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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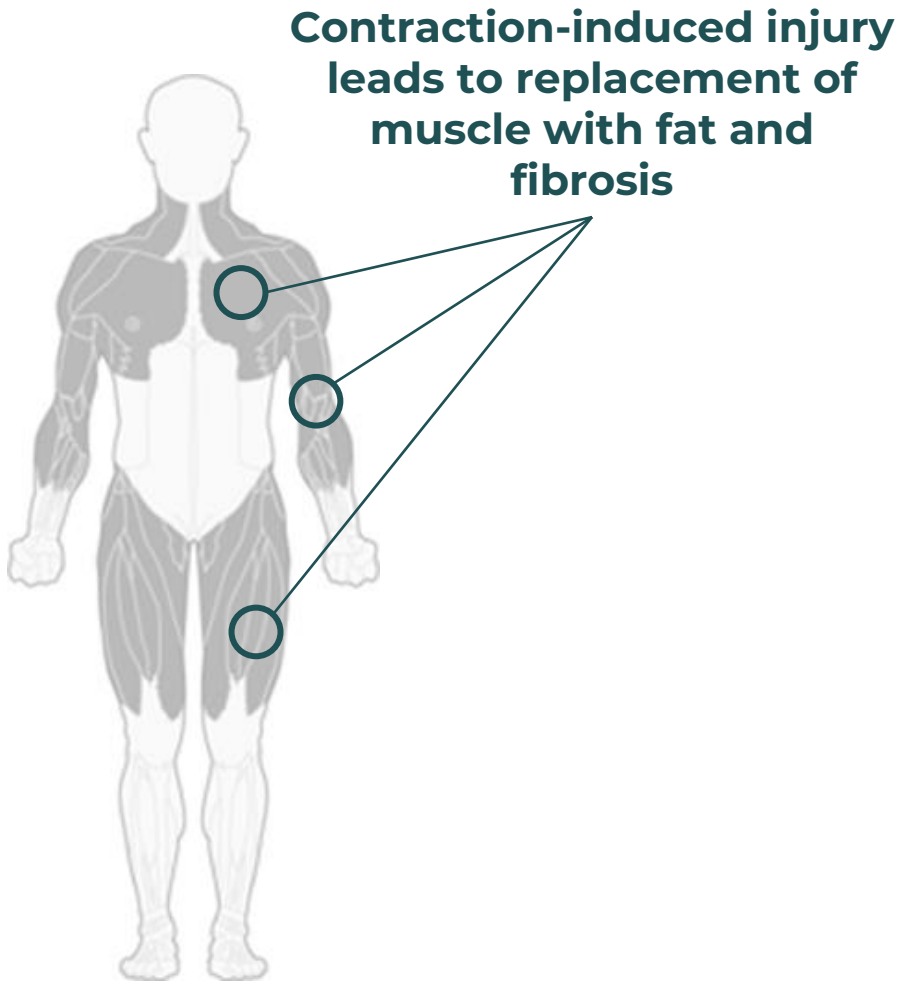
Disclosures

- **Han Phan** serves as principal investigator for Edgewise, Sarepta, Fibrogen, Capricor, Harmony, Scholar Rock, Dyne, Avidity, and Pepgen.
- Other authors are employees of Edgewise and may own stock.
- **EDG-5506** is investigational and not approved in any territory.

Becker is a severe, underappreciated condition with major unmet medical need and no standard of care

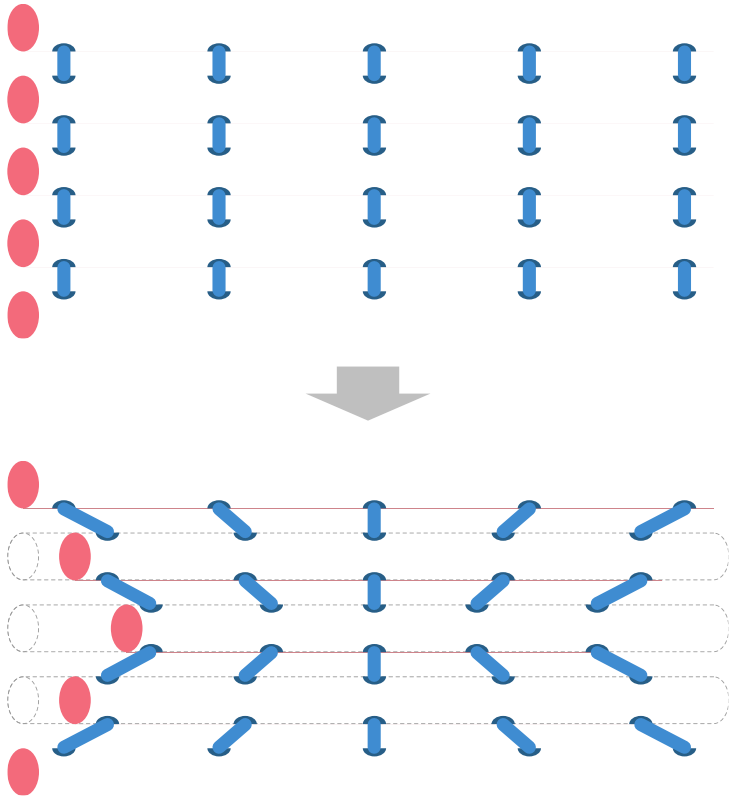


- No approved therapy specifically for Becker
- Becker can lead to relentlessly progressive loss of motor function
- Individuals with Becker lose mobility, function and independence in the prime of their lives

Reference: Straub V, Guglieri M. Curr Opin Neurol, 2023.

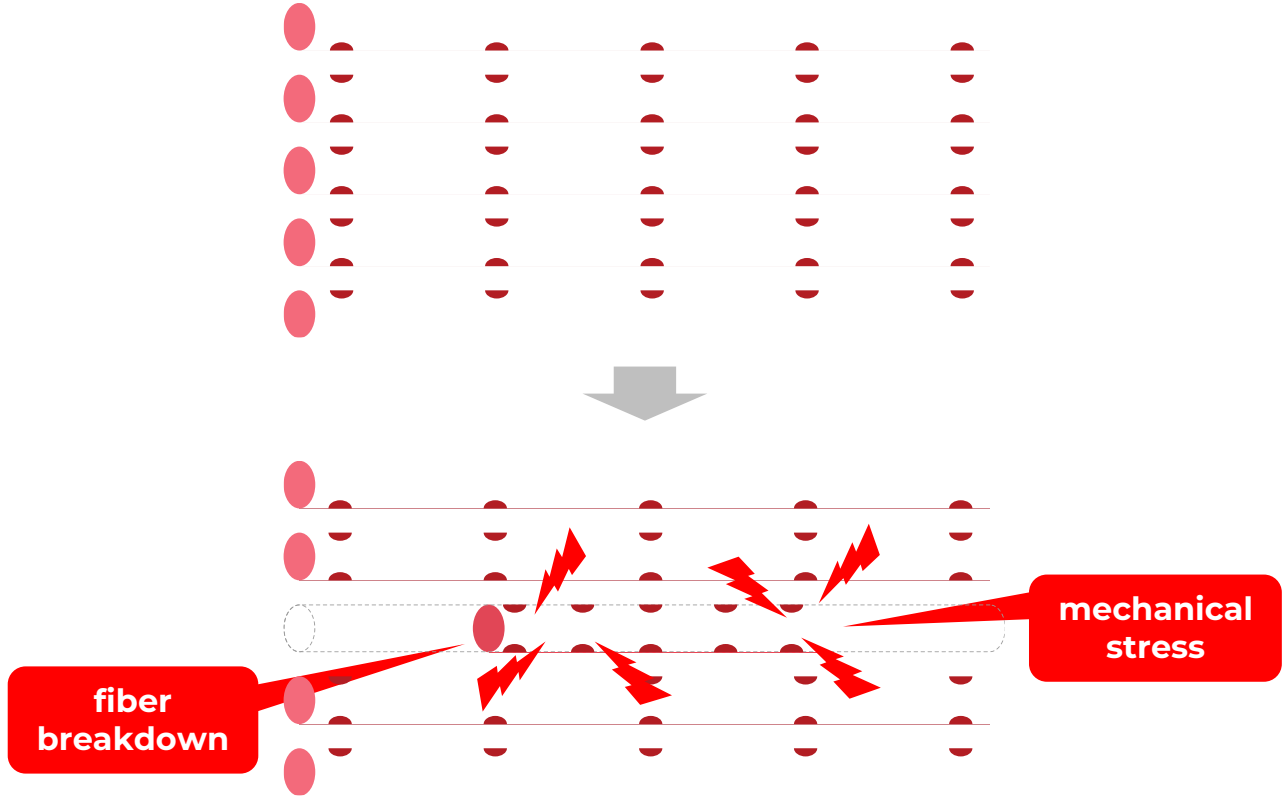
In Becker, **fast muscle fibers** are disproportionately injured by contraction

Healthy muscle contraction



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

Becker muscle contraction



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

EDG-5506 targets fast myosin to protect dystrophic muscle against contraction-induced injury in mouse models

Contracting at 100% without EDG-5506

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

Contracting at 85% with EDG-5506

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

Both videos have been sped up 3x

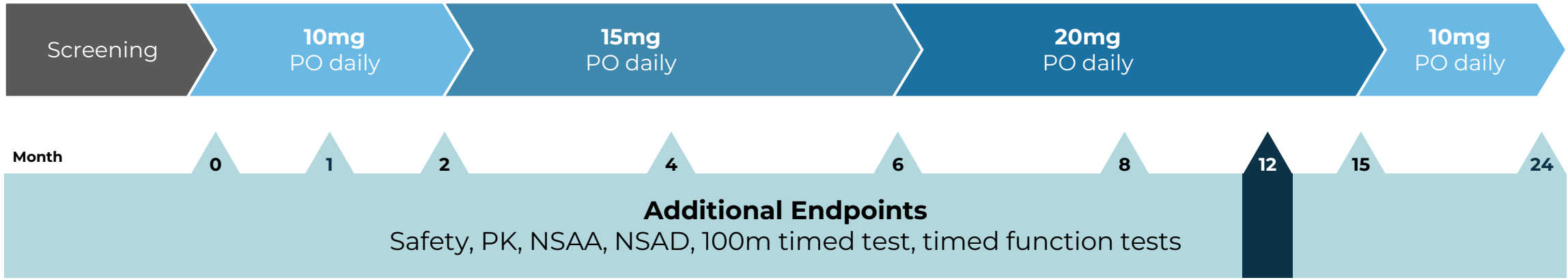
Reference: Russell AJ, et al. J Clin Invest. 2023;133(10):e153837. doi:10.1172/JCI153837

ARCH

An open-label, single-center study to assess EDG-5506 safety and pharmacokinetics in adults with Becker

- **Primary objective:** Safety and tolerability at 12 months (now extended to 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: NCT05160415

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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%

Abbreviations: DXA, dual energy x-ray absorptiometry
Reference: Data on file

ARCH EDG-5506 was **well-tolerated at all doses**

	NUMBER OF PATIENTS REPORTING >1 AE AFTER 12 MONTHS OF DOSING
Dizziness	4 (33%)
COVID-19	4 (33%)
Arthralgia	4 (33%)
Somnolence	3 (25%)
Headache	3 (25%)
Nasopharyngitis	3 (25%)
Fall*	3 (25%)
Viral URI	3 (25%)
Influenza	2 (17%)
Sinusitis	2 (17%)
GERD	2 (17%)
Procedural pain	2 (17%)

No dose reductions/ adjustments, treatment discontinuations, or SAEs

* Unassociated with other AEs and typical of falls observed in Becker patients
Reference: Data on file

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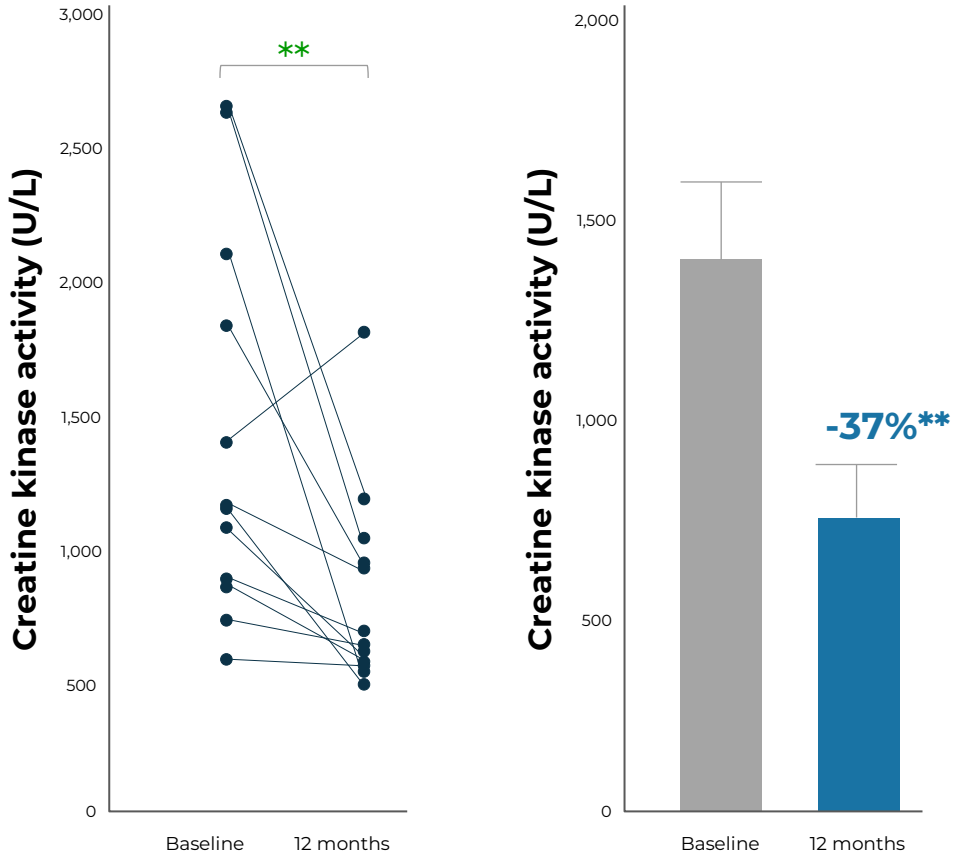
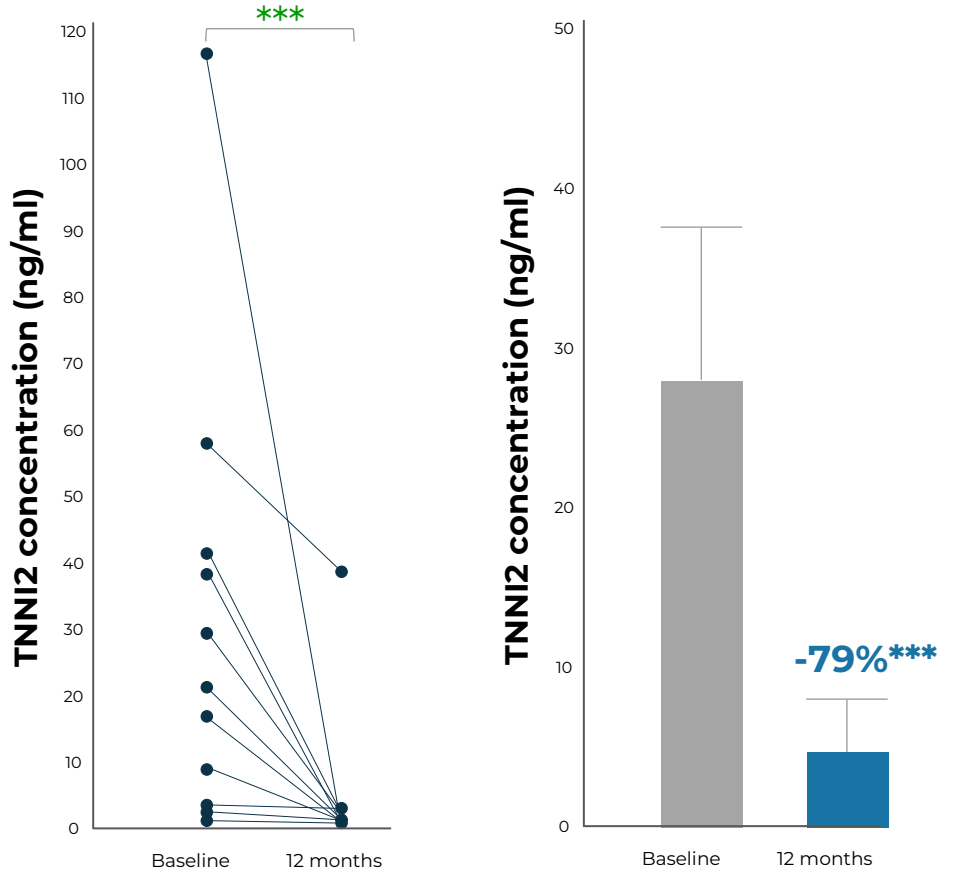
EDG-5506 led to a **sustained decrease in biomarkers of muscle damage** after 12 months of dosing

Creatine kinase (CK)

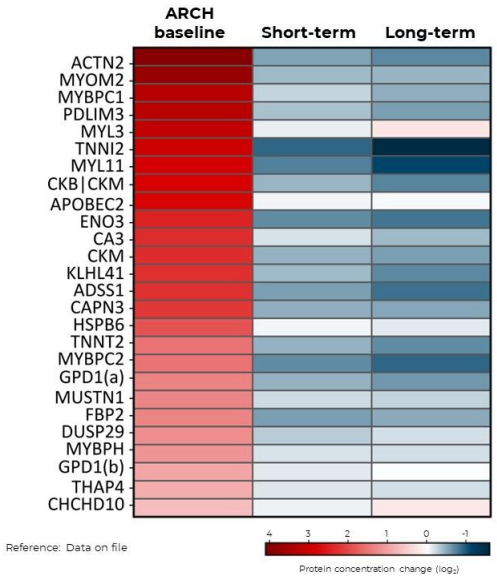


Fast skeletal muscle troponin I (TNNI2)



TNNI2 data projected from SOMAscan; % difference from baseline shown; Means ± SEM (**p=0.001 and ***p<0.0001)
Reference: Data on file

With EDG-5506, a broad range of muscle injury proteins beyond CK and TNNI2 were decreased



SomaScan® analysis of ARCH samples show a consistent circulating fingerprint of muscle damage biomarkers beyond CK and TNNI2

Please refer to Poster M145: "Characterization of Short- and Long-Term Proteomic Response to the Fast Skeletal Myosin Inhibitor, EDG-5506, in BMD"

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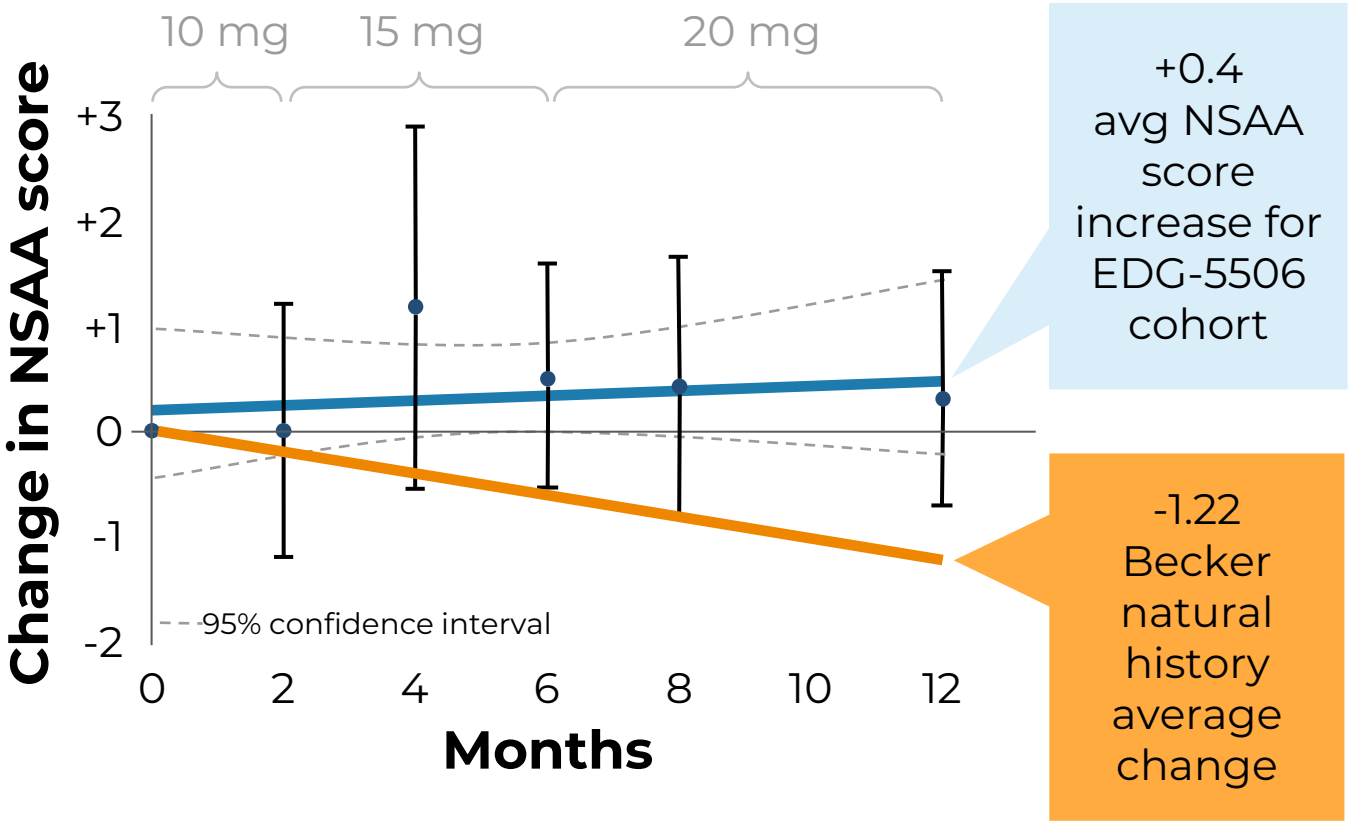
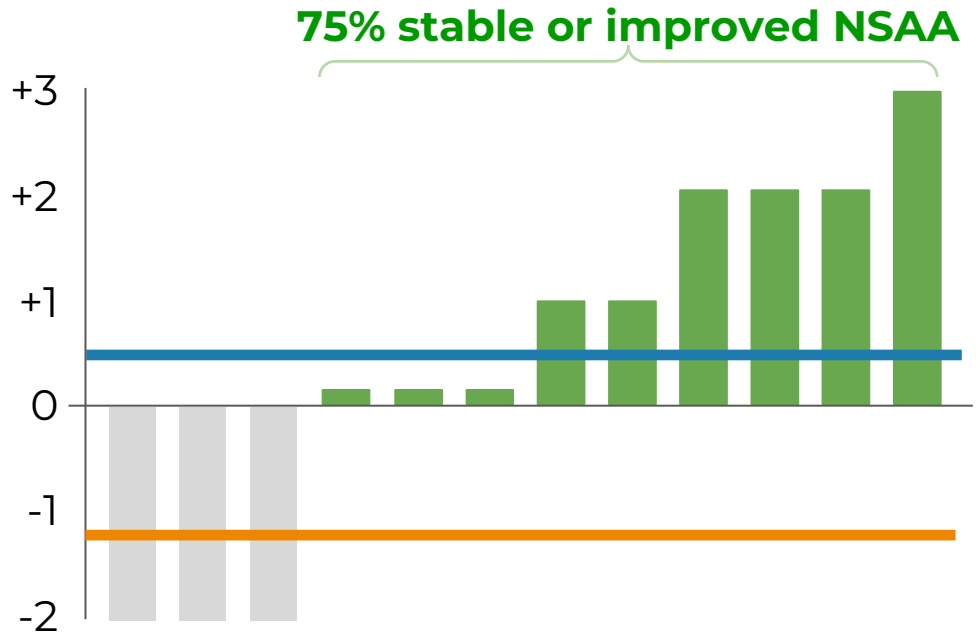
NSAA mean +0.4 improvement relative to -1.2 point predicted by natural history

NSAA change over 12 months



Individual ARCH participant NSAA responses at 12 months



Means ± 95% CI; Natural history based on data presented by Bello at MDA (2022) and van de Velde NM et. al., Neurology, 2021
Abbreviations: NSAA, North Star Ambulatory Assessment
Reference: Data on file

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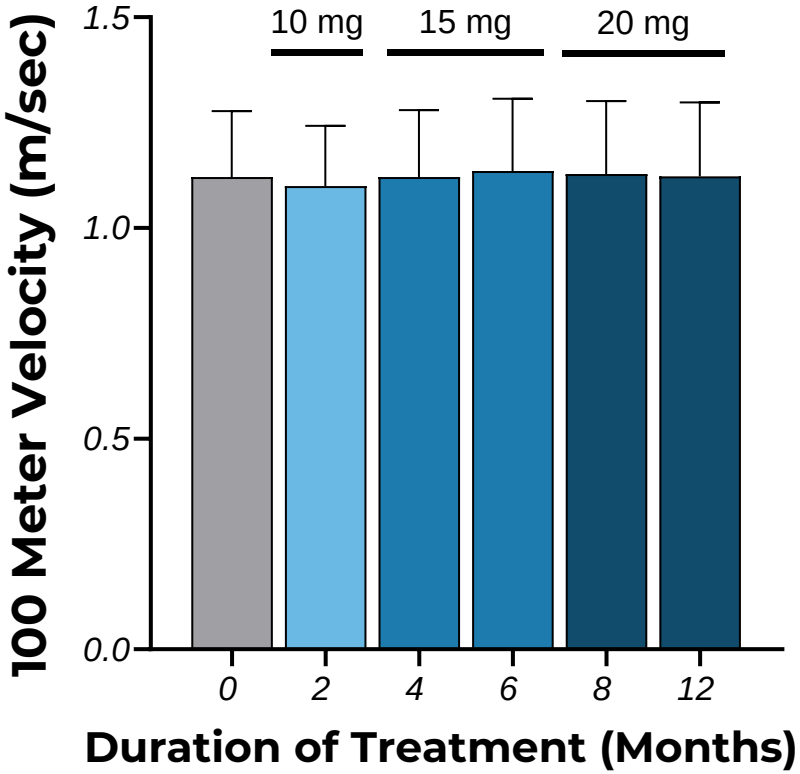
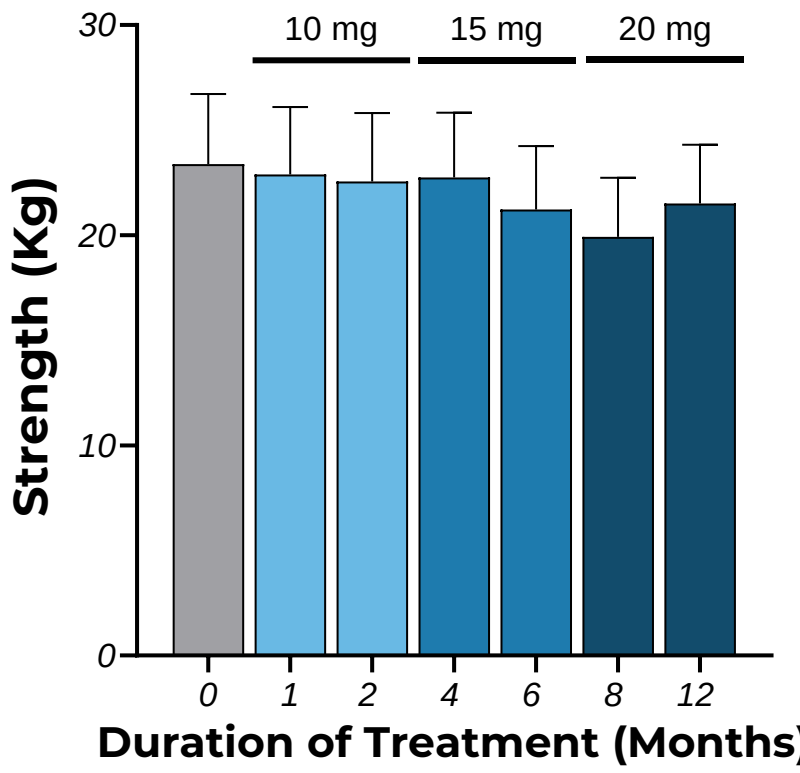
No decline from baseline at 12 months on other functional endpoints

100-Meter Timed Test Velocity



No statistically significant change at 12 months

Maximum Grip Strength



No statistically significant change at 12 months

All N=12, except for 2 missing values, month 4 and 8 for which last observation was carried forward)
Mean ± SEM
Reference: Data on file

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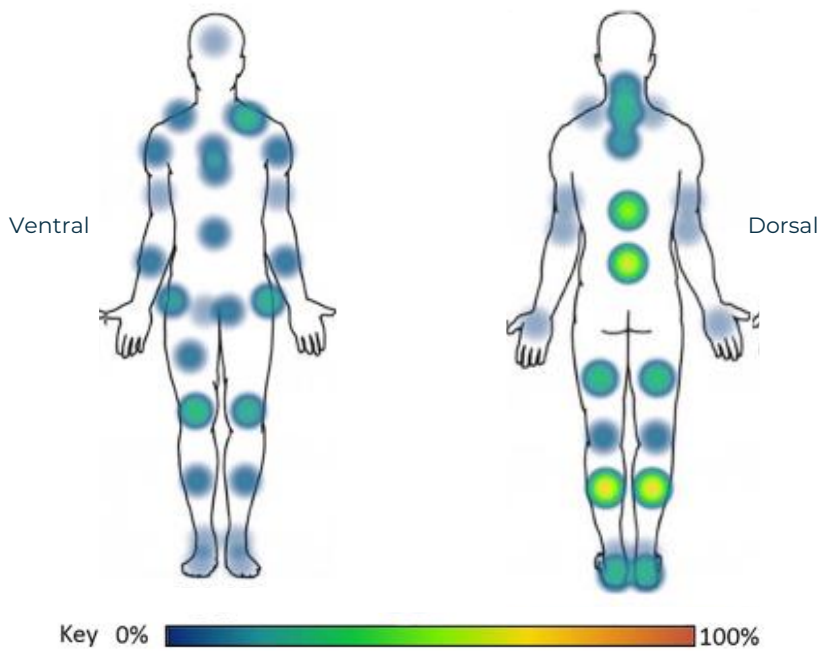
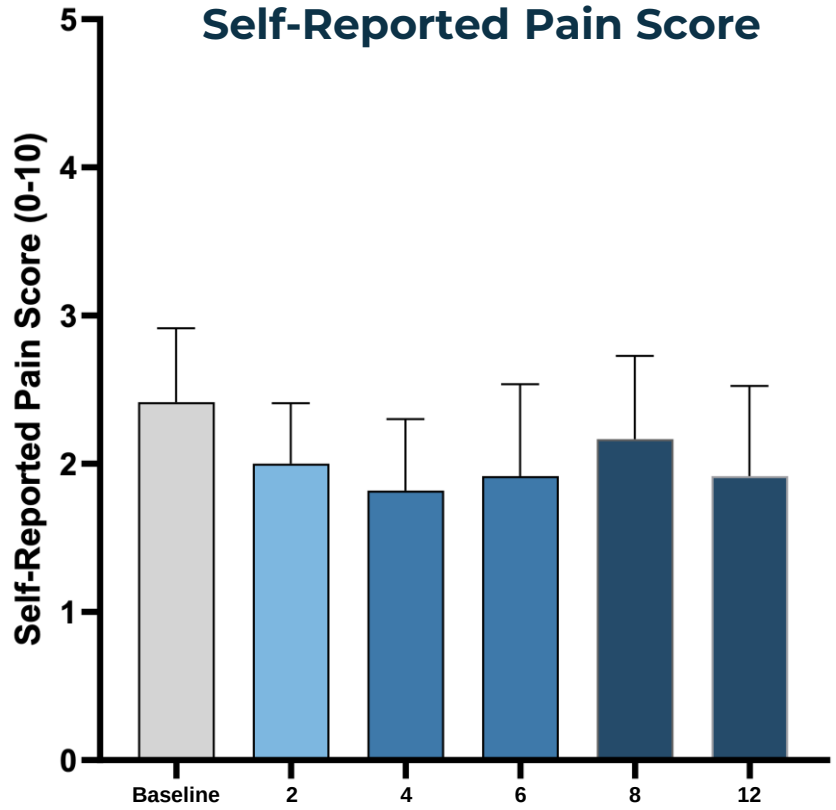
Self-reported pain scores trended better after 12 months with EDG-5506

Becker individuals report diffuse pain, particularly in back and calves





While the ARCH study is not placebo controlled, a positive trend in self-reported pain scores was observed after 12 months of EDG-5506 dosing

Means ± SEM;
References: 1. Data on file; 2. Jacques MF, et. al., 2019, PLOS ONE

ARCH Outcomes of the ARCH study

Safety	Biomarkers	Function	Pivotal dose identified
Well-tolerated at all doses	Demonstration of **rapid, sustained and significant decreases** in multiple biomarkers of muscle damage	**Stabilization of functional assessments** with trends toward improvement	Maximal biomarker response at 10 mg dose PK/PD supportive of **10 mg dose for pivotal cohort** (NCT05291091)

Overall, the ARCH trial identified key factors for the design of a potentially registrational trial

GRAND CANYON Pivotal study in Becker

An 18-month long trial to evaluate the effect of EDG-5506 on efficacy and safety in individuals living with Becker

Key inclusion criteria:

- ✓ Male, ages 18-50
- ✓ Mutation in *DMD* gene with Becker phenotype
- ✓ Ambulatory with NSAA between 5 and 32

Anticipated to enroll 120 adult males diagnosed with Becker in the US and Europe

*NCT05291091

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Appendix

Edgewise THERAPEUTICS

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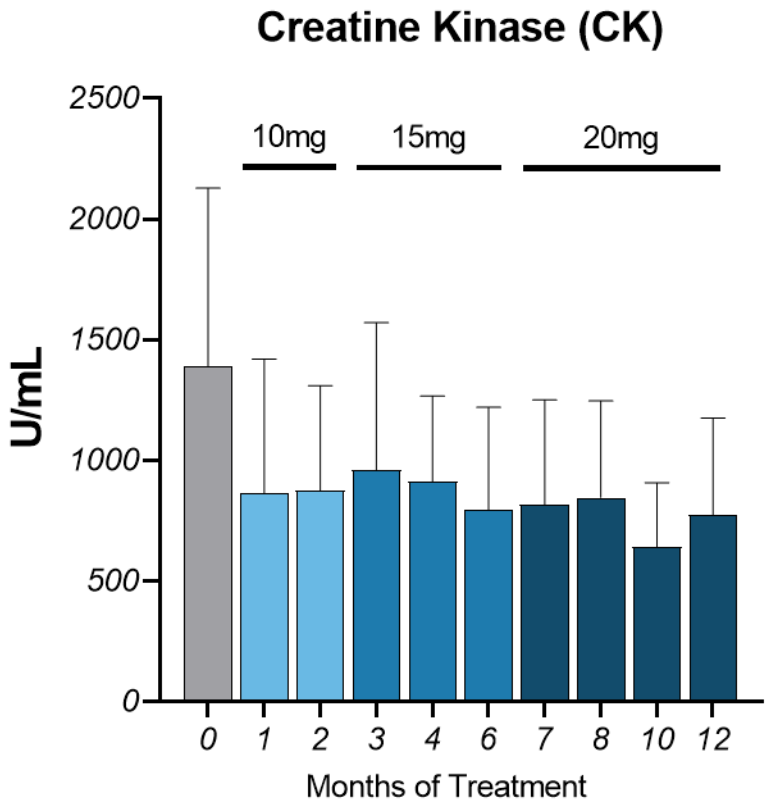
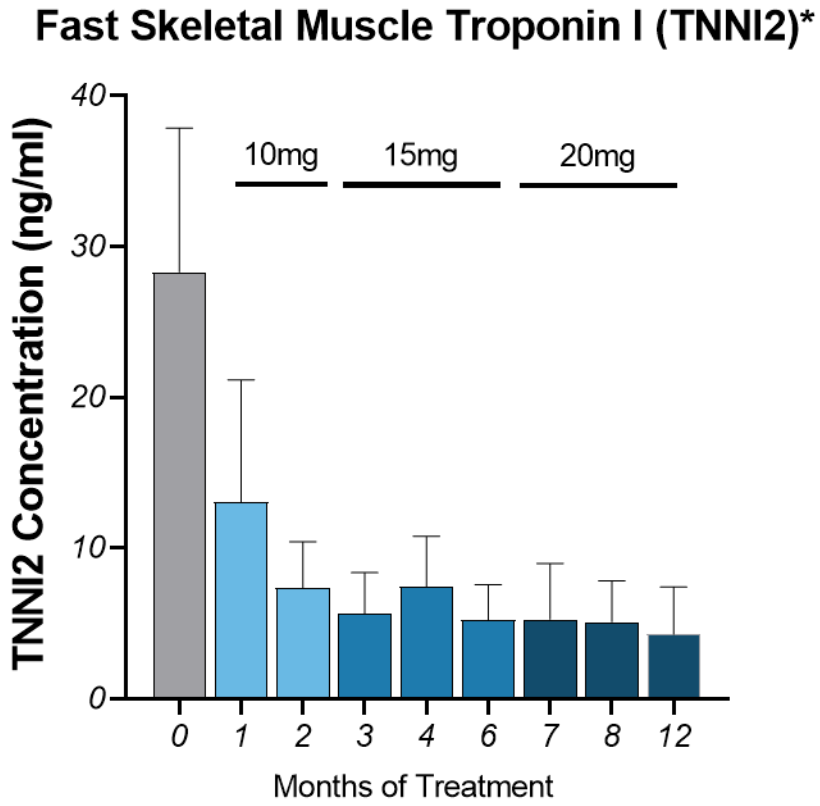
Biomarkers of muscle damage show **near maximal decrease at 2 months** of 10 mg daily dosing





Rapid, significant and sustained decreases in biomarkers of muscle damage

Means ± SEM; * Fast skeletal muscle troponin I assessed by SOMAscan
Reference: Data on file