Targeting Fast Muscle Myosin: A Novel Approach to Protecting Muscle in the Dystrophinopathies
Disclosures

• 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; and statements regarding Edgewise’s expectations relating to its clinical trials and clinical development of EDG-5506 including the expected milestones and timing of such milestones. 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 clinical trials for, obtain approvals for and commercialize EDG-5506; changes in Edgewise’s plans to develop and commercialize EDG-5506; the potential for clinical trials of EDG-5506 to differ from preclinical, interim, preliminary, topline or expected results; Edgewise’s ability to enroll patients in its ongoing and future clinical trials; 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, including 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; 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.

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Program Overview

• Joanne M Donovan, MD, PhD, Chair, Chief Medical Officer, Edgewise
  
  Introduction

• Barry J. Byrne, MD, PhD, Associate Chair of Pediatrics and Director of the Powell Gene Therapy Center at the University of Florida.
  
  Clinical Course of Dystrophinopathies with a Focus on Becker Muscular Dystrophy

• Nevin Steiner, Patient Advocate
  
  Living with Becker Muscular Dystrophy

• Alan Russell, PhD, Chief Scientific Officer, Edgewise
  
  The Edgewise Approach: Targeting Fast Myosin to Decouple Injury from Muscle Contraction in DMD and BMD

• Sam Collins, MBBS, PhD, Vice President, Clinical Development. Edgewise
  
  Clinical Update on EDG-5506

• Panel discussion to follow
Housekeeping

- Microphones are available for those in person to ask questions
  - Please wait until the end and the panel session to ask questions
- For those attending virtually, we will be monitoring your questions on-line
Becker muscular dystrophy is a serious dystrophinopathy with a variable clinical course. However, once declining, individuals have a relentless course of disease progression.

Living with Becker poses multiple challenges.

Contraction-induced injury in fast muscle fibers is a key aspect of the pathophysiology of BMD and DMD, and modulation of fast myosin can protect muscle fibers from contraction-induced injury.

EDG-5506 decreased biomarkers of muscle injury in individuals with BMD and clinical studies for BMD and DMD are underway.
Clinical Course of Dystrophinopathies with a Focus on Becker Muscular Dystrophy

Barry Byrne, M.D., Ph.D.

3/21/2023
Becker Muscular Dystrophy Arises from Mutations of the Dystrophin Gene that Produce a Protein with Decreased Function

- In-frame mutation of the dystrophin gene results in a truncated form of the protein
  - ~10% have out-of-frame mutation
- Incidence: ~1 in 18,450 male live births
- Global prevalence of BMD estimated at 1.6 per 100,000 people (95 CI 1.1–2.4 per 100,000 people)
- Median survival 67 yrs
BMD and Duchenne Muscular Dystrophy (DMD) are Related Dystrophinopathies

The combination of dystrophin functionality and background genetics place Becker individuals on a spectrum with Duchenne muscular dystrophy.
Becker Muscular Dystrophy Manifests with Progressive, Debilitating Weakness

- **BMD is heterogenous**
- Symptom onset from 5 to 60 years old, typically between ages **8 to 13**
  - 90% >20 yr old patients have symptoms of weakness
- **Walking problems** usually noticed around age 15/16, with progression, resulting in disability and loss of ambulation
- The most common cause of death is **heart failure** from cardiomyopathy

Heart Rhythm 2012; 9: 1890-1895
Cardiac Involvement is Common in BMD

- There is a discordance between skeletal myopathy and cardiomyopathy
- Severe cardiomyopathy can lead to destination VAD and/or cardiac transplantation
- In 15 consecutive patients from a neuromuscular clinic, cardiac disease developed in adults:

<table>
<thead>
<tr>
<th></th>
<th>LVEF ≥ 60% (N=5)</th>
<th>LVEF &lt; 60% (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>65 (61-70)</td>
<td>42 (27-54)</td>
</tr>
<tr>
<td>Age</td>
<td>14 (11-26)</td>
<td>42 (23-56)</td>
</tr>
</tbody>
</table>

Yilmaz, 2008, J Cardiac Magnetic Resonance
Weakness Develops as a Result of Muscle Loss and Fat Replacement

• Average fat fraction in BMD individuals similar to DMD, but a broad distribution

• Greater fat accumulation in select muscles compared to Duchenne for a given functional status
BMD: A Heterogeneous but Progressive Disease

Individuals with NSAA near maximal have low degree of fat infiltration

Individuals with NSAA below 32 have more severe fat infiltration and progressive disease over 1 year

Increasing fat infiltration
Majority of BMD Patients Show Functional Decline

- In the most comprehensive natural history study to date over ~5 years, the majority of patients have progressive decline
- BMD individuals with a baseline NSAA score of 10-32 exhibit an estimated yearly NSAA decline of -1.22 points
- Age is not a good predictor of functional decline, but baseline function does predict decline

<table>
<thead>
<tr>
<th>Baseline NSAA Score</th>
<th>Estimated Yearly Change</th>
<th>Standard Error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>
Correlation between NSAA and Timed Functional Measures

- Data from the CINRG consortium
- Similar to Leiden and Padua datasets, poor association between function and age
- Good correlation between timed function tests and NSAA with loss of linearity at higher NSAA
Compromised Ambulation in BMD

Use of Assistive Devices for Mobility is Common in BMD Adults

<table>
<thead>
<tr>
<th></th>
<th>2 to 18 years</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>I can get around on my own but I sometimes need help from a mobility device.</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>I use a wheelchair or other mobility device and rarely or never walk.</td>
<td>8%</td>
<td>34%</td>
</tr>
<tr>
<td>I usually or always walk on my own without help or mobility devices.</td>
<td>74%</td>
<td>51%</td>
</tr>
</tbody>
</table>

- The average age of adult respondents 35 yrs
- Almost half of adults used a mobility device

PPMD Duchenne Registry Data from 334 young BMD (average 19.9 yrs)

Source: Data on file;
Other Symptoms - 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
Key Takeaways

- Becker muscular dystrophy is a serious dystrophinopathy with a variable clinical course. However, once declining, individuals have a relentless course of disease progression.

- Living with Becker poses multiple challenges.

- Contraction-induced injury in fast muscle fibers is a key aspect of the pathophysiology of BMD and DMD, and modulation of fast myosin can protect muscle fibers from contraction-induced injury.

- EDG-5506 decreased biomarkers of muscle injury in individuals with BMD and clinical studies for BMD and DMD are underway.
NEVIN STEINER’S BMD JOURNEY
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Targeting Fast Myosin to Decouple Injury from Muscle Contraction in DMD and BMD

Alan Russell, Ph.D.
The Dystrophin Complex Helps Prevent Injury in Contracting Fibers

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

Muscle fibers from different motor units contract independently.

Long muscle fibers are more dependent upon dystrophin to help support fibers.
Skeletal Muscle is Comprised of Slow (type I) and Fast (type II) Fibers
Present as a mixed mosaic in all muscles

Defined by their myosin motor protein

Humans are ~ 50/50% fast/slow
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

Fast Muscle Fibers are Preferentially Affected in DMD

Distribution of Fetal MHC by Fiber Type

**Normal**

- % of total fibers: Slow, Fast
- % of total which contains fetal MHC

**DMD**

- % of total fibers: Slow, Fast
- % of total which contains fetal MHC

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

Abbreviations: Myosin heavy chain, MHC
Injury Biomarkers Tell the Same Story: Fast but not Slow Fiber Biomarkers are Elevated in BMD and DMD

- 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

† ~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 New Strategy to Rebalance Dystrophic Muscle

Contraction causes excessive degeneration

Fast fibers are injured

Protecting muscle is predicted to preserve function
The Target – Fast Skeletal Muscle Myosin

Myosin
Hydrolyzes ATP to bind actin and generate force
Development of a Potent, Selective Fast Skeletal Muscle Myosin Inhibitor, EDG-5506

Muscle myofibril ATPase

![Graph showing normalized ATPase activity vs concentration for different muscle types.]

Isolated myosin S1 subfragment ATPase

![Graph showing normalized ATPase activity vs concentration for different myosin S1 subfragments.]

Skinned fast rabbit psoas fibers

![Graph showing normalized tension vs pCa for different concentrations of EDG-5506.]

Mouse EDL muscle ex vivo

![Graph showing force vs time for different concentrations of EDG-5506.]

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**Fast Skeletal**

**Cardiac**

**Slow Skeletal**

**Fast Muscle S1**

**Cardiac Ventricle S1**

**Smooth Muscle S1**

**DMSO**

**0.1 µM EDG-5506**

**0.6 µM EDG-5506**

**1 µM EDG-5506**

**10 µM EDG-5506**
EDG-5506 Stops Fiber Breakdown in Contracting DMD Muscle

DMD muscle (mdx mouse) no treatment

Contracting at 100%

DMD muscle (mdx mouse) 0.3 uM EDG-5506

Contracting at 85%

Claflin, Su and Brooks. U Michigan

mdx mouse lumbrical muscle – 20, 1 second maximal isometric contractions (video sped up)
Protection from Injury Improves Skeletal Muscle and Heart Health in DBA/2 mdx Mice

- Muscle mass
- Grip Strength
- Cardiac Fibrosis

12-15 Months Treatment
Example - EDG-5506 Decreases CK and Increases Activity in DMD Dogs

Decreased injury biomarker (plasma CK)

Increased activity measured with an activity monitor
Muscle Injury Directly Impairs Muscle Function
Edema, pain and strength deficits could be alleviated with EDG-5506

- Acute contraction-induced muscle injury causes **pain, edema and loss of strength** in healthy people
- These features are also prominent in DMD and BMD and are present **prior to the onset of fibrosis**
- Protection against contraction-induced injury with EDG-5506 has the potential to **improve function by reducing acute injury and should protect against long term functional loss** due to fibrosis
- Activity improvements and decreased edema in preclinical models (GRMD, mdx)

Key Takeaways

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ARCH: An Open-Label Study of EDG-5506 in Adults with BMD

Insights from Biomarkers

Sam Collins, MBBS, PhD

March 2023
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

1. **Screening**
   - Biomarkers, NSAA, NSAD, Timed Function Tests

2. **EDG-5506**
   - 10 mg/day for 2 months

3. **EDG-5506**
   - 15 mg/day for 4 months

4. After 6 months all participants dose-escalated to 20 mg/day EDG-5506
Baseline Characteristics: BMD Participants Had Significant Functional Impairment and Decreased Muscle Mass

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BMD Participants (N=12)</th>
<th>Age Normative Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</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>NSAA</td>
<td>15.5 (range 4-31)</td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine (mean, mg/dL)</td>
<td>0.44</td>
<td>0.92 - 1.16</td>
</tr>
<tr>
<td>Serum CK (mean, U/L)</td>
<td>1,390</td>
<td>&lt;210</td>
</tr>
<tr>
<td>DXA % Lean Mass</td>
<td>54.9%</td>
<td>&gt;75%</td>
</tr>
</tbody>
</table>

Source: Data on file
Biomarkers and Baseline Characteristics:
Decreased Muscle Mass = Decreased Function

Graph 1: NSAA (0-34) vs. Creatinine
- NSAA (0-34) on Y-axis
- Creatinine on X-axis
- Scatter plot with linear trend line

Graph 2: NSAA (0-34) vs. DXA lean mass
- NSAA (0-34) on Y-axis
- DXA lean mass on X-axis
- Scatter plot with linear trend line
After 6 Months EDG-5506 Led to a Sustained Decrease in Biomarkers of Muscle Damage

Creatine Kinase

Fast Skeletal Muscle Troponin I (TNNI2)

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

* % difference from mean baseline shown; Means ± SEM

Source: Data on file

TNNI2 data projected from somascan

** p<0.001
Biomarkers Show Near-Maximal Decrease at 10 mg Dose

**Means ± SEM; Source: Data on file**

*p < 0.05; **p < 0.01; ***p < 0.001**

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**CK**

**Fast Troponin I**

_Predicted from Somascan_

**Myoglobin**

---

Ben Barthel – poster #119
EDG-5506 hypothesis – preventing damage preserves function
With EDG-5506 NSAA and NSAD Trended toward Improvement Relative to Natural History

NSAA and NSAD are Integrated Measures of Function

Dashed lines show 95% CI on the linear regression

Means ± SEM; Source: data on file
Natural history based on data presented by Luca Bello at MDA (2022) and van de Velde NM et. al., Neurology, 2021
Use of Plasma Proteomics to Identify Additional Biomarkers

• Muscle Injury leads to leak of CK and TNNI2 into the circulation

• Use of SomaScan® proteomics facilitates a comprehensive analysis of other proteins associated with injury and the response to EDG-5506 in BMD
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. healthy volunteers
- 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: Early Effect at 2 Weeks in Phase 1

- 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

- The lowering persisted through 6 months of dosing with EDG-5506 in the 002 study

* EDG-5506 20 mg

Source: Data on file
EDG-5506 rapidly decreases biomarkers of muscle damage but what about longer term effects?
Use of Plasma Proteomics to Identify Longer Term Response to EDG-5506

Exposure to EDG-5506

Muscle Injury

Adaptive Change?
**Is a SomaScan® Signature of Long-Term Response Emerging with Treatment?**

- 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

**Delayed decreasing proteins (n=337)**

**Delayed decreasing proteins - normalized mean concentration**
### Long-term Shift is from Skeletal Muscle to Inflammation Biomarkers

#### Short-term Proteins

<table>
<thead>
<tr>
<th>Tissue</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal Muscle</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathway</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Contraction</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Purine Biosynthesis</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Glucose Metabolism</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Actin folding</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

#### Long-term Proteins

<table>
<thead>
<tr>
<th>Tissue</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid/Immune</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Pancreas</td>
<td>p&lt;0.01</td>
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</table>

<table>
<thead>
<tr>
<th>Pathway</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil Degranulation</td>
<td>p&lt;0.001</td>
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<tr>
<td>Platelet Degranulation</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Interleukin-7</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Complement Activation</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Ben Barthel – poster #119

Source: Data on file
Examples of Inflammatory Protein Changes

IL-3 is a Hematopoietic Cytokine Associated with Allergic Inflammation

IL-37 is an Anti-Inflammatory Cytokine in the IL-1 Family
- Activation of anti-inflammatory pathways
- Improved exercise capacity

Source: Data on file
Conclusions

• EDG-5506 produces rapid and sustained improvement in biomarkers

• Clinical biomarkers of muscle damage improve rapidly

• A number of proteins respond more slowly and are associated with improvements in inflammation and exercise capacity

• Further data available on the poster by Ben Barthel – poster #119
Currently Enrolling Studies

**CANYON**
Phase 2 in Adults and Adolescents with Becker Muscular Dystrophy (US, UK, Netherlands)

**LYNX**
Phase 2 in Children with Duchenne Muscular Dystrophy (US)

Edgewise Booth #732
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Questions?