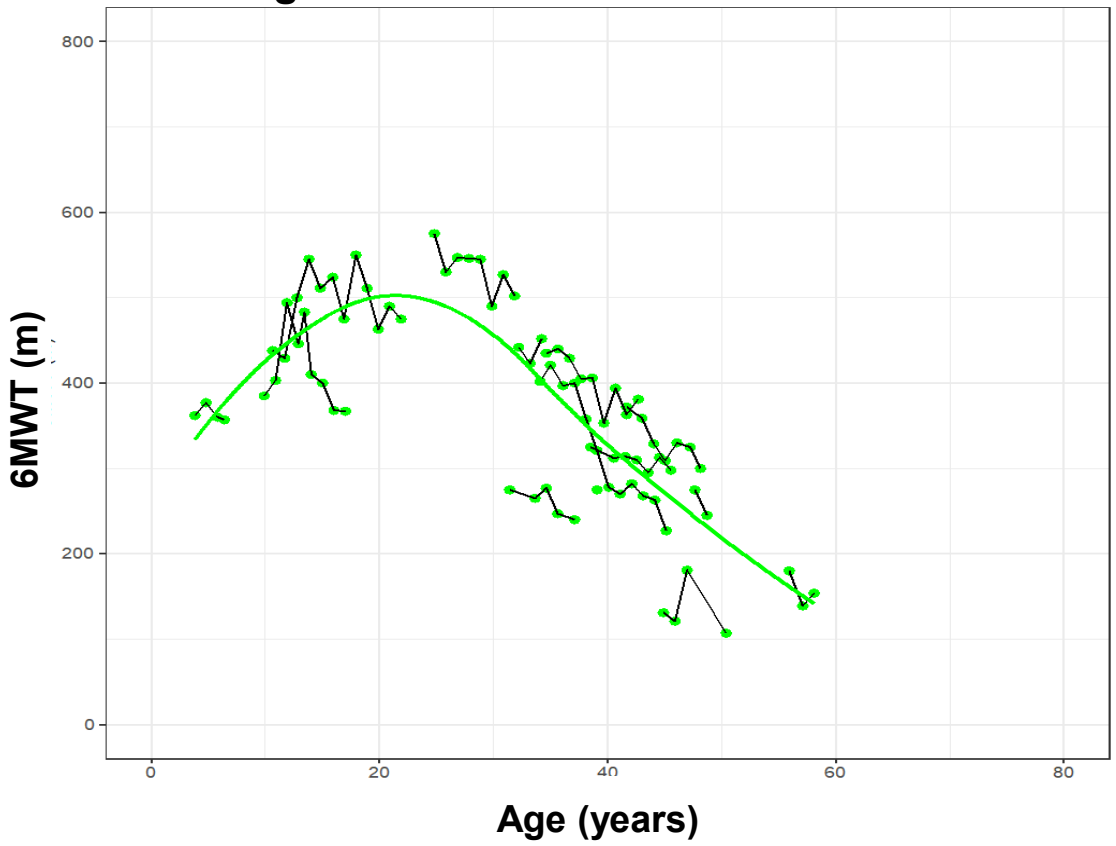
Measure	Group	n (pts)	n (evals)	Estimate of yearly change	SE	p-value
6MWT	All	86	440	**-4.81**	0.60	**< 0.0001**
	del 45-48	14	84	**-7.30**	0.93	**< 0.0001**
	del 45-47	13	69	**-10.54**	1.07	**< 0.0001**
	del x-51	11	47	**-3.04**	1.47	**0.05**
	del 48	12	55	-2.84	1.79	n.s.
	del 45-55	5	8	3.15	1.04	n.s.
	del 48-49	3	15	**-7.25**	0.91	**< 0.0001**
	nonsense	3	22	**-6.85**	1.81	**0.001**

Reference: Data on File

Padova Cohort: Longitudinal 6MWT - del 45-47

- del 45-47 patients are predicted to have the greatest decrease in 6MWT annually.

Longitudinal 6MWT - del 45-47 cohort



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6MWT	All	86	440	**-4.81**	0.60	**< 0.0001**
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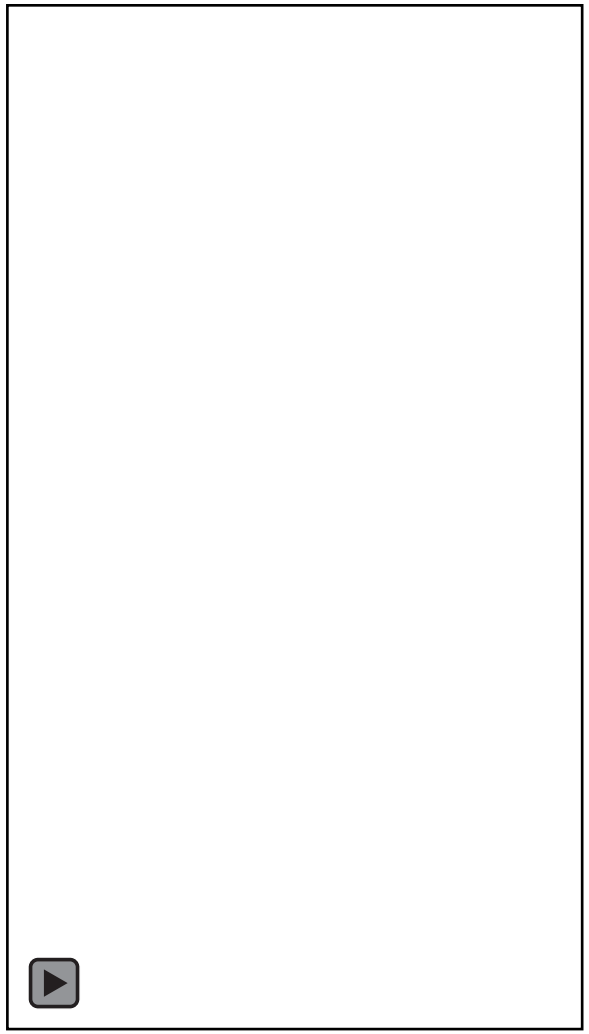
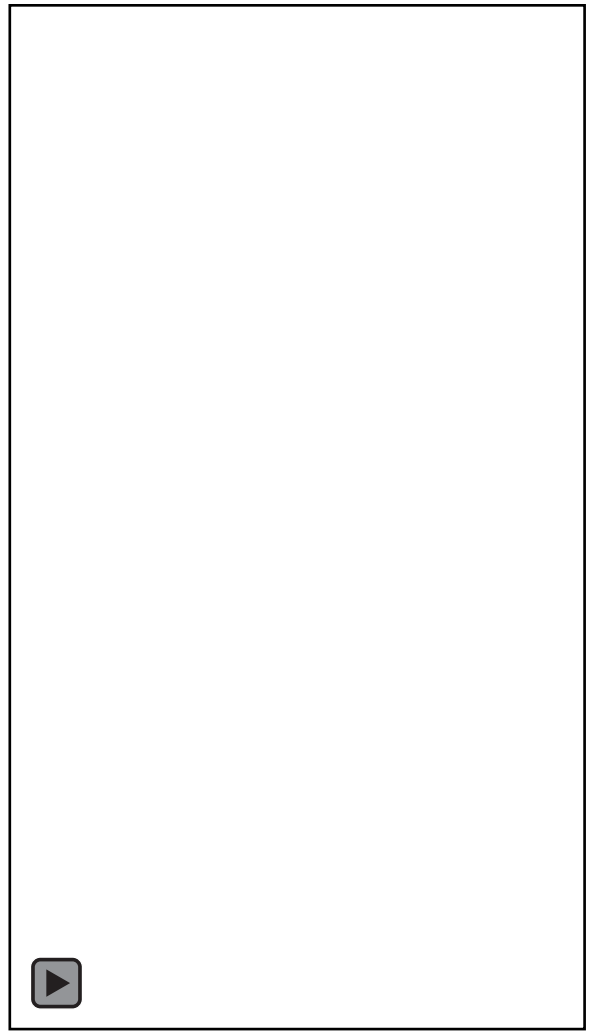
	del 48-49	3	15	**-7.25**	0.91	**< 0.0001**
	nonsense	3	22	**-6.85**	1.81	**0.001**

Reference: Data on File

Although patients may be able to perform functions included in the assessments, they compensate for weakness

The videos below show a patient, age 38, with deletion of exons 45-47, performing functional assessments.

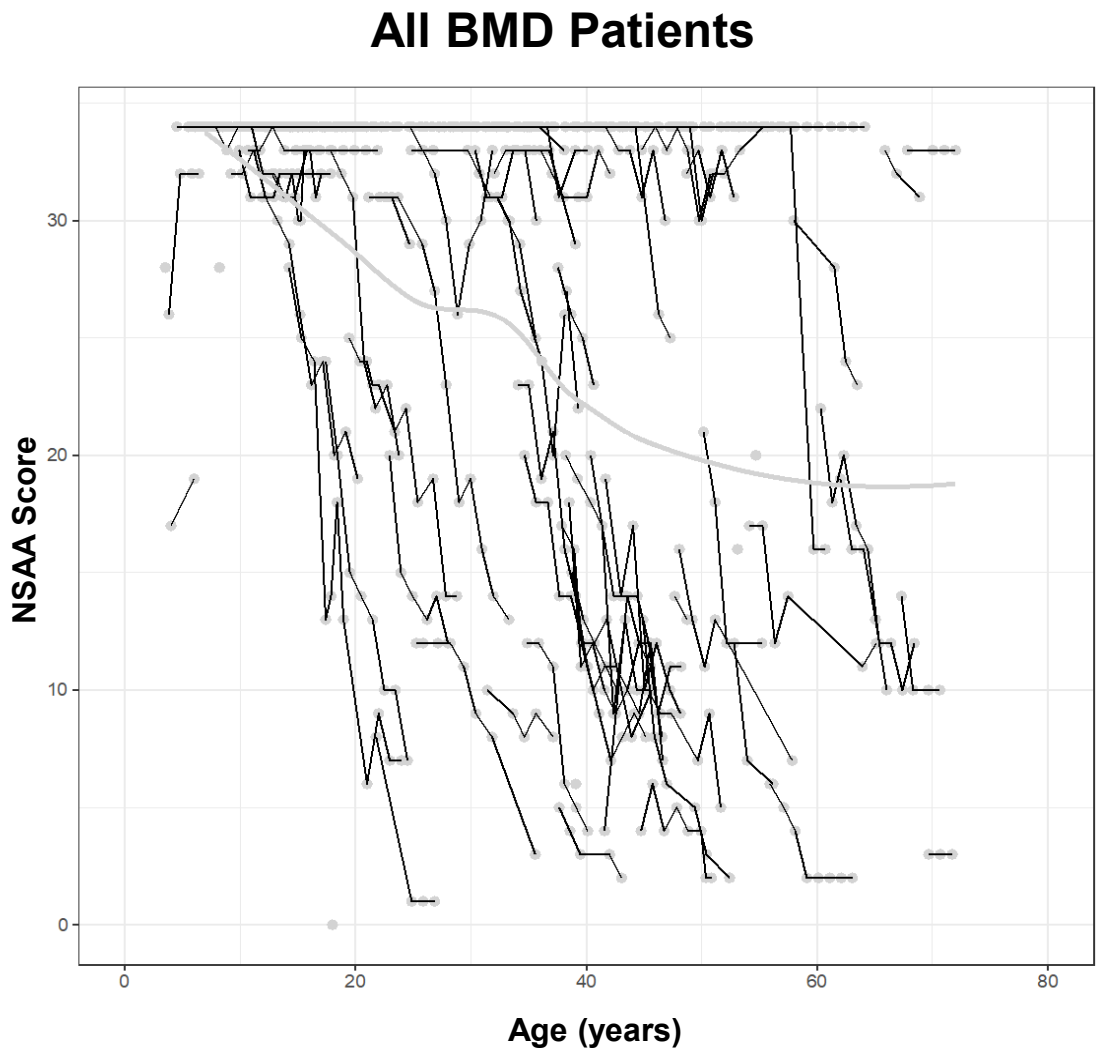




No significant yearly decrease with basal NSAA > 32

With basal NSAA > 32, there is no significant yearly decrease.

Baseline NSAA score	n (>18 y)	n (evals)	Estimate of yearly change	SE	p-value
All	89	504	-0.63	0.04	< 0.0001
34	36	193	-0.04	0.01	0.0043
33	8	44	0.01	0.04	n.s.
30-32	8	52	-0.95	0.17	< 0.0001
25-29	4	26	-1.40	0.25	< 0.0001
20-24	9	72	-1.28	0.04	< 0.0001
15-19	8	49	-0.68	0.06	< 0.0001
10-14	7	34	-0.96	0.13	< 0.0001
5-9	4	17	-0.01	0.03	n.s.
0-4	5	17	0.04	0.08	n.s.

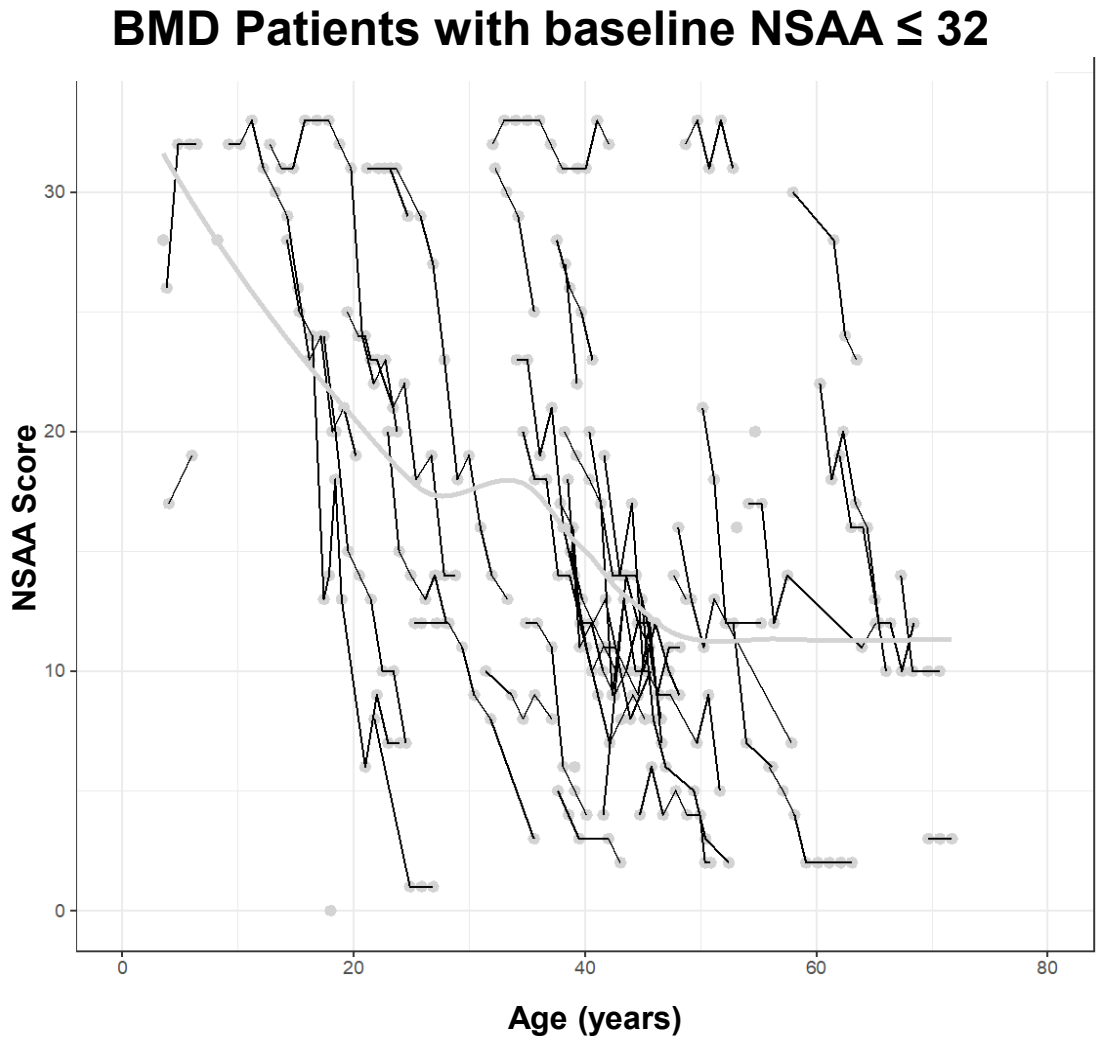


Reference: Data on File

Significant decreases seen in patients wtih baseline score ≤ 32

- However, with patients that have a baseline NSAA score ≤ 32, have significant decrease.
- Once functional decline begins, patients tend to experience a consistent and steep decline in function.

Baseline NSAA score	n (>18 y)	n (evals)	Estimate of yearly change	SE	p-value
All	89	504	-0.63	0.04	< 0.0001
34	36	193	-0.04	0.01	0.0043
33	8	44	0.01	0.04	n.s.
30-32	8	52	-0.95	0.17	< 0.0001
25-29	4	26	-1.40	0.25	< 0.0001
20-24	9	72	-1.28	0.04	< 0.0001
15-19	8	49	-0.68	0.06	< 0.0001
10-14	7	34	-0.96	0.13	< 0.0001
5-9	4	17	-0.01	0.03	n.s.
0-4	5	17	0.04	0.08	n.s.



Reference: Data on File

Overview of current Becker natural history studies

This 5-year data adds to the community's current understanding of Becker and shows that there is significant NSAA changes over time in ambulatory patients.

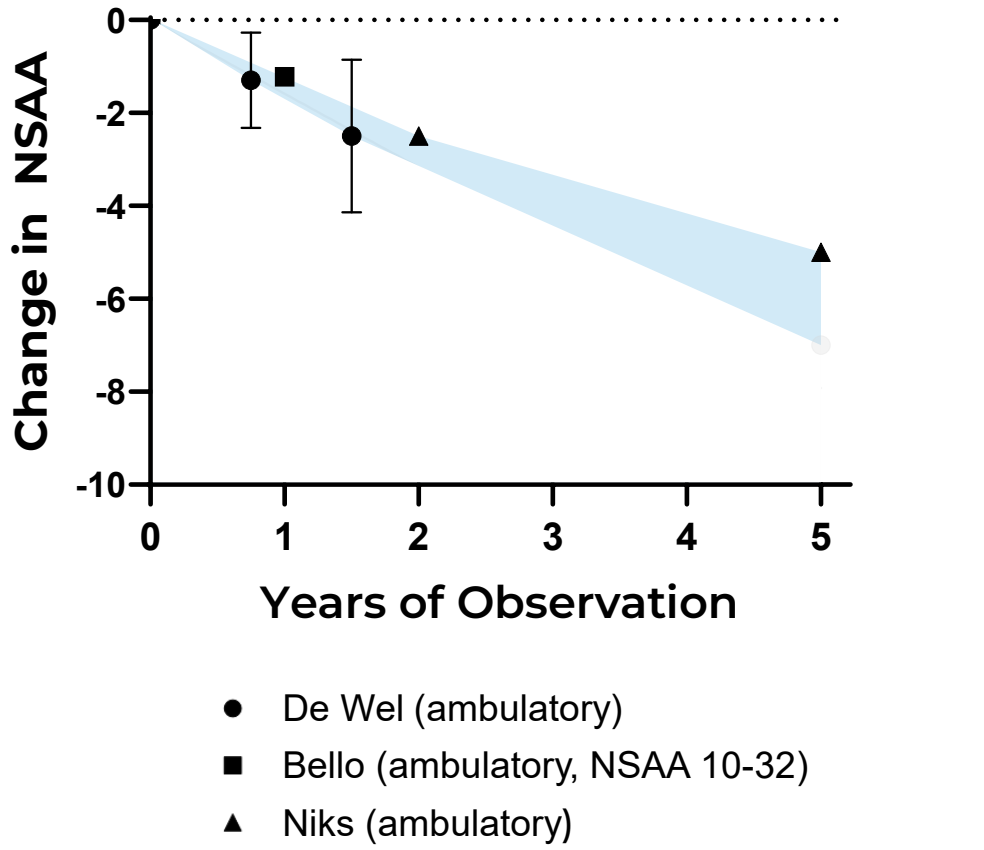
Study	Length of Study	N	Estimated Mean NSAA Change (Points Per Year)	P-value
Bello L, et al. Sci Rep. 2016	1 year	69	-0.9	$p < 0.001$
De Wel B, et al. Eur J Neurol. 2024	1.5 years	21	-1.8	$p = 0.010$
Van de Velde NM, et al. Neurology. 2021	2 years	24	-1.25	$p = 0.002$
Bello L, et al. Unpublished data	5 years	107	-0.63	$p < 0.0001$

Studies are currently ongoing with Italian Telethon and CINRG.

Natural history of NSAA across Becker publications

- The North Star Ambulatory Assessment (NSAA) is a multi-item scale utilized in muscular dystrophy natural history studies to longitudinally assess functional measures.
- Currently available studies observe significant NSAA changes over time in ambulatory patients.
- These natural history studies in Becker patients support that NSAA decline is consistent in Becker patients who are already progressing.

Natural history of Becker muscular dystrophy



Reference: 1. Bello L, et al. Presented at MDA. 2022. 2. De Wel B, et al. Eur J Neurol. 2024. 3. Van de Velde NM, et al. Neurology. 2021.; 95% CI shown

Conclusion

- Natural history is important for understanding of disease progression, patient care, and clinical trial development.
- Recent 5-year natural history data adds to the community's understanding of Becker and shows that there are significant NSAA changes over time in ambulatory patients.
- In totality, the current natural history studies supports that once functional decline begins, individuals with Becker continue on a predictable trajectory to irreversible muscle loss.
- Additional natural history research is on-going.

Acknowledgements

- Elena Pegoraro
- Eric P. Hoffman
- Pietro Riguzzi
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- Giuliana Capece
- Martina Penzo
- Angela Petrosino
- Elena Sogus
- Andrea Barp
- Domenico Gorgoglione
- Sara Vianello
- Daniele Sabbatini
- Yetrib Hathout
- Emily Canessa
- Utkarsh Dang
- The Italian BMD Network
- Edgewise Therapeutics
- All participating patients and families
- All of you for listening

Outcome measures in Becker muscular dystrophy and an overview of the sevasemten clinical program

Craig McDonald, MD

Professor and Chair
Department of Physical Medicine & Rehabilitation
Professor of Pediatrics
Director of MDA Neuromuscular Disease Clinics
University of California Davis Health

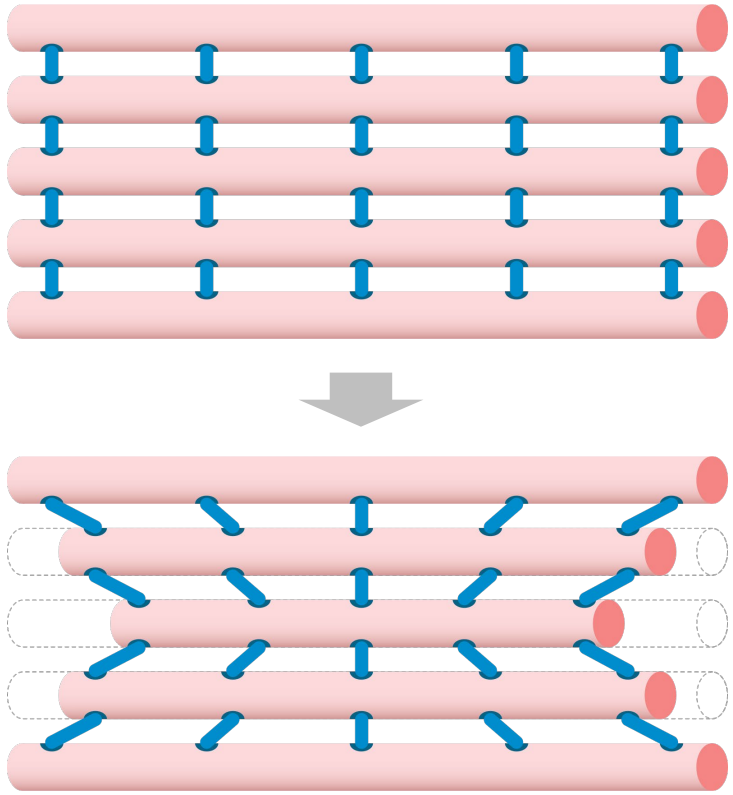
Disclosures

Sevasemten (EDG-5506) is an investigational agent that is not approved for use by any regulatory authority in any territory.

Prof. 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.

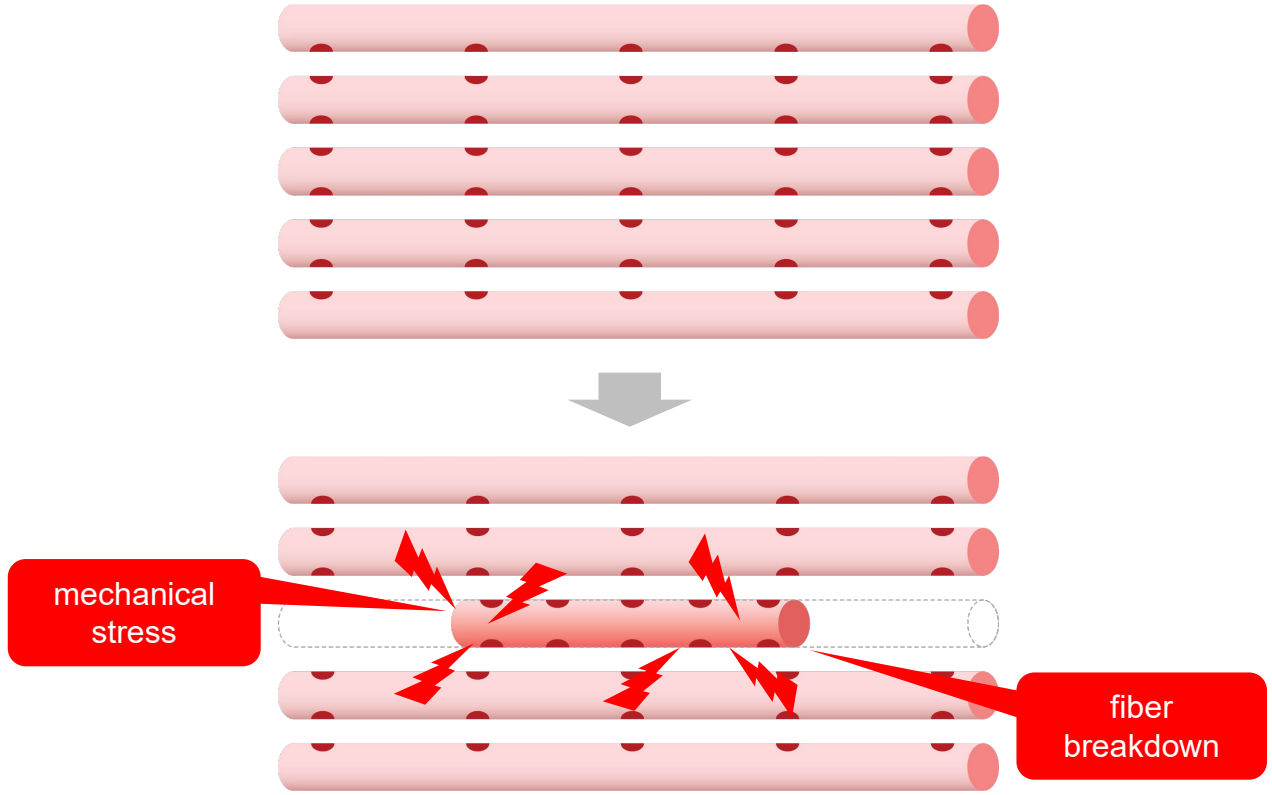
In dystrophinopathy, fast muscle fibers are disproportionately injured by contraction

Healthy muscle contraction



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

Dystrophic muscle contraction

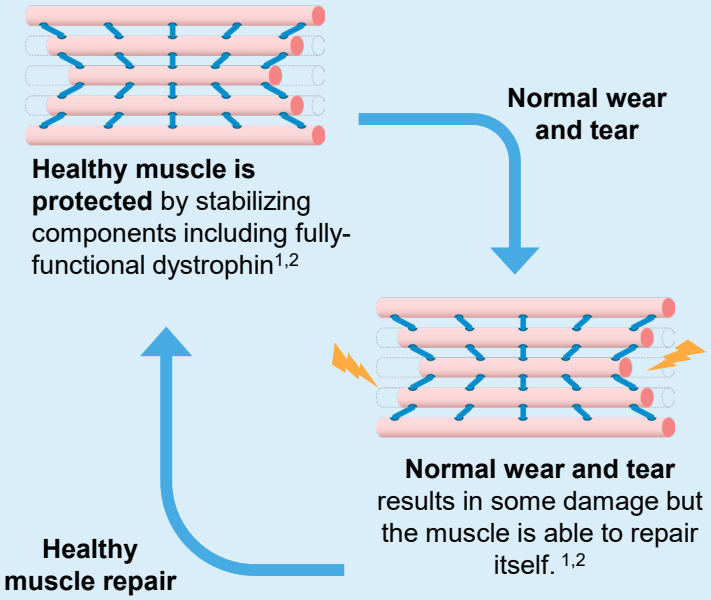


Contraction-induced muscle injuries occur in the absence of full-length dystrophin.

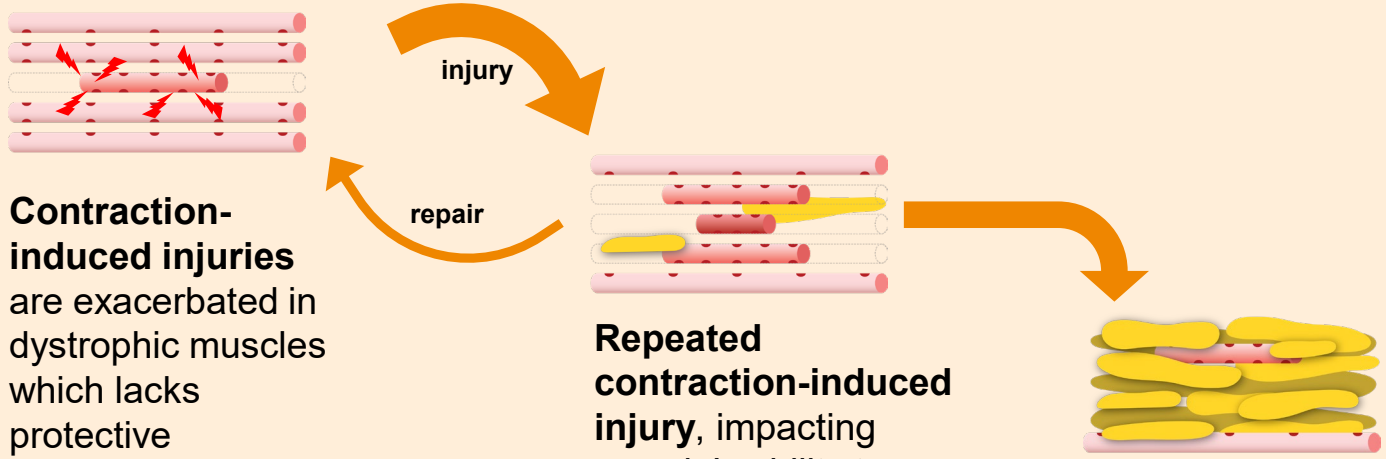
Contraction-induced muscle injury is the root driver of disease progression in muscular dystrophy

Contraction from daily activities

HEALTHY MUSCLE



DYSTROPHIC MUSCLE



Contraction-induced injuries are exacerbated in dystrophic muscles which lacks protective components including fully-functional dystrophin.[2]

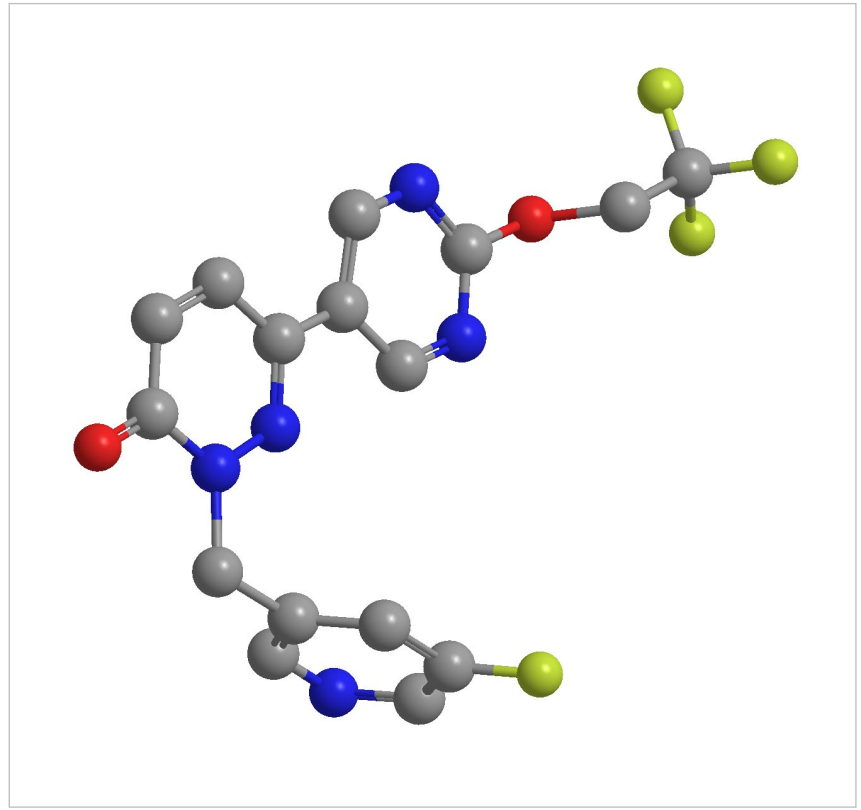
Repeated contraction-induced injury, impacting muscle's ability to repair itself.[3]

Fat and scar replacement of muscles leads to muscle loss and eventual loss of function.[3]

Reference: 1. Goldstein JA, et al. J Gen Physiol. 2010;136(1):29-34. 2. Aartsma-Rus A, et al. J Med Genet. 2016;53(3):145-51.3. Tulangekar A, et al. Biomedicines. 2021;9(10):1366.

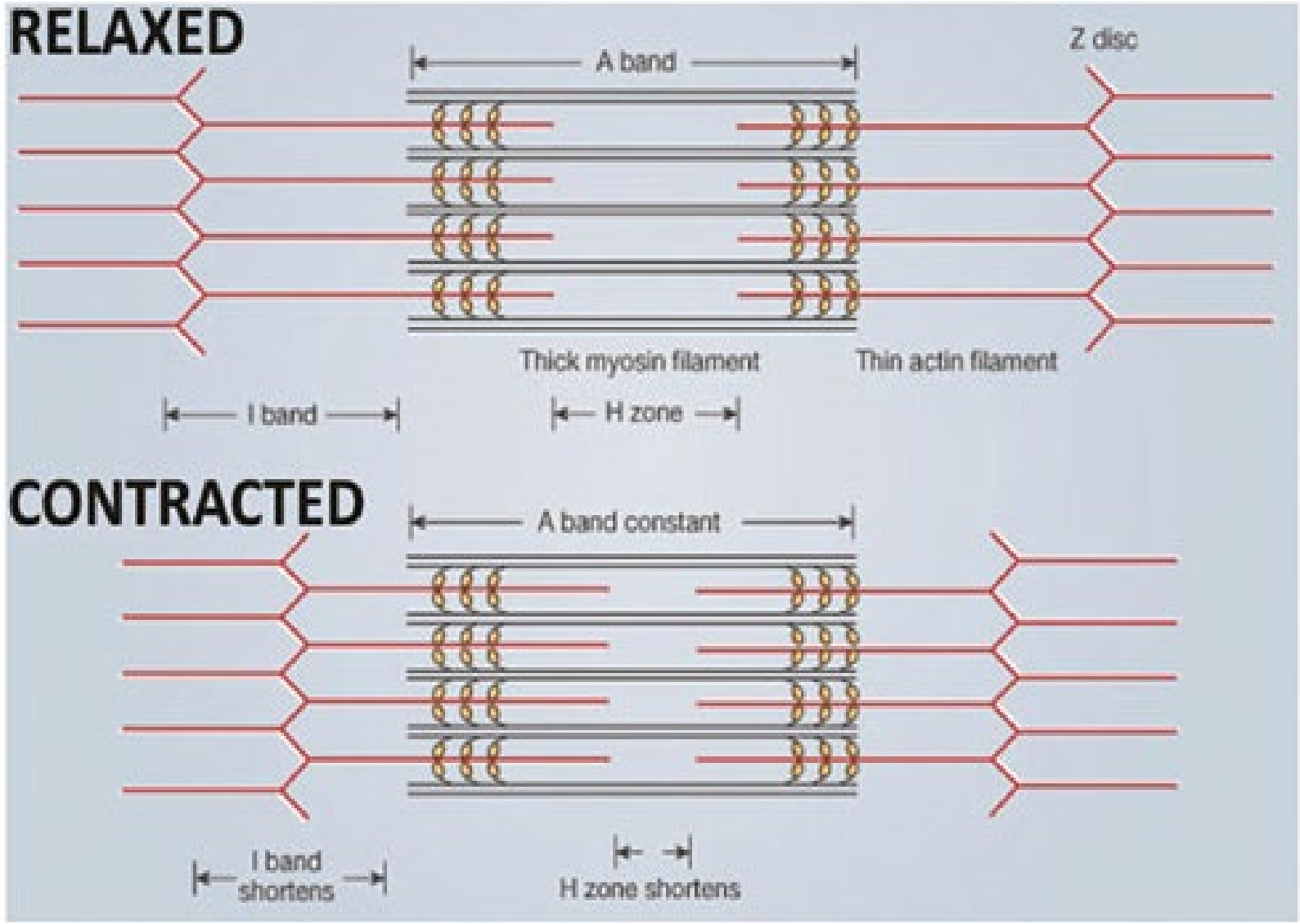
Sevasemten overview

- **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 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**

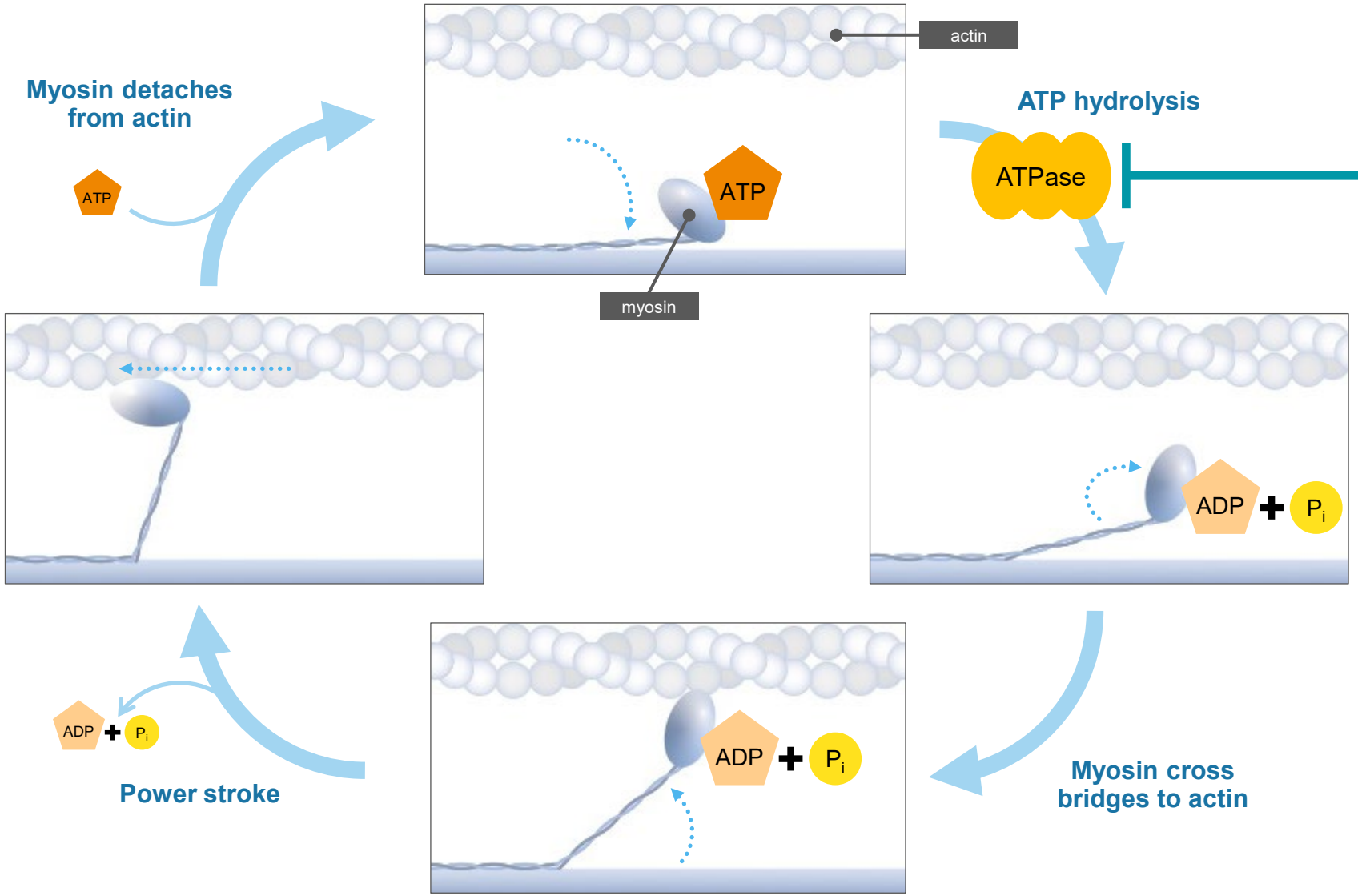


Note: Sevasemten is an investigational agent that is not approved for use by any regulatory authority in any territory.

Muscle contraction and sarcomere shortening: Involves the sliding of actin past myosin generating muscle tension



Myosin-actin coupling requires hydrolysis of ATP: Sevasemten inhibits ATPase activity, reducing myosin-actin contraction activity

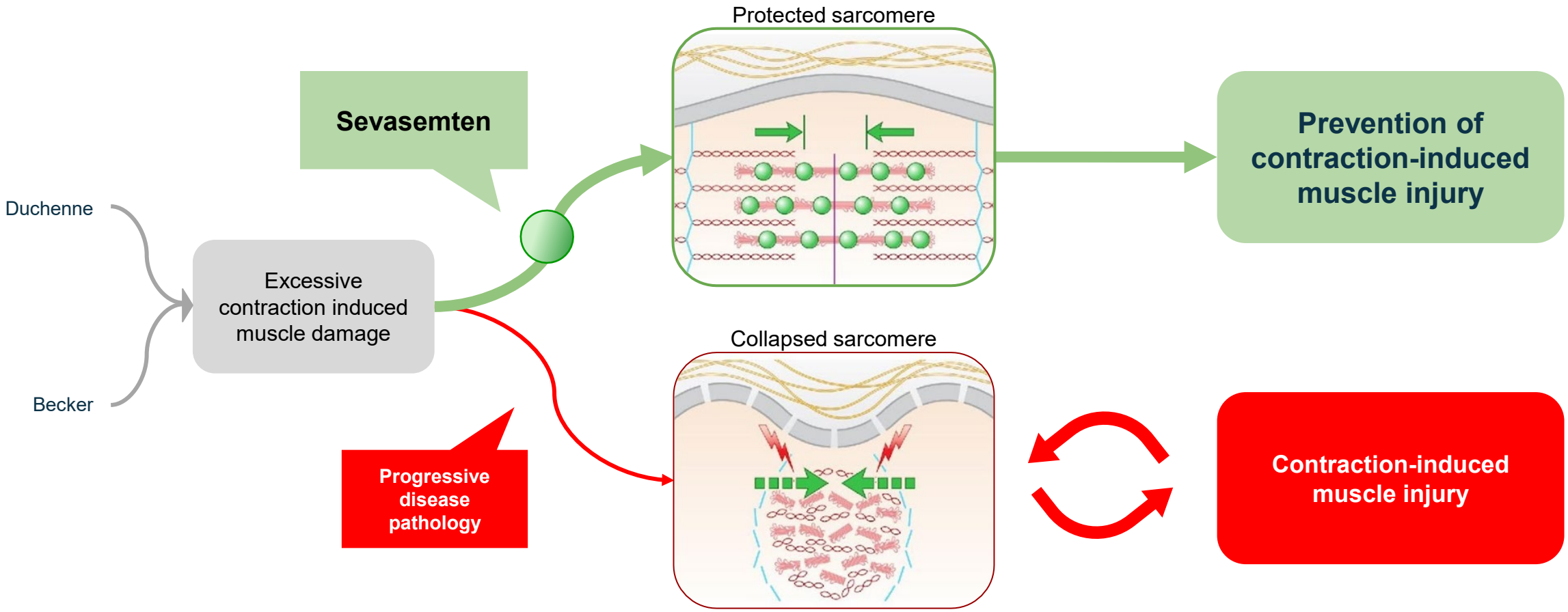


Sevasemten is an allosteric inhibitor of ATPase activity

Preventing hypercontraction of fast myofibers may prevent myofiber degeneration and preserve skeletal muscle function in Duchenne/Becker

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

Sevasemten: An investigational first-in class fast myofiber (type II) myosin inhibitor designed to protect against contraction-induced muscle injury



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

Ongoing sevasemten clinical development program

Becker

ARCH
Phase 1 Open Label – Becker
Completed

CANYON
Phase 2 – Becker
Active, not recruiting

DUNE
Phase 2 – Becker, Limb-Girdle, McArdle
Active, not recruiting

GRAND CANYON
Pivotal Cohort – Becker
Recruiting

MESA
Open Label Extension Study – Becker
Enrolling by invitation

GRASP-01-002
Natural History Study – Becker
Enrolling

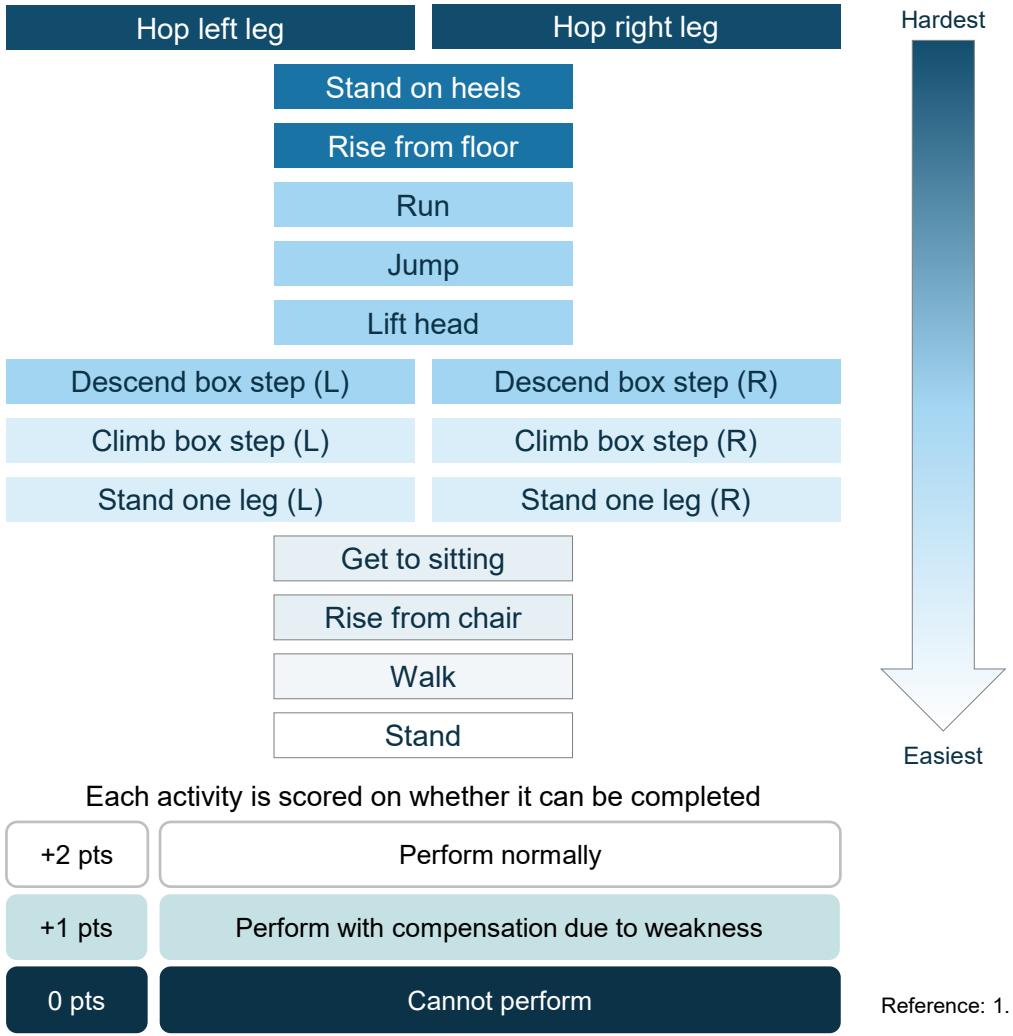
Duchenne

LYNX
Phase 2 – Duchenne
Recruiting

FOX
Phase 2 – Duchenne (on gene therapy)
Recruiting

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



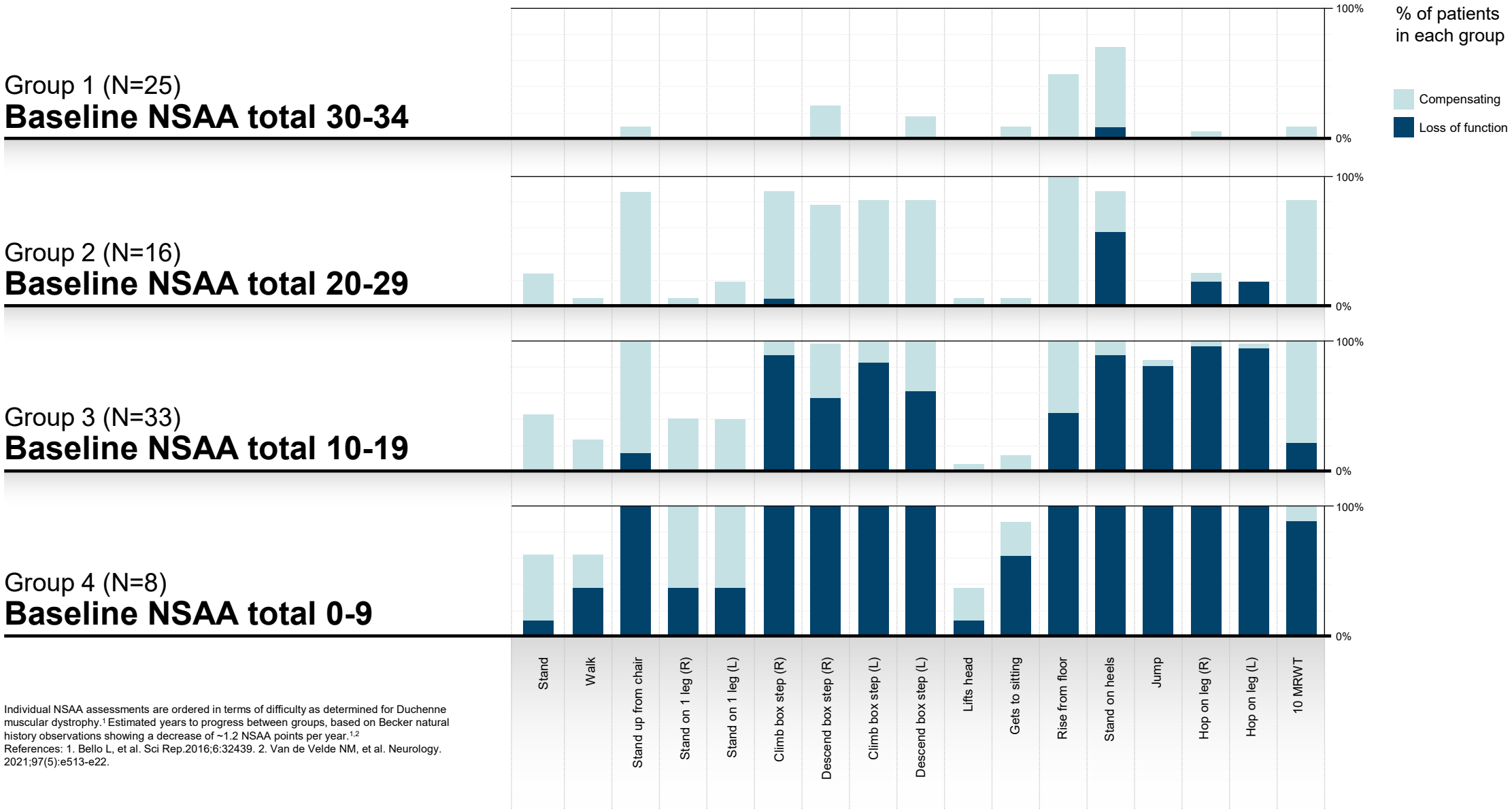
Real-world implications for Becker individuals

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

For more information on NSAA validation using Rasch analysis, please see WMS poster #322P

Reference: 1. Mazzone ES, et al. Neuromuscular Disorders. 2009;19(7):458-461.

As NSAA scores decline, individuals with Becker may increase compensation and experience rapid loss of function



Individual NSAA assessments are ordered in terms of difficulty as determined for Duchenne muscular dystrophy.[1] Estimated years to progress between groups, based on Becker natural history observations showing a decrease of ~1.2 NSAA points per year.[1,2]

References: 1. Bello L, et al. Sci Rep.2016;6:32439. 2. Van de Velde NM, et al. Neurology. 2021;97(5):e513-e22.

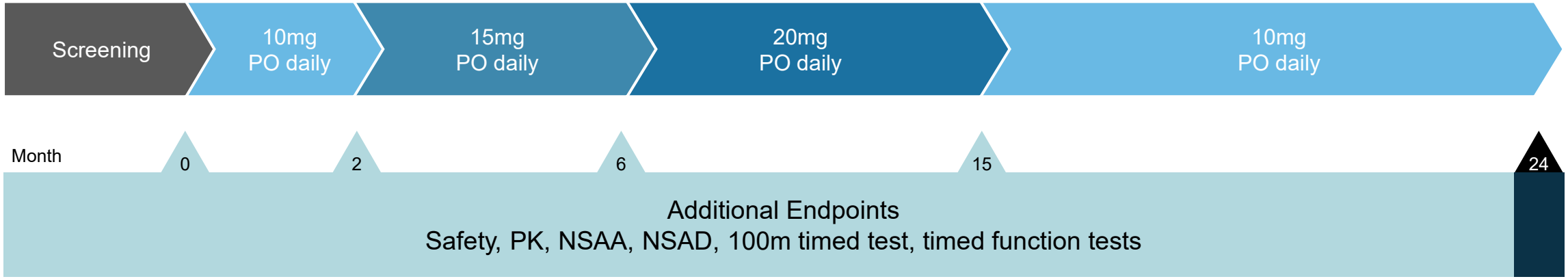
ARCH

An update: 24-month data results

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



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

Participants had significant functional impairment & decreased muscle mass at baseline

CHARACTERISTIC	BECKER PARTICIPANTS (n=12)	AGE NORMATIVE VALUES
Age (SD)	33 (8) years	–
Functional Measures (median)		
10-meter walk/run	8.4 sec	< 4 sec
Rise from floor	6/12 could perform	< 3 sec
NSAA	15.5 (range 4-31)	–
Serum Creatinine (mean, mg/dL)	0.44	0.92 - 1.16
Serum CK (mean, U/L)	1,390	<210
DXA % Lean Mass	55%	>75%

Adults with similar baseline NSAA scores expected to decrease by 1.2 points per year[2,3]

Abbreviations: DXA, dual energy x-ray absorptiometry

Reference: 1. Phan H, et al. Oral presentation presented at: American Academy of Neurology; April 13-18, 2024; Denver, CO.
2. Bello L, et al. Sci Rep. 2016. 3. Van de Velde NM, et al. Neurology. 2021.

Mutation Status

Mutation	n
del 45-47	5
del 45-48	4
del 45-53	1
del 3, 4, 6, 8, 9	1
c.6762+3 A>T splice variant	1

10/12 carry deletions associated with progressive Becker phenotype.

Reference: Data on file

Sevasemten well-tolerated at all doses

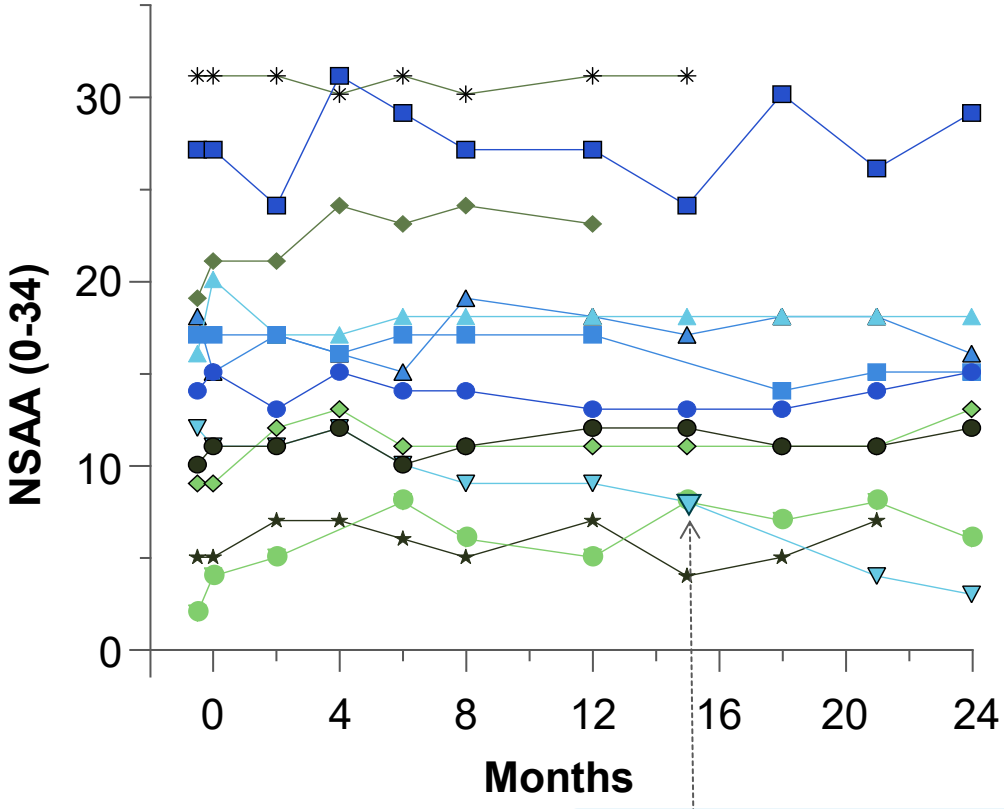
Treatment Emergent AE (seen in >1 subject)	After One Year	After Two Years
COVID-19	4	5
Fall*	3	4
Dizziness	4	4
Arthralgia	4	4
Nasopharyngitis	3	3
URI	3	3
Procedural pain	2	3
Headache	3	3
Somnolence	3	3
GERD	2	3
Influenza	2	3
Sinusitis	2	2

- No dose reductions or adjustments
- No treatment discontinuations due to AEs
- No SAE
- Withdrawals:
  - 3 (2 of whom are planning to enroll in separate open-label extensions)

*Falls are typical for Becker patients and are not related to dizziness
AEs, adverse events; SAE, serious adverse events
Reference: Phan H, et al. Oral presentation presented at: American Academy of Neurology; April 13-18, 2024; Denver, CO.

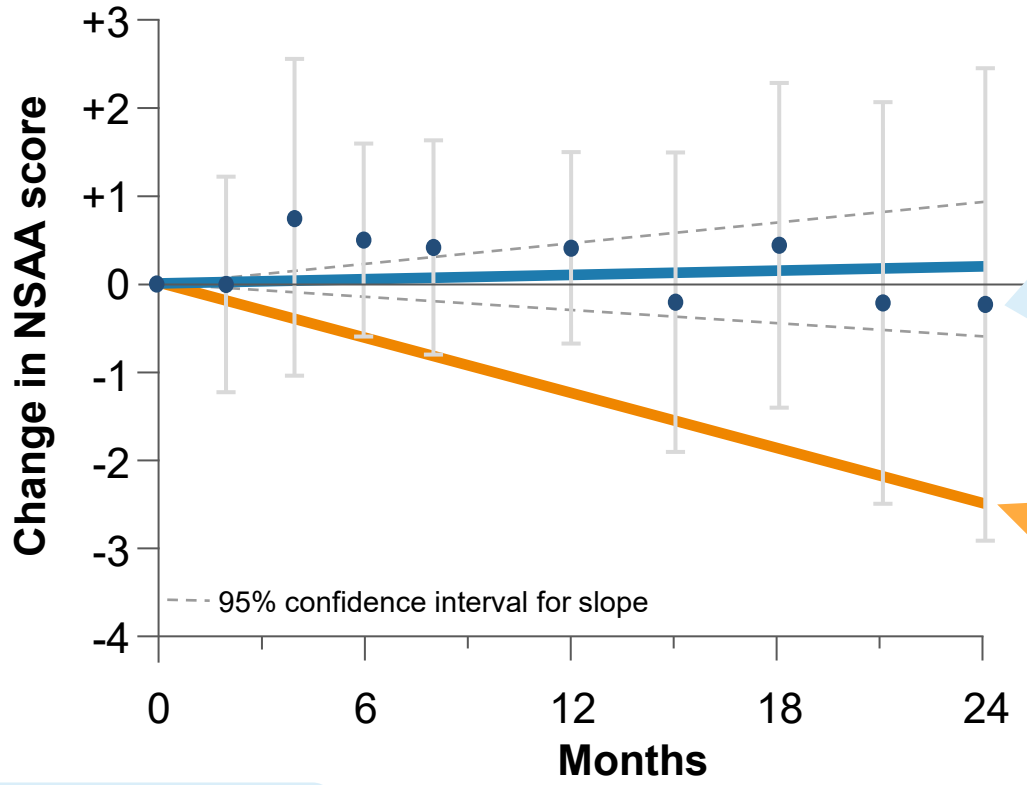
NSAA stabilized, diverging from natural history at 24 months

NSAA responses



NOTE: ▽patient had meniscal tear and surgery after month 15

NSAA change*



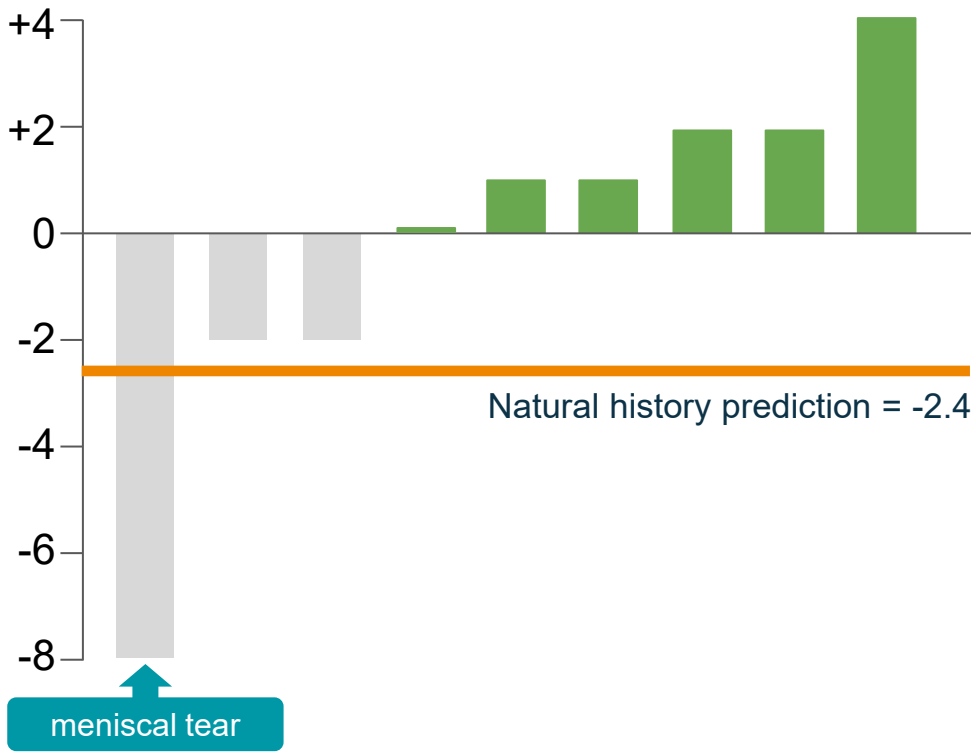
-0.2 mean change in NSAA with sevasemten at 24 months

-2.4 natural history average change

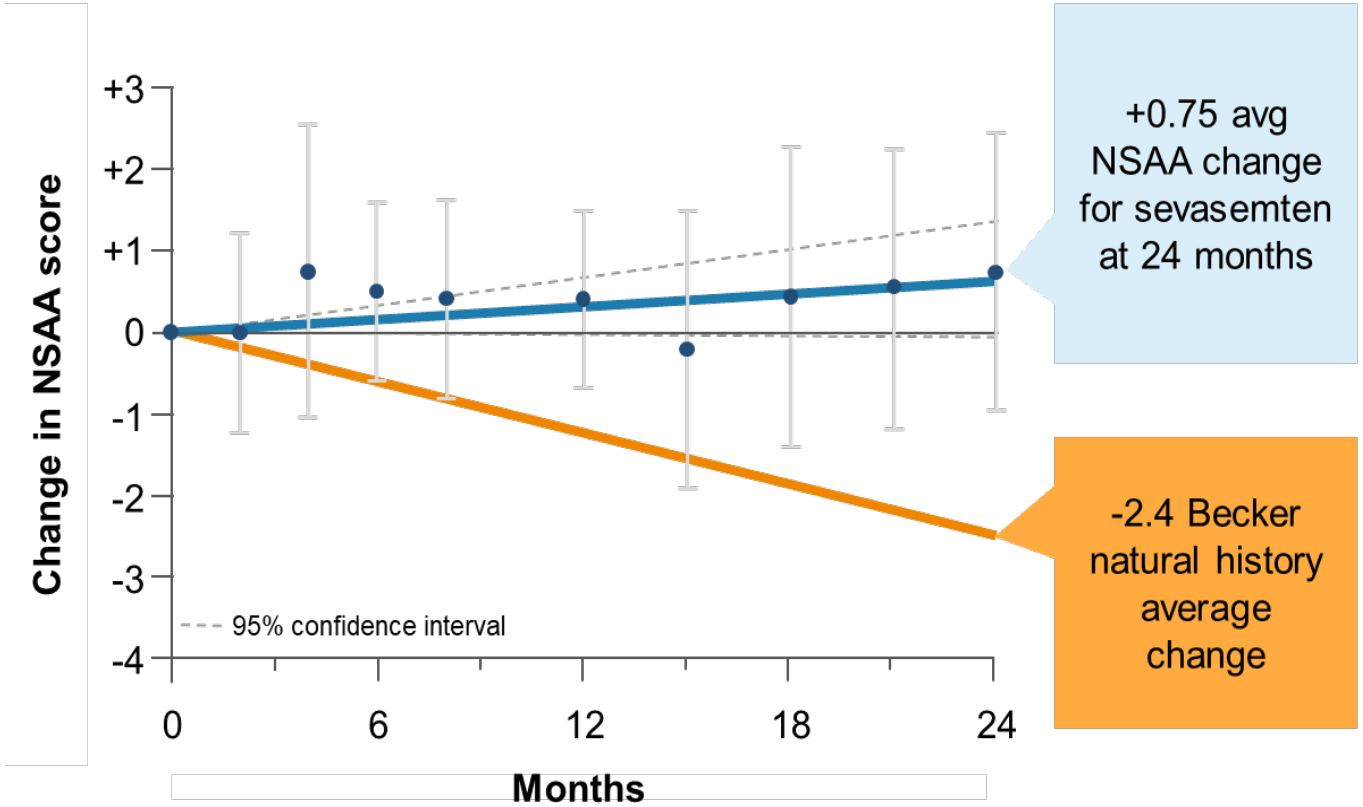
*All data through 24m, including patient recovering from meniscus surgery
Natural history based on data presented by Bello at MDA (2022) and van de Velde NM et. al., Neurology, 2021
Mean ± 95% confidence intervals
Abbreviations: NSAA, North Star Ambulatory Assessment
Reference: Phan H, et al. Oral presentation presented at: American Academy of Neurology; April 13-18, 2024; Denver, CO.

NSAA stabilized, diverging from natural history at 24 months

Individual ARCH participant NSAA responses at 24 months



NSAA change excluding patient with knee injury*

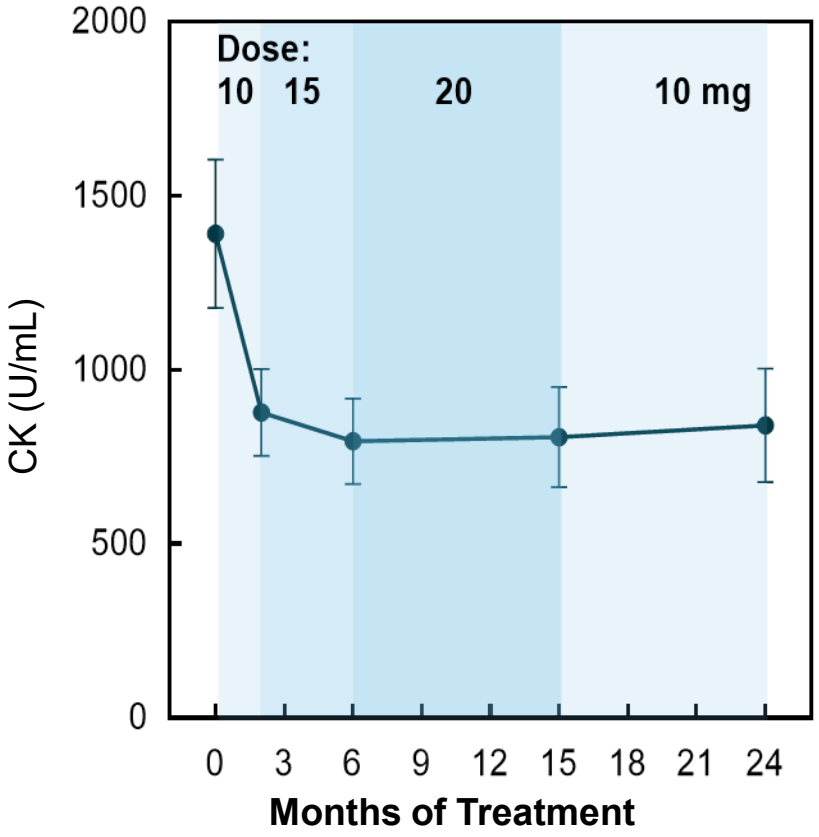


*All data through 24m, EXCLUDING patient recovering from meniscus surgery
Natural history based on data presented by Bello at MDA (2022) and van de Velde NM et. al., Neurology, 2021
Mean ± 95% confidence intervals
Abbreviations: NSAA, North Star Ambulatory Assessment
Reference: Phan H, et al. Oral presentation presented at: American Academy of Neurology; April 13-18, 2024; Denver, CO.

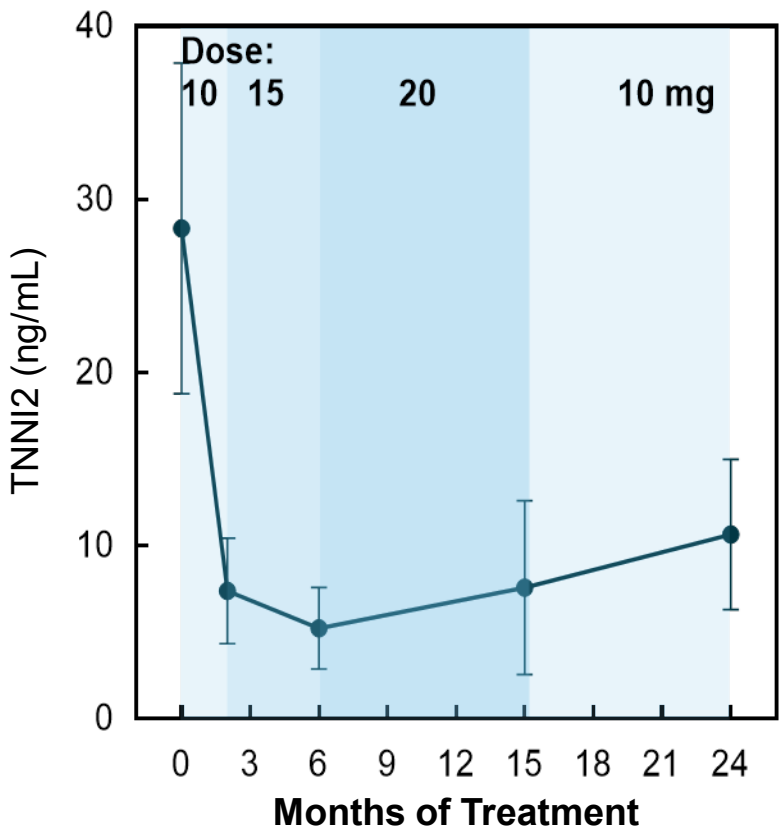
For more information on the ARCH trial results, please see WMS poster #351P

Biomarkers of muscle damage show rapid and sustained decreases with sevasemten

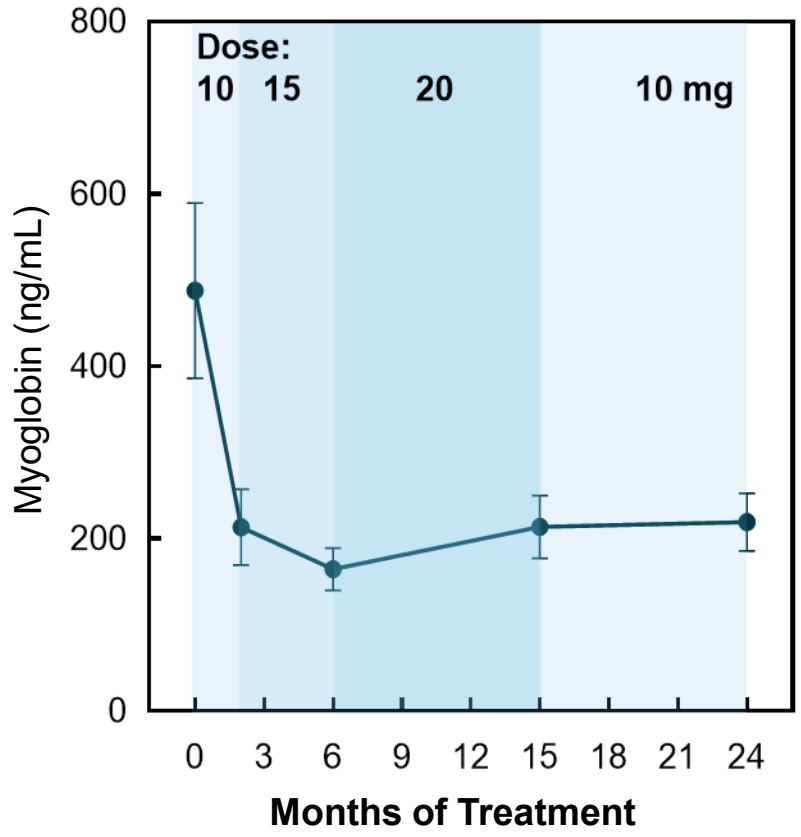
Creatine Kinase (CK)



Fast skeletal muscle troponin I (TNNI2)



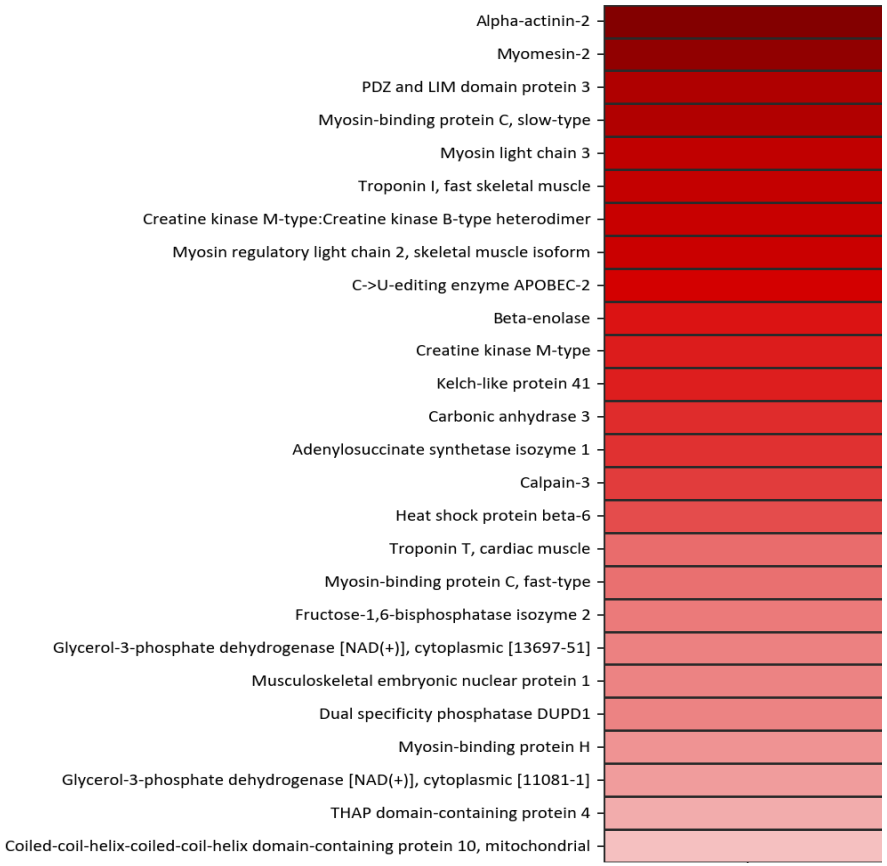
Myoglobin



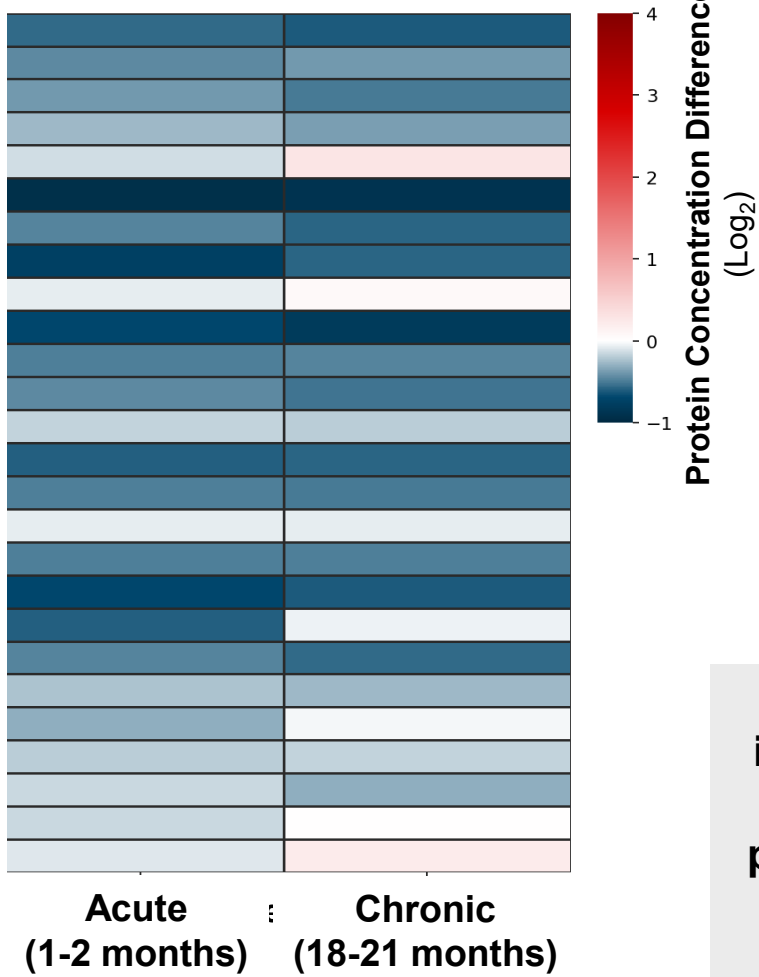
All participants
Mean ± SEM
Reference: Phan H, et al. Oral presentation presented at: American Academy of Neurology; April 13-18, 2024; Denver, CO.

Muscle injury proteins are reduced with sevasemten and decreases are maintained with long-term treatment

A characteristic set of muscle injury proteins are elevated at baseline in Becker



Change from baseline with sevasemten treatment



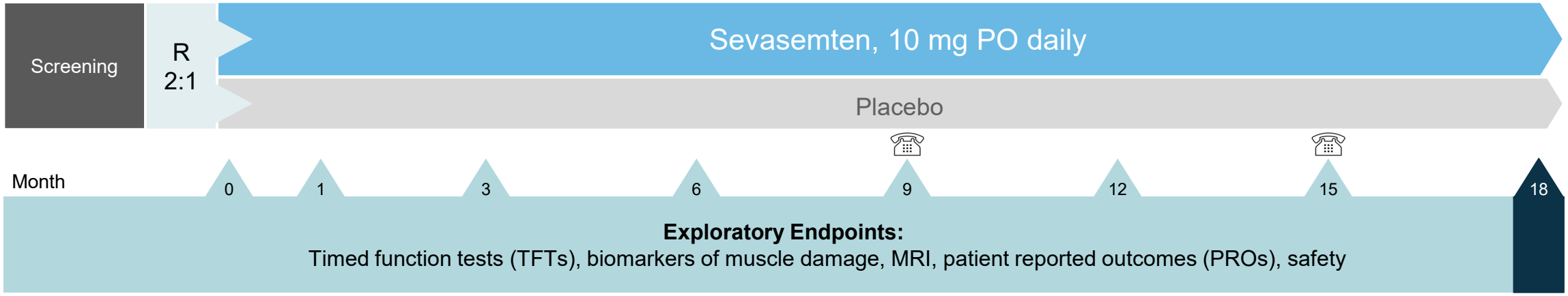
For more information on the ARCH trial proteomics, please see WMS poster #349P

Reference: Barthel B, et al. Poster presented at the 29th Annual Congress of the World Muscle Society; October 8-12, 2024; Prague, Czechia. #349P.

Global, multi-center, placebo-controlled study of sevasemten; pivotal cohort & potentially registrational

- **Population:** Adults with Becker with NSAA 5-32, not on corticosteroids
- **Enrollment:** 120 adults with Becker
- **Primary endpoint:** NSAA at 18 months
- **Secondary Endpoints:** 100 m timed test, biomarkers of muscle damage, MRI

Study design - 18 months



Abbreviations: R, randomization; NSAA, North Star Ambulatory Assessment.

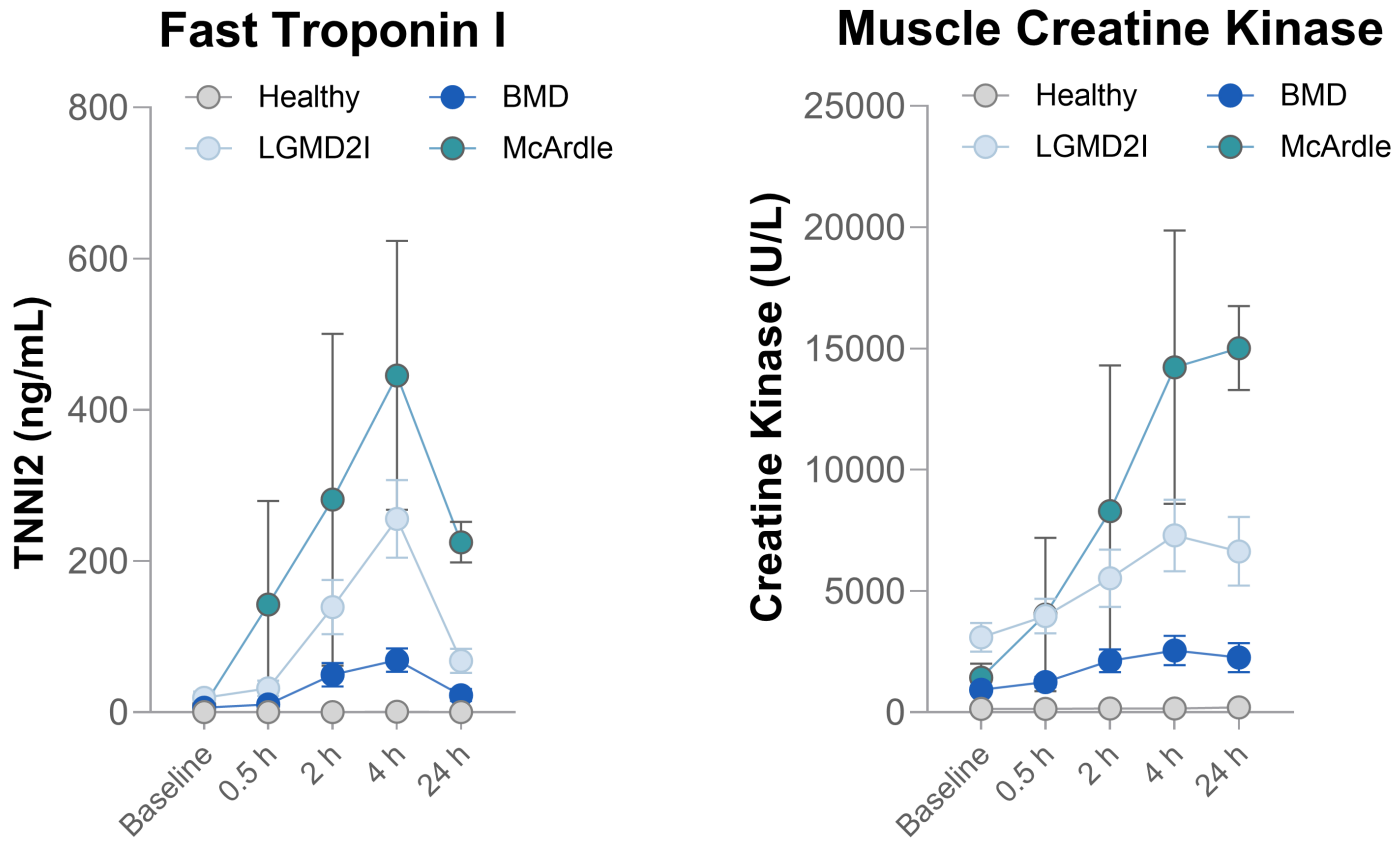
References: 1. ClinicalTrials.gov. NCT05291091. https://clinicaltrials.gov/ct2/show/NCT05291091. 2. Data on file.

DUNE

A Phase 2 study of the effect of sevasemten on biomarker response to exercise in adults with Becker muscular dystrophy, McArdle disease, or Limb-Girdle muscular dystrophy

Study rationale: effect of exercise on SomaScan panel of biomarkers of fast muscle fiber damage

Dr. John Vissing and colleagues previously demonstrated that exercise in Becker, LGMD2I/LGMDR9, and McA caused transient increases in circulating muscle injury proteins.

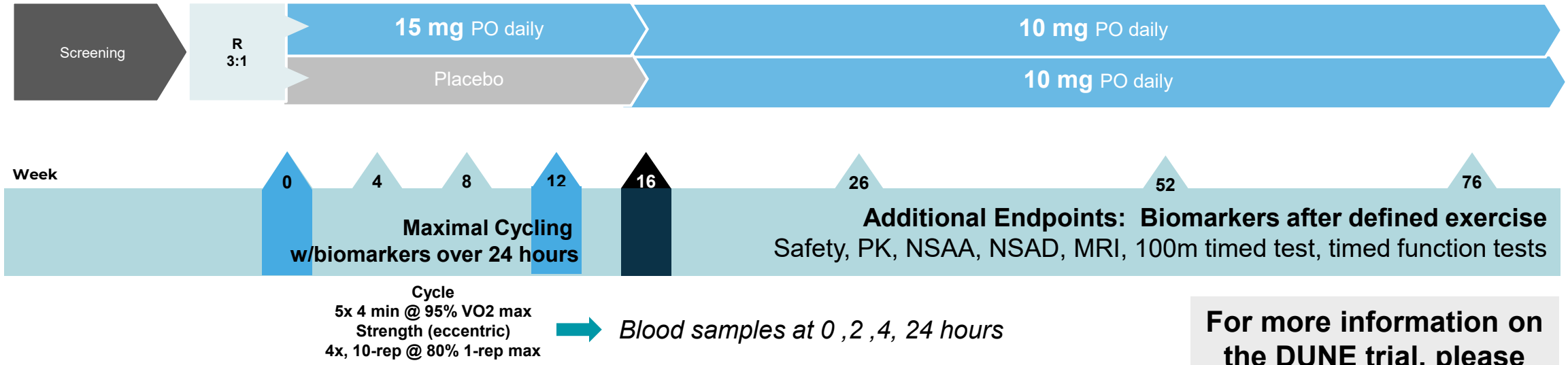


Becker, Becker muscular dystrophy; LGMD2I, Limb-girdle muscular dystrophy type 2I; LGMDR9, Limb-girdle muscular dystrophy R9; McA,McArdle disease

Reference: Stemmerik MG, et al. Poster presented at the 29th Annual Congress of the World Muscle Society; October 8-12, 2024; Prague, Czechia. #732LBP.

A 2-part, single-center Phase 2 study of sevasemten in Becker, McArdle, and Limb-Girdle adults

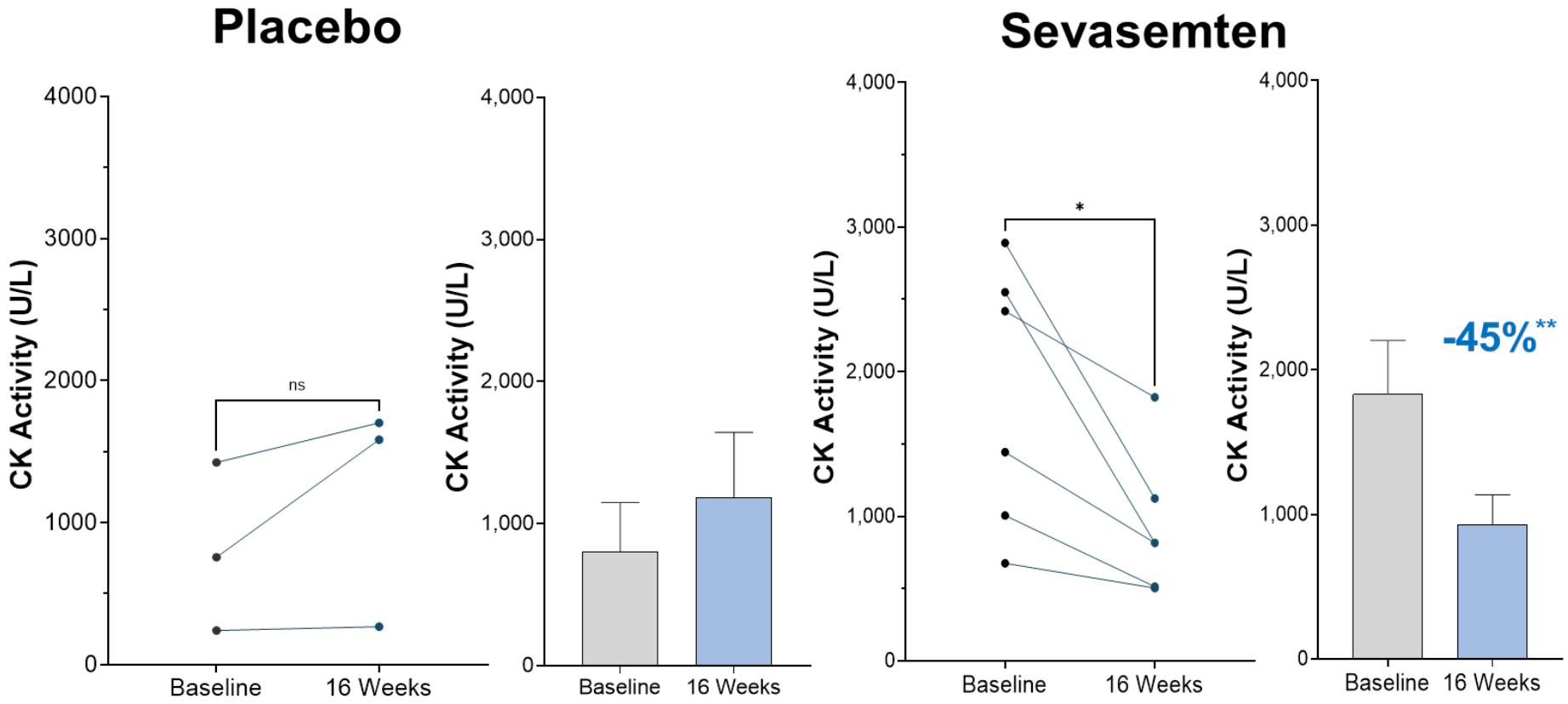
- **Objective:** Does sevasemten reduce elevations in biomarkers of muscle damage after exercise?
- **Enrollment:** 21 adult participants (9 Becker, 3 McArdle, and 9 Limb-Girdle)
- **Key inclusion criteria:** Ambulatory individuals aged ≥ 18 years with confirmation of genetic disease, not on corticosteroids
- **Primary endpoints:** Safety, change in serum CK (interim analysis at 16 weeks)
- **Secondary Endpoints:** Biomarker response, individual safety parameter changes, sevasemten plasma concentration changes



CK, creatine kinase; R, randomization; HR, heart rate; NSAA, North Star Ambulatory Assessment; NSAD, North Star Ambulatory Assessment for Limb Girdle-type Dystrophies; BMD, Becker muscular dystrophy; LGMD2I, Limb-girdle muscular dystrophy type 2I; McA,McArdle disease,
Reference: Stemmerik MG, et al. Poster presented at the 29th Annual Congress of the World Muscle Society; October 8-12, 2024; Prague, Czechia. #732LBP.

For more information on the DUNE trial, please see WMS poster #732LBP

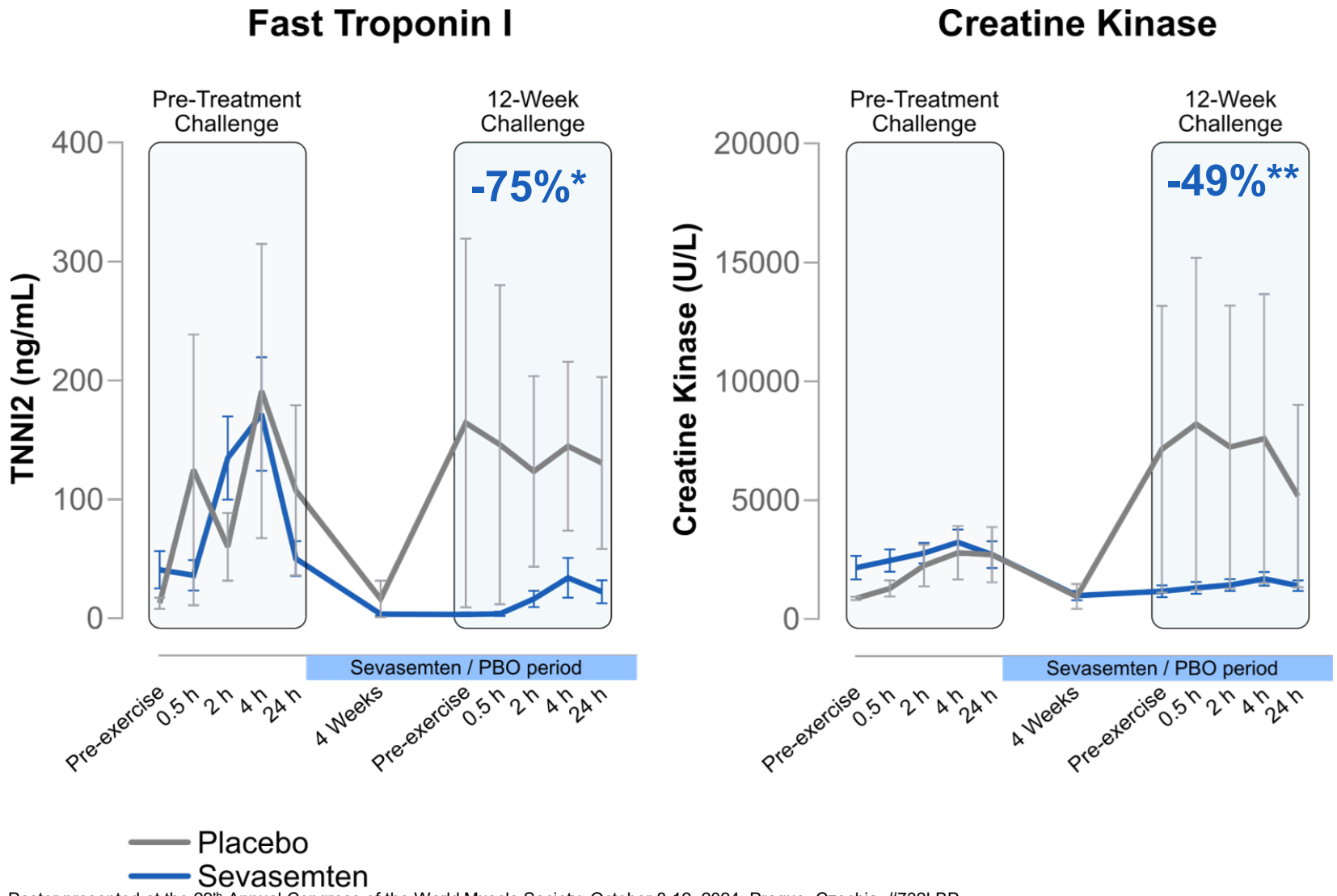
Primary endpoint: in Becker patients, sevasemten significantly reduced CK after 16 weeks



With sevasemten, CK was significantly decreased compared to baseline (**p<0.01) and compared to placebo (*p<0.05) during a period of normal activity.
At 12 weeks with sevasemten, fast muscle troponin I (TNNI2) was decreased by 89% (p<0.01) compared to baseline and to placebo (p<0.05).

Becker, Becker muscular dystrophy; CK, creatine kinase
Reference: Stemmerik MG, et al. Poster presented at the 29th Annual Congress of the World Muscle Society; October 8-12, 2024; Prague, Czechia. #732LBP.

In Becker patients, sevasemten significantly reduced TNNI2 and CK over 24 hours post-exercise



*p<0.05 **p<0.001

Reference: Stemmerik MG, et al. Poster presented at the 29th Annual Congress of the World Muscle Society; October 8-12, 2024; Prague, Czechia. #732LBP.

Conclusions

- NSAA scores are clinically meaningful outcomes in Becker clinical trials.
- Sevasemten an investigational, orally administered, fast skeletal myosin inhibitor, was well-tolerated with rapid and sustained reductions in multiple biomarkers of muscle damage.
- Functional improvements compared to the expected natural history decline in the NSAA scores were observed.
- The increase in biomarkers of muscle damage after controlled high-level exercise is mitigated by sevasemten.
- These results support ongoing investigations of sevasemten in Becker

Thank you!

Thank you for joining us today!

Additionally, we wish to thank the patients, investigators, study site personnel, and all those helping to facilitate clinical trials and to improve care!

For more information, please visit us at the Edgewise booth **(Booth #21).**

To inquire about clinical trials,
please email studies@edgewisetx.com or visit clinicaltrials.gov.