#351P

Sevasemten, a Fast Myosin Inhibitor, in Adults with Becker Muscular Dystrophy Results in Reduced Muscle Damage Biomarkers and Functional Stabilization

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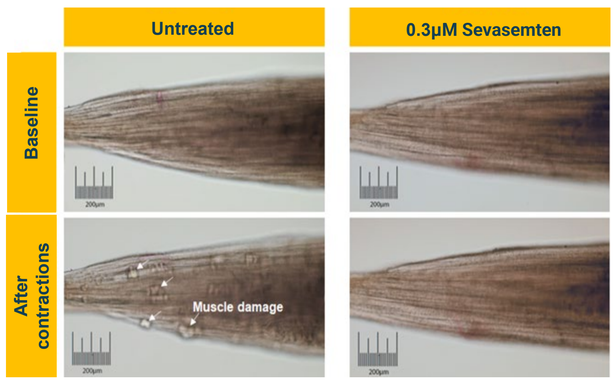
Background

Becker is a severe condition with major unmet medical needs and no standard of care. Becker can lead to relentlessly progressive loss of mobility. There are currently no available therapies for Becker.[1]

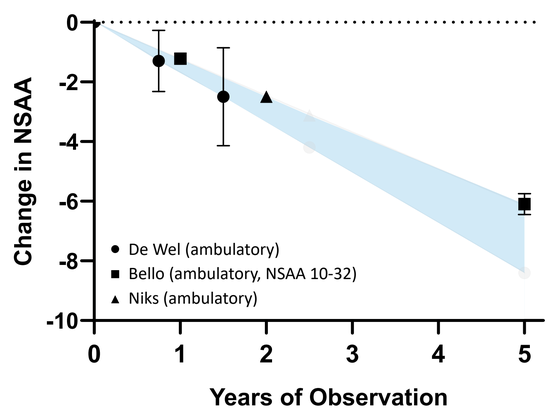
In Becker, exaggerated contraction-induced muscle injuries occur due to the lack of dystrophin. Fast muscle fibers are disproportionately injured by contraction in Becker.[2,3]

Sevasemten (EDG-5506) is an investigational fast myosin inhibitor that modulates fast skeletal muscle and is designed to prevent contraction-induced muscle damage while preserving function.[3]

Sevasemten prevents contraction-induced damage and fiber breakdown in mouse dystrophic muscle[3]



Natural history of Becker muscular dystrophy



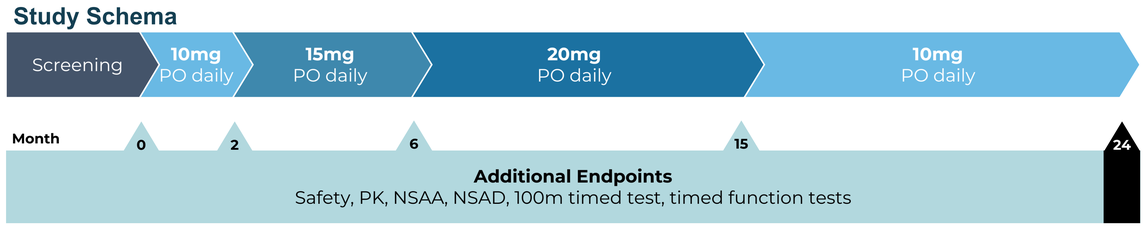
The North Star Ambulatory Assessment (NSAA) is a multi-item scale utilized in Becker natural history studies to longitudinally assess functional measures.

Currently available studies observe significant NSAA changes over time in ambulatory Becker patients. [4,5,6]

These natural history studies in Becker patients demonstrate that NSAA decline is consistent in Becker patients who are already progressing.

Methods

Study Schema



Study Design

The ARCH study (NCT05160415) is a 24-month phase 1b open-label study of safety, PK and biomarkers in 12 adults with Becker.

Key Inclusion Criteria

Ambulatory males ages 18 to 55 years with dystrophin mutation and Becker phenotype, not on corticosteroids, who could complete 100-m timed test.

Baseline Characteristics

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%

Results

After 24 months, sevasemten was well-tolerated.

There were no serious adverse events and no withdrawals or dose reductions due to adverse events.[5]

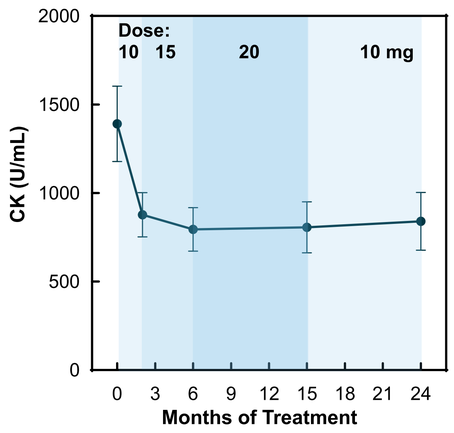
Rapid reductions in biomarkers of muscle damage were sustained to 24 months.

CK and TNNI2 (a specific marker of fast fiber damage), and myoglobin were reduced early and sustained over 24 months. SomaScan® analysis of ARCH samples after short-term and long-term treatment show a consistent fingerprint of decreased muscle proteins in circulation beyond CK, TNNI2, and myoglobin.[5]

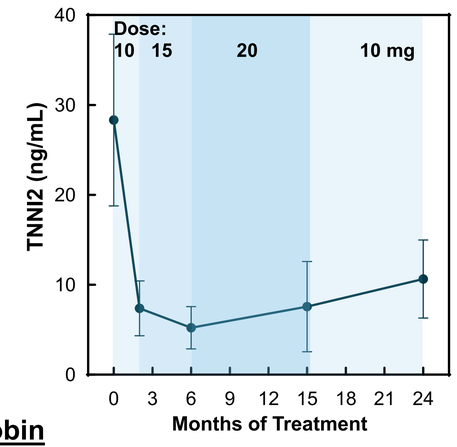
Treatment Emergent AE (seen in >1 subject)	After One Year	After Two Years
COVID-19	4	5
Fall*	3	4
Dizziness	4	4
Arthralgia	4	4
Nasopharyngitis	3	3
URI	3	3
Procedural pain	2	3
Headache	3	3
Somnolence	3	3
GERD	2	3
Influenza	2	3
Sinusitis	2	2

*Falls are typical for Becker patients and are not related to dizziness

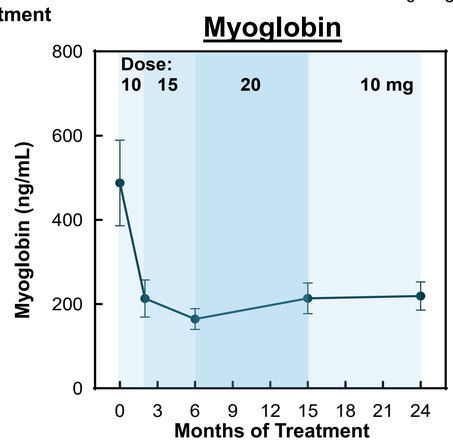
Creatine Kinase (CK)



Fast Skeletal Muscle Troponin I (TNNI2)



Myoglobin



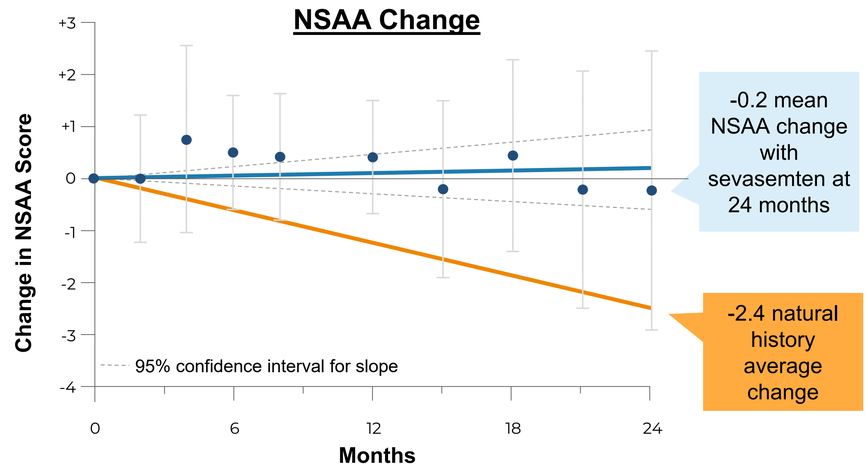
All graphs - mean ± SEM

Results

Comparison of NSAA change with natural history

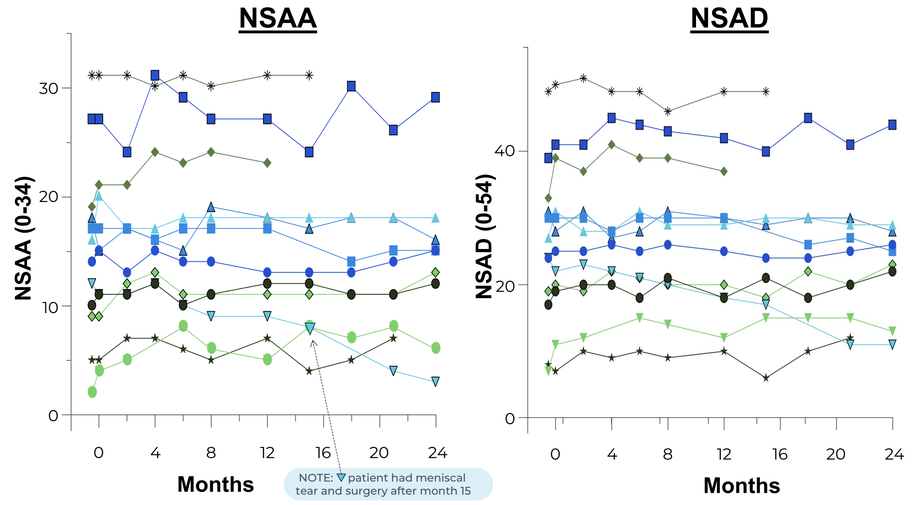
With sevasemten treatment, NSAA stabilized diverging from natural history at 24 months.[4,5,6]

NSAA Change



Individual NSAA and NSAD Scores

Individual NSAA and NSAD trajectories show stability.

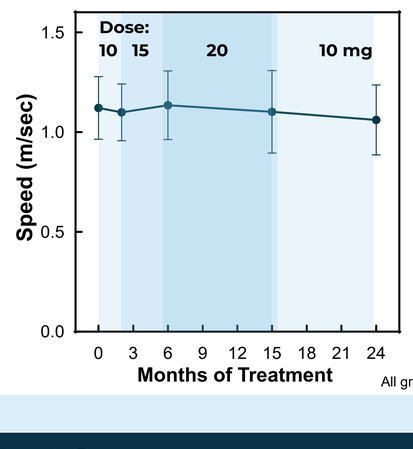


Meniscal tear and surgery procedure was unrelated to the study.

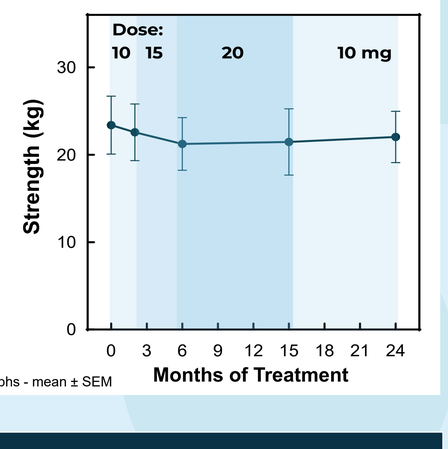
Hand grip strength and measures of endurance

The 100-meter timed test velocity and maximum grip strength was consistent across doses with no statistically significant change over 24 months.[5]

100-Meter Timed Test Velocity



Maximum Grip Strength



All graphs - mean ± SEM

Conclusions & Next Steps

- After 24 months, sevasemten was well-tolerated and demonstrated rapid, sustained and significant decreases in multiple biomarkers of muscle damage along with stable NSAA and NSAD trajectories.
- These results support the design of the pivotal GRAND CANYON study (NCT05291091), an 18-month trial to evaluate the effects of sevasemten on safety and functional measures in individuals living with Becker. It is anticipated to enroll 120 adult males with Becker in about 50 sites across the US and Europe.

References

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Disclaimer
Sevasemten (EDG-5506) is an investigational drug that is not approved in any territory. The authors are employees or consultants for Edgewise Therapeutics and may hold stock and/or stock options.

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