EDG-5506 Targets Fast Skeletal Myosin to Protect Dystrophic Muscle and Reduce Muscle Damage Biomarkers in a Phase 1 Trial in Becker Muscular Dystrophy (BMD)

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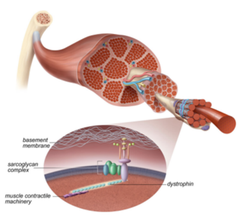
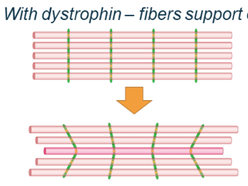
Dystrophin Protects Muscles from Stress During Contraction Rather than Powering Contraction

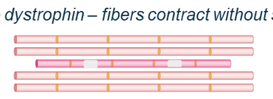
Dystrophin connects contractile proteins to the membrane and surrounding matrix of fibers



With dystrophin – fibers support each other



No dystrophin – fibers contract without support

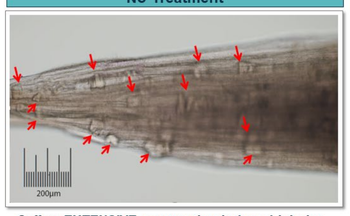


Loss of muscle leads to a loss of function

EDG-5506 Aims to Prevent Contraction-Induced Damage in Dystrophic Muscle

- Fast (Type II) muscle fibers are affected early and disproportionately in BMD and DMD
- EDG-5506 is a highly selective inhibitor of fast skeletal myosin ATPase, without effects on slow, cardiac, or smooth muscle myosin

DMD Muscle (*mdx* mouse)
No Treatment



Suffers **EXTENSIVE contraction-induced injuries**

DMD Muscle (*mdx* mouse)
Treated with 0.3 µM EDG-5506

Contraction-induced injuries COMPLETELY prevented

Claflin, Su and Brooks. U Michigan

mdx mouse lumbrical muscle – 20, 1 second maximal isometric contractions (video sped up)

EDG-5506 Phase 1 Study Conducted in Healthy Volunteers and Participants with Becker Muscular Dystrophy

Healthy Volunteers

- Single Ascending Doses: up to 135 mg, administered as suspension
- Multiple Ascending Doses: up to 40 mg/day, administered as suspension or solid dose form for 14 days

Subjects with Becker Muscular Dystrophy

- Multiple Doses: 20 mg/day, administered as solid dose form for 14 days
- Participants were monitored as inpatients for 16 days, with follow-up 1 and 4 weeks after completion of dosing.

Primary Endpoints
- Safety and tolerability

Secondary/Exploratory Endpoints
- Pharmacokinetics, pharmacodynamics
- Assess target tissue engagement judged by muscle/plasma ratio in BMD
- Measurement of serum biomarkers of muscle damage in BMD: CK, fast troponin (TNNI2), myoglobin and SOMAscan, a proteomic panelC

In healthy volunteers, well tolerated, well absorbed, extended half life of ~17 days

In BMD, well tolerated, well absorbed,

Participants in the BMD Phase 1b Had Significant Baseline Functional Impairment

Characteristic	BMD Participants (N=7)	Age Normative Values
Age	33.8 years	
Functional Measures (median)		
10-meter walk/run	8.3 sec	< 4 sec
Rise from floor	20 sec	< 3 sec
Serum Creatinine (mean, mg/dL)	0.58	0.92 - 1.16
Serum Creatine Kinase (mean CK, U/L)	1,347	< 205

- Functional tests show significantly compromised or lost function
- Low creatinine consistent with decreased muscle mass
- Elevated CK levels reflect ongoing muscle damage

EDG-5506 was Well-Tolerated in BMD Subjects

TEAE	Placebo N=2 n (%)	EDG-5506 (20 mg) N=5 n (%)	Total N=7 n (%)
Any TEAE	**2 (100%)**	**5 (100%)**	**7 (100%)**
Dizziness	2 (100%)	5 (100%)	7 (100%)
Euphoric mood	0	2 (40%)	2 (29%)
Musculoskeletal stiffness	0	2 (40%)	2 (29%)
Somnolence	0	2 (40%)	2 (14%)
Diarrhea	0	1 (20%)	1 (14%)
Nausea	0	1 (20%)	1 (14%)
Fatigue	0	1 (20%)	1 (14%)
Vessel puncture site bruise	0	1 (20%)	1 (14%)
Back pain	0	1 (20%)	1 (14%)
Pain in jaw	0	1 (20%)	1 (14%)
Headache	0	1 (20%)	1 (14%)
Presyncope	0	1 (20%)	1 (14%)
Nasal congestion	0	1 (20%)	1 (14%)
AEs of special interest	**0**	**0**	**0**

- No SAEs
- No discontinuations
- All AEs were mild (Grade 1); AEs were transient and generally declined with increasing exposure

EDG-5506 Concentrates in Both Healthy and Dystrophic Muscle, Demonstrating Delivery of Drug to the Target, Fast Myosin

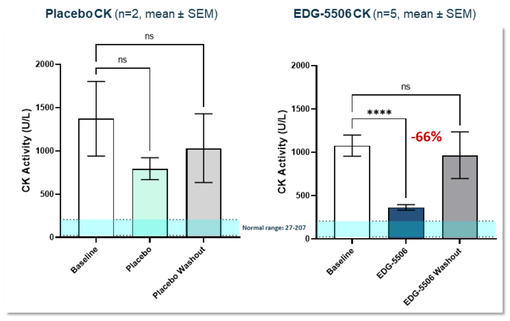
		Daily Dose	Muscle (ng/g)*
Liquid Formulation	Healthy Adults	5 mg*	980
	Healthy Adults	10 mg*	2,740
	Healthy Adults	20 mg	4,360
Solid Dosage Form	Healthy Adults	20 mg	6,140
	Healthy Adults	40 mg	6,570
	Becker Muscular Dystrophy	**20 mg**	**5,155****

* Concentrations after 14 days are estimated to be half of steady state
** vastus lateralis biopsy levels adjusted for ~60% fat fraction in BMD subjects

Target human muscle exposure range: 1,000-4,100 ng/g

* for 10 days, after dose of 10 and 20 mg for 4 days, respectively

Key Biomarkers of Muscle Damage Significantly Decreased with EDG-5506

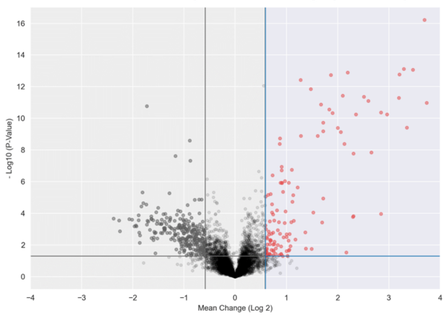


Data on file; Average shown for Days 8-14; % difference from mean baseline shown. Washout at Day 42

- CK significantly decreased with EDG-5506 treatment, approaching normal range
- Modest placebo decrease with known effect on CK with limited activity during study confinement
- AST and myoglobin also decreased with EDG-5506 treatment to approach the normal range

Using SOMAscan 7,000 Analyte Set, A Proteomic Signature for BMD Was Identified

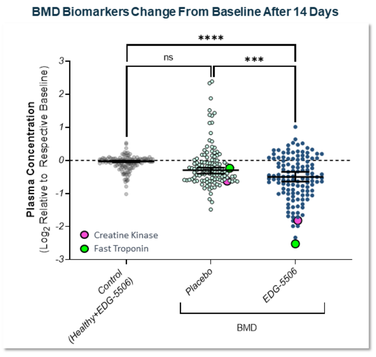
Baseline BMD vs. Healthy Biomarker Fingerprint Analysis



- SOMAscan allows unbiased protein profiling of elevated plasma markers in BMD
- Baseline plasma samples (n=7) were compared to baseline samples taken from HVs (n=25)
- Proteins filtered by magnitude of change (≥1.5X) and adjusted *p* value (<0.05) vs. HV
- Baseline analysis identified a fingerprint of elevated proteins in BMD
- Most significant proteins are from muscle and metabolic pathways consistent with muscle injury

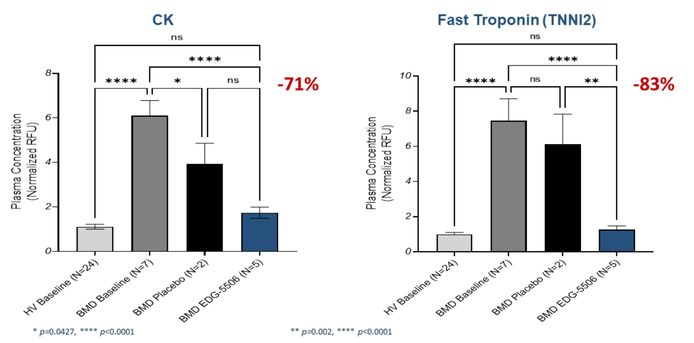
The Majority of BMD Signature Proteins are Lowered by EDG-5506

BMD Biomarkers Change From Baseline After 14 Days



- BMD proteomic fingerprint unchanged in control group following EDG-5506 treatment
- BMD participants treated with EDG-5506, saw a significant decrease in proteins elevated at baseline, both relative to the control group and to BMD participants on placebo

With SOMAscan CK and Fast Troponin Reduced to Levels Near Those Observed in HVs Following Treatment with EDG-5506



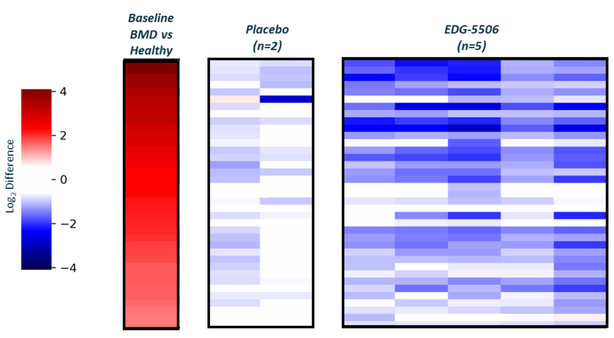
* p=0.0427, **** p<0.0001

** p=0.002, **** p<0.0001

Mean ± SEM

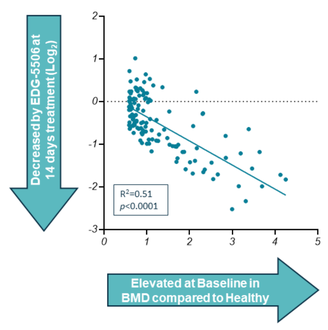
Biomarkers Most Elevated in BMD are Decreased Most with EDG-5506

Change in Most Elevated BMD Biomarkers with 14 Days EDG-5506 Treatment



Universal response across treated individuals with greatest decrease in the most elevated biomarkers

Elevated Biomarkers Decrease Most Following EDG-5506



- Close association of elevated BMD biomarkers with EDG-5506 response reveals a significant relationship to biomarker lowering
- Overall, this suggests a broad normalization of the BMD proteomic signature rather than a change in just a subset of biomarkers

ARCH

Principal Investigator: Han Phan, MD
Rare Disease Research, Atlanta GA

One Year Open-Label Study Design

- An open-label, single-center study of EDG-5506 to assess the safety and pharmacokinetics (PK) of EDG-5506 in adults with Becker muscular dystrophy (BMD)
  - 12 patients enrolled, ambulatory with BMD, including all from Phase 1 study

Screening
Biomarkers, NSAA, NSAD, Timed Function Tests

→ EDG-5506 10 mg/day for **2 months**

→ All participants dose-escalated to 15 mg/day* EDG-5506

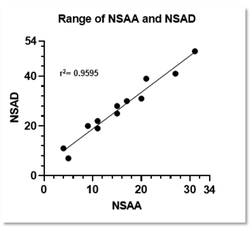
** Protocol allows subsequent dose adjustment after 4 months at 15 mg dose*

Participants in the BMD Open-Label Study Had Significant Baseline Functional Impairment

BMD Patients in Open Label Study Had Significant Functional Impairment and Decreased Muscle Mass at Baseline

Characteristic	BMD Participants (N=12)	Age Normative Values
Age	32.8 (8.1) years	
Functional Measures (median)		
10-meter walk/run	8.4 sec	< 4 sec
Rise from floor	6/12 could perform	< 3 sec
Serum Creatinine (mean, mg/dL)	0.44	0.92 - 1.16
Serum Creatine Kinase (mean CK, U/L)	1,390	<210
DXA % Lean Mass	54.9%	~75%

BMD patients had an NSAA range from 4-31



EDG-5506 Continued to be Well-Tolerated in BMD Subjects

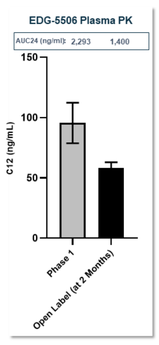
TEAE	EDG-5506 (10 mg) N=12 n (%)
Any TEAE	**7 (58%)**
Dizziness	2 (17%)
Somnolence	2 (17%)
Toothache	1 (8%)
Viral Gastroenteritis	1 (8%)
Back pain	1 (8%)
Flushing	1 (8%)
Procedural pain	1 (8%)
Nasopharyngitis	1 (8%)

- All AEs were mild
- Onset typically in first few days, generally transient
- Dosed at night to mitigate drowsiness

Key Differences Between Phase 1 and Open Label Study

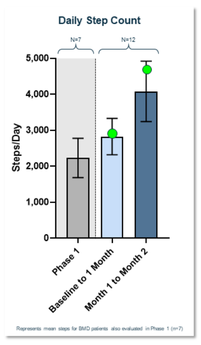
Exposure Levels:

- *Lower because the EDG-5506 dose was lower in ARCH*
- *Lower due to a shorter half life in BMD patients likely associated to decreased overall muscle mass*

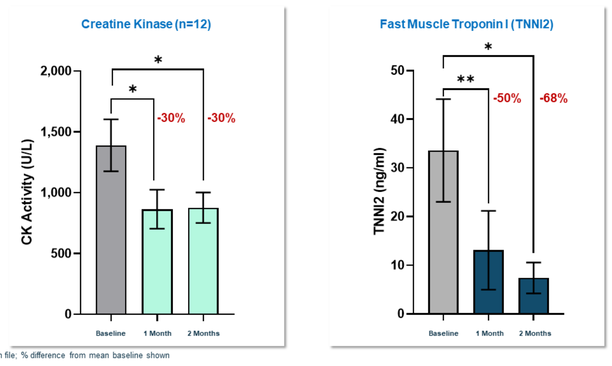


Activity level:

- *Unlike in the Phase 1 study, participants continued typical daily activity level*



2 Months of EDG-5506 Dosing Also Led to Rapid, Significant and Sustained Decrease in CK and Fast Muscle Troponin in BMD Patients



Source: Data on file; % difference from mean baseline shown

Conclusions and Next Steps

- EDG-5506 has been well tolerated in healthy volunteers and subjects with Becker muscular dystrophy
- EDG-5506 is well-absorbed, with pharmacokinetics suitable for once daily dosing, either with or without food, and reaches levels in muscle at which protection from contraction-induced muscle damage was observed
- Reductions in multiple biomarkers of muscle damage were observed in adults with BMD
- By targeting fast skeletal muscle myosin to protect dystrophic muscle, EDG-5506 has potential to be a novel disease-modifying approach in DMD and BMD regardless of mutation type
- A phase 2 study in BMD is ongoing, and a phase 2 study in DMD is planned

The authors are grateful to the participants in the trial

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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