Taking a New Approach to Protect Muscle in Duchenne and Becker Muscular Dystrophy: EDG-5506

Joanne M. Donovan, MD PhD
Edgewise Therapeutics
June 20, 2022
Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties of Edgewise Therapeutics, Inc. ("Edgewise" or the "Company"). All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, are forward-looking statements. Such forward-looking statements include, among other things, statements regarding the potential of, and expectations regarding, Edgewise's drug discovery platform; Edgewise's product candidates and programs, including EDG-5506; the expected milestones and timing of such milestones for EDG-5506 including the expected timing of reporting of data for EDG-5506 and clinical trials; statements regarding the market opportunity for Edgewise's product candidates; statements regarding Edgewise's pipeline of product candidates and programs; and statements regarding Edgewise's financial position including its liquidity. In some cases, you can identify forward-looking statements by terminology such as "estimate," "intend," "may," "plan," "potentially" "will" or the negative of these terms or other similar expressions.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: negative impacts of the COVID-19 pandemic on Edgewise's operations, including clinical trials; risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early clinical stage company; Edgewise's ability to develop, initiate or complete preclinical studies and clinical trials for, obtain approvals for and commercialize any of its product candidates; changes in Edgewise's plans to develop and commercialize EDG-5506 or any other product candidates; the potential for clinical trials of EDG-5506 or any other product candidates to differ from preclinical, interim, preliminary, topline or expected results; Edgewise's ability to enroll patients in its ongoing and future clinical trials; operating results and business generally; Edgewise's ability to raise funding it will need to continue to pursue its business and product development plans; regulatory developments in the United States and foreign countries; Edgewise's reliance on third parties, contract manufacturers and contract research organizations; Edgewise's ability to obtain and maintain intellectual property protection for its product candidates; risks associated with access to capital and credit markets; the loss of key scientific or management personnel; competition in the industry in which Edgewise operates; Edgewise's ability to develop a proprietary drug discovery platform to build a pipeline of product candidates; general economic and market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section entitled “Risk Factors” in documents that Edgewise files from time to time with the Securities and Exchange Commission. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

This presentation concerns product candidates that are under clinical investigation, and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). It is currently limited by federal law to investigational use, and no representation is made as to its safety or effectiveness for the purposes for which it is being investigated.
Edgewise Approach to Preventing Disease Progression in Duchenne and Becker Muscular Dystrophy: *Protect susceptible muscle fibers*

Fast muscle fibers are more susceptible than slow muscle fibers to mechanical stress.

In diseased animal models, **EDG-5506** protected susceptible muscle fibers and prevented long-term development of damage.

In the clinic **EDG-5506** rapidly decreased biomarkers of muscle damage.
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 not dystrophin leads to a loss of function.
DMD Boys Gain Function Even in the Absence of Dystrophin

- As boys get older, they progressively lose ground compared to typically developing boys
- Boys with Duchenne can have nearly normal NSAA scores
- Protecting muscle from damage should halt disease progression

Maximum indicates range for NSAA items for age-appropriate assessment

Mercuri et al., 2016 PLOS
Contraction Leads to Extensive Degeneration in Dystrophic Muscle

- Exaggerated force loss with eccentric contraction
- Associated with calcium influx and activation of apoptotic, necrotic and proteolytic pathways

See Poster #6
Fast Muscle Fibers are More Prone to Disruption in Response to Eccentric Exercise in Unaffected Individuals

More Disruption in Fast Muscle Fibers vs. Slow Muscle Fibers

- 30 mins controlled eccentric exercise
- Muscle biopsy taken immediately after exercise

More Stem Cell Mobilization in Fast Muscle Fibers

- After 12-week exercise program


Fast Muscle Fibers are Preferentially Affected in DMD

**Distribution of Fetal MHC by Fiber Type**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Normal (%) of total fibers</th>
<th>Normal % of total which contains fetal MHC</th>
<th>DMD % of total fibers</th>
<th>DMD % of total which contains fetal MHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>e30</td>
<td>0.9</td>
<td>0.7</td>
<td>3.8</td>
<td>3.0</td>
</tr>
<tr>
<td>1 day</td>
<td>1.3</td>
<td>1.2</td>
<td>3.3</td>
<td>3.2</td>
</tr>
<tr>
<td>14 days</td>
<td>3.9</td>
<td>3.7</td>
<td>3.3</td>
<td>3.2</td>
</tr>
<tr>
<td>0.9</td>
<td>6.6</td>
<td>6.5</td>
<td>3.8</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Abbreviations: Myosin heavy chain, MHC

Enrichment of muscle regeneration biomarkers in fast but not slow muscle fibers of young DMD boys

Regeneration marker expressed mostly in fast but not slow fibers
Susceptible Fast Fiber Muscle Biomarkers are Elevated in DMD and BMD

- Age ranges: Control 6-73 years, BMD 6-68 years, DMD 2-33 years

**** p < 0.0001

132 DMD samples from Newcastle University Biobank, 52 BMD samples from the CINRG consortium and 52 healthy volunteers from Chen collaboration

† The ~83% of volunteers had fast troponin levels below the LLQ of the ELISA, while only 4% of BMD and 6% of DMD patients had non-measurable levels of fast troponin

Reference: Barthel et. al., Muscle and Nerve, March 2021
A Novel Strategy to Rebalance Dystrophic Muscle?

Would selective inhibition of fast fiber contraction stop muscle degeneration but allow mixed fast/slow muscles to still function?
EDG-5506 Aims to Prevent Contraction-Induced Damage in Dystrophic Muscle

**DMD Muscle (mdx mouse)**

**No Treatment**

Suffers **EXTENSIVE** contraction-induced injuries

**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 Human Muscle Levels of 1,000-4,100 ng/g Projected to Provide Clinical Benefit Based on Preclinical Data

**Human Target-Tissue Exposures**:  

<table>
<thead>
<tr>
<th>Human Target</th>
<th>Tissue Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 ng/g</td>
<td>1,900 ng/g</td>
</tr>
<tr>
<td>2,756 ng/g</td>
<td>5,200 ng/g</td>
</tr>
<tr>
<td>4,036 ng/g</td>
<td>4,950 ng/g</td>
</tr>
<tr>
<td>4,131 ng/g</td>
<td>7,794 ng/g</td>
</tr>
</tbody>
</table>

- **1,900 ng/g**: Protection from lengthening injury in *mdx* mice  
- **5,200 ng/g**: Corrected membrane damage and injury biomarkers with exercise in *mdx* mice  
- **4,950 ng/g**: GRMD dogs improved biomarkers and increased habitual activity  
- **7,794 ng/g**: Retained muscle function, reduced fibrosis and prevented kyphosis in DBA/2J-*mdx* mice

**Muscle Concentration of EDG-5506 in Preclinical Models**

*Target human muscle levels adjusted for relative proportion of fast muscle fibers*
BMD and DMD represent a continuum of the same disease; Edgewise’s approach aims to treat across the disease spectrum, regardless of dystrophin mutation.
EDG-5506 Phase 1 Study Conducted in Healthy Volunteers and Participants with Becker Muscular Dystrophy

**Trial Design**

- Phase 1a SAD in HVs*
  - 0.5 mg
  - 1.5 mg
  - 5 mg
  - 15 mg
  - 45 mg
  - 90 mg
  - 135 mg
- Phase 1a MAD in HVs (14 Days Daily Dosing)
  - 10 mg x 4 days/5 mg x 10 days
  - 20 mg
- Phase 1b BMD Cohort (14 Days Daily Dosing)
  - 20 mg
  - 40 mg

* All HV cohorts were randomized 3:1 active:placebo

**Key Endpoints**

**Primary Endpoints**
- Safety and tolerability at 20 mg over a 14-day period in BMD

**Secondary/Exploratory Endpoints**
- Pharmacokinetics, pharmacodynamics
- Assess target tissue engagement judged by muscle/plasma ratio in BMD
- Measurement of serum biomarkers of muscle damage

Participants were monitored as inpatients for 16 days, with follow-up 1 and 4 weeks after completion of dosing.
### 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>$5 \text{ mg}$*</td>
<td>980</td>
</tr>
<tr>
<td>Healthy Adults</td>
<td>$10 \text{ mg}$*</td>
<td>2,740</td>
</tr>
<tr>
<td>Healthy Adults</td>
<td>20 mg</td>
<td>4,360</td>
</tr>
<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>

* 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

- 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

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

See Poster #54
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
With SOMAscan CK and Fast Troponin Reduced to Levels Near Those Observed in HVs Following Treatment with EDG-5506

**CK (mean ± SEM)**

-71%

**Fast Troponin I (mean ± SEM)**

-83%

See Poster #55
Biomarkers Most Elevated in BMD are Decreased Most with EDG-5506

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

Elevated in BMD vs Healthy

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

**Trial Design**

- **Population:** Ambulatory adults with BMD
  - Confirmed dystrophin mutation with characteristic phenotype
  - Open to all 7 participants from the Phase 1 study, with additional participants for a total of 12

- **Single site (Atlanta GA)**

- **Duration:** 1 year

- **Dose:** based on pharmacokinetic modeling
  - Tablets, dosed at night
  - 10 mg/day starting dose with planned dose escalation to 15 mg/day

- **Assessments include safety, tolerability, biomarkers, PK**
  - Biomarkers: CK, myoglobin, fast/slow/cardiac troponin
  - SOMAscan
  - Functional measures at baseline, with anticipation to follow longer term
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)

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 6 months at 15 mg dose

Interval between Phase 1 and open-label was ~3 months
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

<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

\[ r^2 = 0.9595 \]
EDG-5506 Continued to be Well-Tolerated in BMD Subjects

<table>
<thead>
<tr>
<th>TEAE</th>
<th>EDG-5506 (10 mg) N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Viral Gastroenteritis</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

- 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

![Graphs showing EDG-5506 Plasma PK and Daily Step Count](attachment:image.png)
2 Months of EDG-5506 Dosing Also Led to Rapid, Significant and Sustained Decrease in CK and Fast Muscle Troponin in BMD Patients

**Creatine Kinase (n=12)**

- Baseline
- 1 Month
- 2 Months

**Fast Muscle Troponin I (TNNI2)**

- Baseline
- 1 Month
- 2 Months

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

* p<0.05; ** p < 0.01
Conclusions

• In the ongoing open-label study of EDG-5506 in BMD participants of 10 mg/day for 2 months:
  — EDG-5506 has been well-tolerated
  — PK at this initial dose approximately 60% of exposure in previous 2 week study
  — Decreases in CK, myoglobin and fast troponin I sustained through 2 months with participants at full daily activity levels

• These results supported dose escalation to 15 mg/day in this study, which is ongoing

• Physical function assessment via NSAA, NSAD, 100-meter walk/run and activity monitoring ongoing
  — Update planned at 6-month timepoint
EDG-5506 is Being Developed for Becker and Duchenne Muscular Dystrophy

- Intended to preserve and improve function in Becker and Duchenne muscular dystrophy (BMD and DMD) with any mutation
- Goal to prevent damage to muscle by protecting the most susceptible fast muscle fibers
- Potential to be used in combination with other therapeutic approaches for dystrophinopathies
- Designed to stop the damage where it begins
# Ongoing and Upcoming Clinical Studies with EDG-5506

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Status</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 OL Study (BMD) <em>(NCT05160415)</em></td>
<td>Steady-state PK, biomarker response and longer-term safety</td>
<td>Fully Enrolled</td>
</tr>
<tr>
<td><strong>ARCH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural History Study in BMD <em>(NCT05257473)</em></td>
<td>Observational natural history study in BMD adults and adolescents</td>
<td>Enrolling</td>
</tr>
<tr>
<td><strong>CANYON</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2 BMD <em>(NCT05291091)</em></td>
<td>Multi-dose OLE</td>
<td>1H22 Start</td>
</tr>
<tr>
<td><strong>DUNE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2 LGMD 2I, BMD and McArdle Biomarker Study <em>(NCT04349566)</em></td>
<td>Multi-dose OLE</td>
<td>2H22 Start</td>
</tr>
<tr>
<td><strong>DUNE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2 DMD Dose Ranging Study <em>(ambulatory boys)</em></td>
<td>Multi-dose OLE</td>
<td>2H22 Start</td>
</tr>
</tbody>
</table>
THANK YOU to the individuals with BMD who participated in these clinical trials
Edgewise is Selecting BMD Patients with a Baseline NSAA of 10-32 for Phase 2

### Predictive Value of Baseline NSAA Score – Adult BMD Progression

<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>All</td>
<td>-0.63</td>
<td>0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>33-34</td>
<td>-0.03</td>
<td>0.01</td>
<td>ns</td>
</tr>
<tr>
<td>10-32</td>
<td>-1.22</td>
<td>0.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;10</td>
<td>-0.01</td>
<td>0.05</td>
<td>ns</td>
</tr>
</tbody>
</table>

Reference: Presented by Luca Bello at MDA, March 2022