Clinical Development of EDG-5506 in Duchenne and Becker Muscular Dystrophy

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BMD and Duchenne Muscular Dystrophy (DMD) Represent Severe Dystrophinopathies

Spectrum of Severity Across Dystrophinopathies

Functional Dystrophin

Normal Levels

No Damage

Intensity of Muscle Damage

BMD and DMD represent a continuum of the same disease; Edgewise’s approach aims to treat across the disease spectrum, regardless of dystrophin mutation
Schematic of Clinical Development of EDG-5506 to Date

Phase 1 in Healthy Adults and Adults with Becker Muscular Dystrophy

ARCH Open-label Study in Becker Muscular Dystrophy

CANYON Phase 2 in Adults and Adolescents with Becker Muscular Dystrophy

LYNX Phase 2 in Children with Duchenne Muscular Dystrophy
EDG-5506 Represents a Novel, Potentially Disease-Modifying MOA for DMD and BMD

The Core Problem in Dystrophinopathies

EDG-5506

Daily mechanical stress on muscle fibers results in muscle damage

- Increased muscle injury biomarkers in plasma
- Replacement of muscle by fat and fibrosis
- Reduced muscle mass

Reduced muscle function

Preventing muscle breakdown should preserve muscle, reduce inflammation and protect/improve function in individuals with DMD/BMD
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 liquid formulation
- Multiple Ascending Doses: up to 40 mg/day, administered as liquid formulation or solid dose form for 14 days

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

**Ambulatory Subjects with Becker Muscular Dystrophy (BMD)**
- 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.

In BMD, well tolerated, well absorbed with somewhat shorter half life

**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 panel
Overview of Healthy Volunteers (HVs) Phase 1a SAD/MAD with EDG-5506

EDG-5506 was generally well tolerated with no serious adverse events observed. Most common AEs were somnolence and dizziness, which were generally mild and transient.

Plasma PK showed good oral absorption with or without food, and an extended half-life, consistent with extensive distribution to muscle as was observed preclinically.

EDG-5506 muscle concentrations well above anticipated efficacious levels.
Participants in the BMD Phase 1b Had Significant Baseline Functional Impairment

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

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

Source: Data on file
### EDG-5506 Concentrates in Healthy and Dystrophic Muscle, Demonstrating Delivery of Drug to the Target, Fast Myosin

<table>
<thead>
<tr>
<th>Liquid Formulation</th>
<th>Daily Dose</th>
<th>Muscle (ng/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Adults</td>
<td>5 mg*</td>
<td>980</td>
</tr>
<tr>
<td>Healthy Adults</td>
<td>10 mg*</td>
<td>2,740</td>
</tr>
<tr>
<td>Healthy Adults</td>
<td>20 mg</td>
<td>4,360</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solid Dosage Form</th>
<th>Daily Dose</th>
<th>Muscle (ng/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Adults</td>
<td>20 mg</td>
<td>6,140</td>
</tr>
<tr>
<td>Healthy Adults</td>
<td>40 mg</td>
<td>6,570</td>
</tr>
</tbody>
</table>

#### 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

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* Source: Data on file
Using SOMAscan 7,000 Analyte Set, a Proteomic Signature for BMD was Identified

Baseline BMD vs. Healthy Biomarker Fingerprint Analysis

- Baseline plasma samples (n=7) were compared to samples from healthy volunteers (n=25).
- Proteins filtered by magnitude of difference (≥1.5X) and adjusted p value (<0.05) vs. HV.
- Baseline analysis identified a fingerprint of 125 elevated proteins in BMD.
- Most significant proteins are from muscle and metabolic pathways consistent with muscle injury.

Source: Data on file
The Majority of BMD Signature Proteins are Lowered by EDG-5506

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

Change with 14 Days EDG-5506 Treatment

Baseline BMD vs Healthy

Placebo (n=2)

EDG-5506 (n=5)

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

Source: Data on file
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

Source: Data on file
Consistent and Progressive EDG-5506 Effect on Exercise Responsive Markers

- In adults with BMD SOMAscan samples from an exercise study were used to define a proteomic signature that was elevated compared to controls at baseline, and had an exaggerated increase with exercise.
- These proteins, largely characterized by enrichment in muscle, rapidly and progressively decreased with EDG-5506 but not with placebo.

Source: Data on file
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

<table>
<thead>
<tr>
<th>Screening</th>
<th>EDG-5506 10 mg/day for 2 months</th>
<th>EDG-5506 15 mg/day for 4 months</th>
<th>After 6 months all participants dose-escalated to 20 mg/day EDG-5506</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarkers, NSAA, NSAD, Timed Function Tests</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- EDG-5506 10 mg/day for 2 months
- EDG-5506 15 mg/day for 4 months
- After 6 months all participants dose-escalated to 20 mg/day EDG-5506
Participants in the BMD Open-Label Study Had Significant Baseline Functional Impairment

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

BMD patients had an NSAA range from 4-31

![Range of NSAA and NSAD](image)

Source: Data on file
Functional Measures Correlate with Measures of Muscle Mass

100 m walk/run vs. NSAD

100 m walk/run vs. creatinine

% Lean Body Mass vs. NSAD

Source: Data on file
EDG-5506 Continued to be Well Tolerated After Four Months of Dosing with the 15 mg Dose; Six Months Total Dosing

<table>
<thead>
<tr>
<th>Treatment Emergent AEs</th>
<th>2-month (%); 10 mg EDG-5506</th>
<th>4-month period (%); 15 mg EDG-5506</th>
<th>Total 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>2 (17%)</td>
<td>1 (8%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (17%)</td>
<td>1 (8%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>3 (25%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Fall*</td>
<td>-</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Gastroenteritis virus</td>
<td>1 (8%)</td>
<td>-</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Arthropod sting</td>
<td>-</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (8%)</td>
<td>-</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Concussion</td>
<td>-</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Euphoric mood</td>
<td>-</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (8%)</td>
<td>-</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Hiccups</td>
<td>-</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (8%)</td>
<td>-</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>1 (8%)</td>
<td>-</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Road traffic accident</td>
<td>-</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>-</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>-</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Testicular adenoma (benign)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>TMJ syndrome</td>
<td>-</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>1 (8%)</td>
<td>-</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

* Unassociated with other AEs and typical of falls observed in BMD patients

- No dose reductions or adjustments
- No treatment discontinuations due to AEs
Target Plasma PK Achieved After Increasing Dose to 15 mg/day; BMD Patients Showed Continued Activity After 6 Months of Dosing

**EDG-5506 Plasma PK**

- **Mean AUC$_{24}$ (ng/ml):**
  - 2,293
  - 1,454
  - 2,299
  - 2,400

**Patient Step Count**

- Exposure with 15 mg dose reached the target exposures observed with the 20 mg dose in the Phase 1 BMD cohort
- At month 4 & 6 of dosing with EDG-5506 BMD patients continued to show an increased level of activity over that seen at one month and those in the Phase 1b study (who were confined to the Phase 1 unit)

**EDG-5506 Dose:** 20 mg 10 mg 15 mg 15 mg

Source: Data on file
EDG-5506 Led to a Sustained Decrease in CK and Profound Suppression of TNNI2 Demonstrating Target Engagement

Individuals with the Highest Baseline Values Show Greatest Biomarker Effect, Suggesting Protection Against Activity-Induced Damage

*p % difference from mean baseline shown; Means ± SEM  *** p<0.001

Source: Data on file for month 4 (n=10) or 6 (n=2) as available
SOMAscan Signature of Long-Term Response Emerging with Treatment?

- Previous studies focused on rapidly-changing biomarkers of muscle injury with EDG-5506
- This analysis focused on longer-term changes with EDG-5506 in ARCH (N=12)
  - Proteins significantly lower at 6 months compared to both baseline and 1 month samples
- Analysis of these proteins reveals protein signatures enriched for inflammatory pathways
  - Treatment appears to revert this signature to healthy control levels

Source: Data on file
The Natural History of BMD Provides Helpful Context for Interpreting Changes in NSAA in Response to EDG-5506

- Luca Bello’s BMD Natural History Study, the most comprehensive study of its kind to date, demonstrates that NSAA decline is consistent in BMD patients who are already progressing.

- BMD individuals with a baseline NSAA score of 10-32 exhibit an estimated yearly NSAA decline of **-1.22 points**.

- Functional decline in BMD patients is further supported by Leiden data demonstrating a **2.5 points NSAA decrease over 2 years** in unselected ambulatory BMD patients.

<table>
<thead>
<tr>
<th>Baseline NSAA Score</th>
<th>Estimate of Yearly Change</th>
<th>Standard Error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-32</td>
<td>-1.22</td>
<td>0.07</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
NSAA and NSAD Durable Improvements Observed Over 6 Months of EDG-5506 Relative to Natural History

NSAA Represents an Integrated Measure of Function

Dashed lines show 95% CI on the linear regression
Diffuse Pain in Becker Muscular Dystrophy

- Self-reported pain over the previous 3 months in Duchenne and Becker muscular dystrophy (DMD N=15, Age 24+/-6 yrs; BMD N=18, Age 42+/-14 yrs)
- 10/18 BMD ambulant
- BMD individuals report more diffuse pain, focus on spine and calves
Self-Reported Pain Scores Also Trended Better Following 6 Months of EDG-5506 Dosing

• While the ARCH study is not placebo controlled, a positive trend in self-reported pain scores was observed after 6 months of EDG-5506 dosing

• Additionally, other patient-reported outcomes, such as mental health, fatigue and sleep, also trended better

• A more comprehensive analysis of the PROs and PROMIS-57 is ongoing
## Ongoing and Upcoming Clinical Studies with EDG-5506

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 OL Study (BMD) <em>(NCT05160415)</em></td>
<td><strong>Fully Enrolled</strong></td>
</tr>
<tr>
<td><strong>ARCH</strong></td>
<td></td>
</tr>
<tr>
<td>Natural History Study in BMD <em>(NCT05257473)</em></td>
<td><strong>Enrolling</strong></td>
</tr>
<tr>
<td>Conducted by the GRASP network</td>
<td></td>
</tr>
<tr>
<td>Phase 2 BMD <em>(NCT05291091)</em></td>
<td><strong>Enrolling</strong></td>
</tr>
<tr>
<td><strong>CANYON</strong></td>
<td></td>
</tr>
<tr>
<td>Phase 2 LGMD 2I, BMD and McArdle Biomarker Study <em>(NCT04349566)</em></td>
<td>2H22 Start</td>
</tr>
<tr>
<td><strong>DUNE</strong></td>
<td></td>
</tr>
<tr>
<td>Phase 2 DMD Dose Ranging Study <em>(ambulatory boys, NCT05540860)</em></td>
<td>2H22 Start</td>
</tr>
<tr>
<td><strong>LYNX</strong></td>
<td></td>
</tr>
</tbody>
</table>

- **Status:**
  - Steady-state PK, biomarker response and longer-term safety
  - Observational natural history study in BMD adults and adolescents
  - Fully Enrolled
  - Enrolling
Phase 2 Study in Adults and Adolescents with Becker

- **Population:**
  - Age 12 to 50 years old, inclusive
  - Confirmed mutation in dystrophin gene with characteristic Becker phenotype
  - Ambulatory
  - Not on corticosteroids

- **Design:** 12-month placebo-controlled

- **Endpoints:**
  - Biomarker (CK) at 12 months
  - Safety
  - MRI fat fraction of upper leg
  - Functional assessments to include NSAA, NSAD
Phase 2 Dose-Ranging Study in Boys with Duchenne

• Planned to start in Q4 2022

• Population:
  — 4 to 9 years old, inclusive
  — Confirmed mutation in dystrophin gene with characteristic phenotype
  — Ambulatory
  — On stable dose of corticosteroids; can be on approved exon-skipping rx

• Design: 3-month placebo-controlled, followed by 9-month open-label

• Endpoints:
  — Safety, pharmacokinetics and biomarkers at 3 months
  — Functional assessments collected for longer term information
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Site Personnel:
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Alvin Nguyen
Darwin Nguyen