Functional and Muscle Damage Biomarker Changes Following Treatment with EDG-5506, a Fast Myosin Modulator, in Adults with Becker Muscular Dystrophy (Becker)

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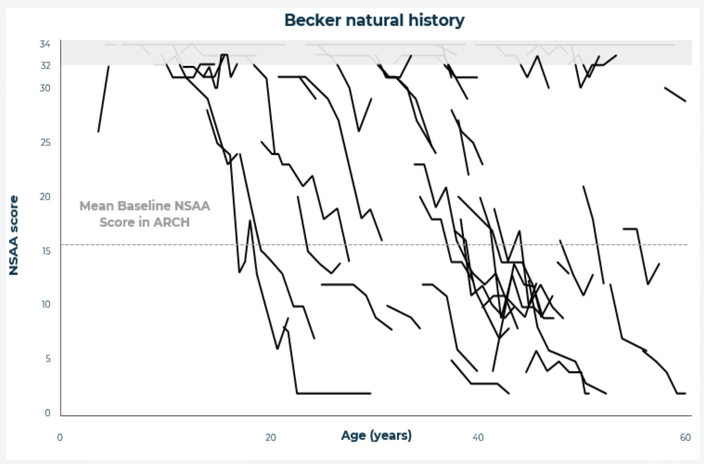
Background

Becker is a severe, underappreciated condition with major unmet medical need and no standard of care. Becker can lead to relentlessly progressive loss of motor function and individuals with Becker lose mobility, function and independence in their prime. No therapy has ever been approved specifically for Becker.[1]

In healthy muscle, dystrophin connects contractile proteins to the membrane and surrounding matrix to protect against contraction-induced injury. 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]

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

EDG-5506 prevents contraction-induced damage and fiber breakdown in mouse dystrophic muscle[3]



The Padova Becker Natural History Study, the most comprehensive study of its kind to date, demonstrates that NSAA decline is consistent in Becker patients who are already progressing. Becker patients with an NSAA score of 10-32 experience a mean 1.2 yearly decline.[4]

Baseline NSAA Score	Estimated Yearly Change	Standard Error	P-value
33-34	-0.03	0.01	NS
10-32	**-1.22**	**0.07**	**<0.0001**

Methods

Study Design

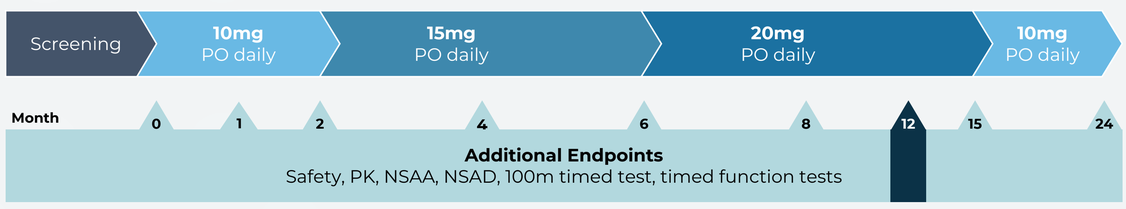
The ARCH study (NCT05160415) is a 24 month phase 1b open-label study of safety, PK and biomarkers in 12 adults with Becker, with a 12 month interim analysis. Biomarker sampling and functional assessments, including North Star Ambulatory Assessment (NSAA), and 100m test were assessed at regular intervals (below).

Key Inclusion Criteria

Ambulatory males aged 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%



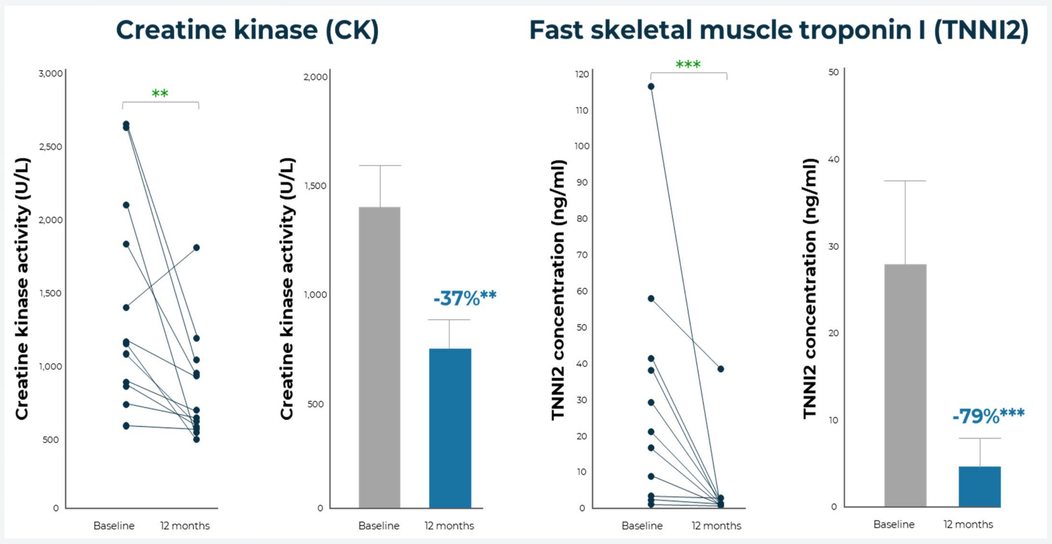
Results

EDG-5506 was well-tolerated and there were no serious adverse events and no withdrawals or dose reduction due to adverse events.

Consistent with the phase 1 study, dizziness (n=4, 33%) and somnolence (n=3, 25%) were among the commonest AE. These occurred early in dosing/dose escalation, generally resolved within a few days and were mitigated by dosing at night.[5]

EDG-5506 treatment was associated with rapid, significant and sustained reduction in biomarkers of muscle damage in adults with Becker treated for 12 months.[5]

At 12 months, CK was reduced by a mean of 37% and TNNI2 – a specific marker of fast fiber damage, was reduced by 79%. SomaScan analysis of ARCH samples after short-term and long-term treatment show a consistent fingerprint of decreased muscle proteins in circulation beyond CK and TNNI2. In addition, average pain scores were reduced across all doses.[5]

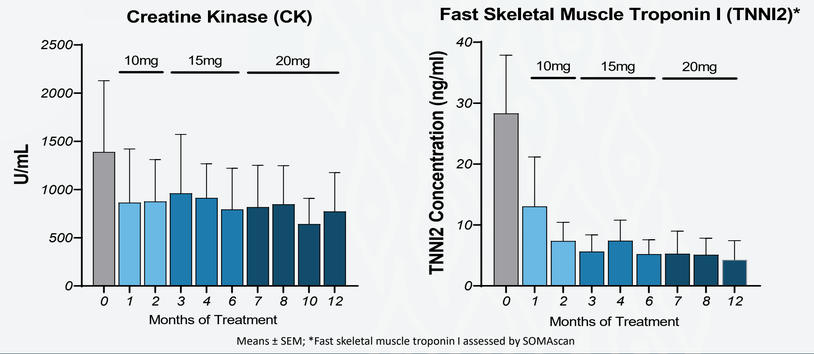


TNNI2 data projected from SOMAscan; % difference from mean baseline shown; All graphs - mean +/- SEM (**p=0.001 and ***p<0.0001)

Results (Continued)

Biomarkers of muscle damage show near maximal decrease at 2 months of 10mg daily dosing

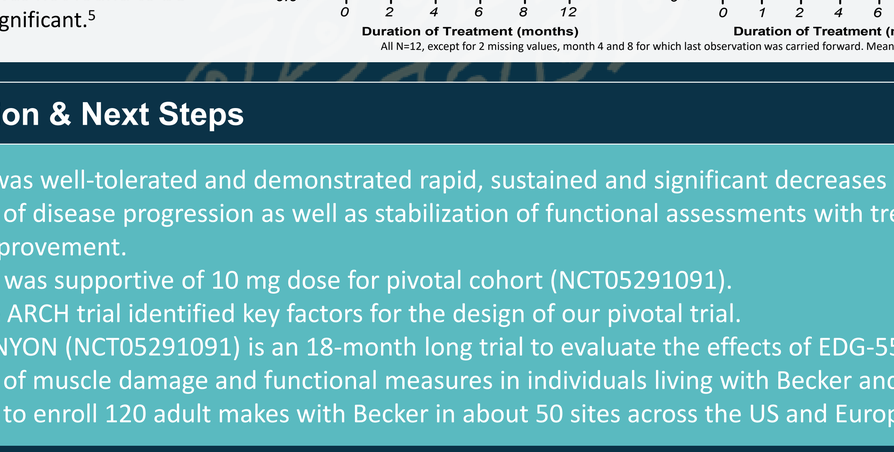
The decrease associated with the 10mg dose supported the selection of 10mg as the dose in our pivotal GRAND CANYON trial (NCT05291091).[5]



Means ± SEM; *Fast skeletal muscle troponin I assessed by SOMAscan

With EDG-5506 treatment, NSAA diverged from natural history

Over 12 months, North Star Ambulatory Assessment (NSAA) shows stabilization (mean increase 0.4 points) and a divergence from expected natural history (1.2-point decline).[4,6]



No significant change over 12 months in grip strength or 100m timed test

The 100-meter timed test velocity was consistent across doses with no statistically significant change, and although the maximum grip strength does show a decrease at 8 months, it was not found to be statistically significant.[5]

All N=12, except for 2 missing values, month 4 and 8 for which last observation was carried forward. Mean ± SEM.

Conclusion & Next Steps

- EDG-5506 was well-tolerated and demonstrated rapid, sustained and significant decreases in multiple biomarkers of disease progression as well as stabilization of functional assessments with trends towards improvement.
- PK/PD data was supportive of 10 mg dose for pivotal cohort (NCT05291091).
- Overall, the ARCH trial identified key factors for the design of our pivotal trial.
- GRAND CANYON (NCT05291091) is an 18-month long trial to evaluate the effects of EDG-5506 on biomarkers of muscle damage and functional measures in individuals living with Becker and is anticipated to enroll 120 adult makes with Becker in about 50 sites across the US and Europe.

References

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Disclaimer
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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