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

Symposium at the 27th International Annual Congress of the World Muscle Society
Halifax NS
14 October 2022
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Agenda

1. Preferential Fast Fiber Injury in Dystrophinopathies (Alan Russell)

2. Targeting Fast Myosin to Decouple Injury from Muscle Contraction in DMD and BMD (Alan Russell)

3. Mechanical Stress Induced Injury: Changes in Biomarkers of Dystrophic Muscle During Exercise in LGMD and BMD (John Vissing)

4. Clinical Course of Dystrophinopathies (Craig McDonald)

5. Clinical Development of EDG-5506 in BMD and DMD (Joanne Donovan)

Presenters

Dr. Alan J. Russell
Edgewise Therapeutics
Chief Scientific Officer

Dr. John Vissing
Director, Copenhagen Neuromuscular Center

Dr. Craig McDonald
World Renowned Neuromuscular Specialist, UC Davis Health

Dr. Joanne Donovan
Edgewise Therapeutics
Chief Medical Officer
Preferential Fast Fiber Injury in Dystrophinopathies

On behalf of H. Lee Sweeney, Ph.D.
Alan Russell, Ph.D.
Chief Scientific Officer
Edgewise Therapeutics
Overview

1. Review of how skeletal muscle force control is achieved
2. Some insights into why human muscle fiber anatomy amplifies the impact of muscular dystrophy
3. Overview on why fast skeletal muscle fibers are more susceptible to injury
Innervation Controls Contraction of Groups of Fibers – The Motor Unit

- A single axon innervates a pool of fast or slow muscle fibers and is termed a **Motor Unit**
  - Each motor unit controls 10->1000 fibers
  - Motor units control fibers of the same type
  - Muscles of the hand and arm have approx. **113 motor units each**

Skeletal Muscle is Comprised of Slow (type I) and Fast (type II) Fibers
Present as a mixed mosaic in all muscles

Type I:
- Slow

Type II a:
- Fast fatigue-resistant

Type II x/d:
- Fast fatigable

Defined by their myosin motor protein

Humans are ~ 50/50% fast/slow
Motor Unit Force Can be Varied by Altering Stimulation Frequency

- The **force-frequency relationship** shows how the force produced by a motor unit varies with discharge rate.
Different Motor Units have Different Thresholds for Initiating Contraction

Motor Unit Recruitment

- Different Motor Units have different thresholds for recruitment
- As muscle effort increases, new motor units are recruited to add to the contractile fiber pool
- As a rule of thumb, smaller slow fiber units are recruited before larger fast units
Together, Rate Coding and Recruitment Work Together to Smoothly Control Muscle Power Output

- This clever system facilitates smooth motor control even under conditions of extreme adversity:
  - Temperature
  - Nutritional deprivation

Oya et al J Physiol 586: 4737, 2009
One Weakness of Human Muscle – Long Limbs = Long Fibers

- Mapping of muscle fibers in the human sartorius muscle
  - The longest muscle in the body (~60 cm)
  - Each muscle fiber has one motor unit endplate
  - Not all fibers span the whole muscle but have *intrafascicular junctions*
  - Other fibers span the whole muscle

*Healthy volunteers*

Human muscle fibers are >7x longer than those in mice

[The Journal of Neuroscience, September 14, 2005 • 25(37):8528–8533
THE ANATOMICAL RECORD 262:301–309 (2001)]
The Dystrophin Complex Helps Prevent Injury in Contracting Fibers

Muscle fibers from different motor units contract independently

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

Long muscle fibers are more dependent upon dystrophin to help support fibers
Regional Stress of Long Muscles in BMD Leads to Uneven Fat Incorporation

Greater fat fraction at the ends of the muscle fiber where stress is the greatest
Eventually, the whole muscle is affected

van de Velde et al., Neurology 2021;97:e513-e522
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

Skeletal Muscle Z-Discs Deform with Stress and have Different Architecture Between Fast and Slow Fibers

Relaxed

Contracted

Fast

Slow
Fast Fibers are also More Sensitive in DMD

Fast Muscle Fibers Are Preferentially Affected in Duchenne Muscular Dystrophy

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New York, New York 10032

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

Black shading indicates eMHC-positive fibers
Injury Biomarkers Tell the Same Story - Fast but not Slow Fiber Biomarkers are Elevated in BMD and DMD

Summary

• Contraction of skeletal muscle is a complex process that relies on a combination of rate coding and recruitment to control power output.

• The dystrophin complex stabilizes fiber contraction by providing support across surrounding fibers.

• When dystrophin is mutated, additional regional stress is placed on fibers.

*Fast fibers are more susceptible to this type of injury.*
Targeting Fast Myosin to Decouple Injury from Muscle Contraction in DMD and BMD

Alan Russell, Ph.D.
Overview

1. Taking advantage of Fast Fiber Susceptibility and integrative flexibility for therapeutic benefit in dystrophinopathies

2. Preclinical data to support this hypothesis
A New Strategy to Rebalance Dystrophic Muscle

Contraction causes excessive degeneration

Fast fibers are injured

Selective inhibition of fast fiber contraction to prevent injury but at a level that doesn’t disrupt 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

Isolated myosin S1 subfragment ATPase

Skinned fast rabbit psoas fibers

Mouse EDL muscle ex vivo
EDG-5506 Stops Fiber Breakdown in Contracting DMD Muscle

Claflin, Su and Brooks. U Michigan

*dmd mouse* lumbrical muscle – 20, 1 second maximal isometric contractions (video sped up)
Protection Associated With Reduced Muscle Permeability

*Ex vivo* Dye Uptake by Contracting Muscle

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>1 µM EDG-5506</th>
<th>5 µM EDG-5506</th>
</tr>
</thead>
</table>

Red = fluorescent procion orange. Taken up by leaky muscle fibers
Green = wheat germ agglutinin (outlines fibers)

*In vivo* Dye Uptake by Leaky Muscle Fibers

Evans blue uptake in non-exercised mdx mice after 3 weeks of treatment

Graph shows mean +/- 1 SEM. Significance calculated by one-way ANOVA with Dunnet’s multiple comparison (****0.0001)
EDG-5506 Reduces DMD Mouse CK After Exercise Testing Without Altering Performance

Rotarod performance

Post-exercise plasma CK (Injury marker)
EDG-5506 Decreases CK and Increases Activity in DMD Dogs

**Decreased injury biomarker (plasma CK)**

- Before dosing
- After dosing with EDG-5506

**Increased activity measured with an activity monitor**

- Before dosing
- After dosing with EDG-5506

![Graph showing decreased CK activity](image1)

![Graph showing increased activity](image2)
Summary

• Allosteric inhibitors of fast skeletal muscle myosin are capable of selective inhibition of force in fast fibers

• Modest inhibition of myosin is sufficient for complete protection against contraction-caused calcium entry and destruction in dystrophic muscle

• Protective doses of selective inhibitor EDG-5506 do not affect coordination or strength in dystrophic mice
  — *Improvement of function observed in DMD dogs*
Muscle Injury in Muscular Dystrophies

John Vissing, M.D., Ph.D.
Director, Copenhagen Neuromuscular Center
at the National Hospital, Rigshospitalet
Eccentric Exercise Causes Muscular Injury in Healthy Volunteers

- Eccentric exercise of the forearm flexors
- Two sets of 35 maximal contractions
- 5 min rest between sets

Source: Figure adapted Clarkson et al, Med Sci. Sports Exercise, 24: 512-520, 1992
Muscle Injury is Associated with Fast but not Slow Muscle Biomarkers
Similar to Health Individuals, Injury Biomarkers are Elevated with Exercise in Becker Muscular Dystrophy and McArdle Disease

20 mins, 95% VO$_2$ Max bike exercise followed by 40 leg presses at 80% 1-RM max
Study Aims: Better Understanding Muscle Injury Biomarkers in Myopathies

- Are there differences between damage to fast vs. slow fibers with exercise in muscular dystrophies?
- Are elevated protein levels in plasma directly caused by exercise-induced muscle injury or are they more reflective of the disease state?
- Is there a proteomic signature for exercise-injury and is it similar among different muscular dystrophies?
Methodology: Exercise Challenge and SOMAscan Analysis

SOMAscan
Modified aptamer-based assay for ~7000 circulating proteins

Assessment | 10 min rest | Exercise Protocol | Post-Exercise Observation
---|---|---|---
VO$_{2\text{max}}$ Test
Quadricep 1-rep max ID

**Cycle**
5x 4 min @ 95% VO$_{2\text{max}}$

**Strength**
4x, 10-rep @ 80% 1-rep max

0 hr 2 hr 4 hr 24 hr

*PI: Mads Stemmerik (CMRC, Rigshospitalet, Copenhagen)*
Understanding the Universality of the Muscle Injury Signature

Mechanical Stress-Induced Damage

- Dystrophin Mutation (BMD)
- Dystroglycan Glycosylation (LGMDR9)
- Membrane Repair (LGMDR12)

Myofibril proteins
### Participants and Demographics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>% Male</th>
<th>Age (yrs)</th>
<th>BMI</th>
<th>VO$_{2\text{Max}}$ (mL min$^{-1}$ kg$^{-1}$)</th>
<th>WMax (J sec$^{-1}$)</th>
<th>% HR$_{\text{Max}}$</th>
<th>1-RM (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>77.8</td>
<td>44 ± 13</td>
<td>24.5 ± 2.4</td>
<td>38.8 ± 3.5</td>
<td>278 ± 53</td>
<td>100 ± 7.2</td>
<td>96 ± 26</td>
</tr>
<tr>
<td>BMD</td>
<td>9</td>
<td>100</td>
<td>33 ± 7</td>
<td>23.6 ± 2.9</td>
<td>22.9 ± 8.5</td>
<td>113 ± 107</td>
<td>94.4 ± 8.9</td>
<td>38 ± 41</td>
</tr>
<tr>
<td>LGMD2L</td>
<td>8</td>
<td>12.5</td>
<td>30 ± 10</td>
<td>22.6 ± 2.7</td>
<td>26.1 ± 8.5</td>
<td>132 ± 71</td>
<td>95.4 ± 5.3</td>
<td>49 ± 29</td>
</tr>
<tr>
<td>LGMD2L</td>
<td>9</td>
<td>66.7</td>
<td>52 ± 9</td>
<td>27.1 ± 4.4</td>
<td>27.6 ± 11.4</td>
<td>176 ± 89</td>
<td>96.6 ± 9.8</td>
<td>70 ± 44</td>
</tr>
</tbody>
</table>

‘Slow Off-rate Modified Apatamer Scan’
Proteins are identified in a complex solution by aptamer-linked precipitation

Protein data is reported as relative to a normalizer, not an exact quantitation
Identification of a Shared Pre-exercise Baseline Signature

32 common elevated proteins

1 common decreased protein
  (Ecto-ADP-Ribosyltransferase)
Exercise Dynamics of Baseline Signature Proteins

Most and least responsive proteins

Responsive proteins show large range of values, indicating significant changes in protein concentration.

Nonresponsive proteins show small range of values, suggesting minimal changes.

Responsive proteins:
- FBP2
- CRZ

Nonresponsive proteins:
- Exercise Nonresponsive
- Exercise Responsive
Validation of the Universal Baseline Signature Using BMD Data

Baseline 33-protein Signature

Copenhagen BMD Exercise Dataset (N=9)

Newcastle Tissue Bank Dataset (N=55)

Similar pattern of elevation and decrease for universal signature

Larger age range in Newcastle set

Baseline Signature Comparison

Validation of the Universal Baseline Signature Using BMD Data
Exercise Responsive and Nonresponsive Proteins Show Opposing Age Correlations

30 - 50% of responsive and nonresponsive proteins exhibit significant correlations with age
Conclusions and Future Questions

We have identified and validated a common signature of biomarkers that are elevated in several muscular dystrophies

Further annotation of these biomarkers by examination of change with exercise is possible

Exercise responsive and nonresponsive markers exhibit opposite directional correlations with age

Can exercise nonresponsive biomarkers be leveraged as more stable indicators of disease progression and/or treatment effects over long time-frames?

Can exercise responsive biomarkers be used as a more sensitive biomarker set to measure muscle injury in an interventional trial?
Acknowledgments

Exercise trial participants and Muscular dystrophy patients

Neuromuscular Center, University of Copenhagen
Mads Stemmerik, Nanna Andersen, Sophie V. Skriver

MRC Centre Biobank for Rare and Neuromuscular Diseases
Dan Cox, Volker Straub, Donors of plasma

Edgewise Therapeutics
Ben Barthel, Alan Russell
Clinical Course of Dystrophinopathies with a Focus on Becker Muscular Dystrophy

Craig McDonald, M.D.
Defining Becker Muscular Dystrophy

- Desire to classify, especially in light of new therapeutics emerging
- Tremendous Variability – due to amount and quality of dystrophin

From PPMD and Community Draft Guidance for Industry: Duchenne Muscular Dystrophy, Becker Muscular Dystrophy, and Related Dystrophinopathies. Developing Potential Treatments for the Entire Spectrum of Disease
Loss of Ambulation in Duchenne Muscular Dystrophy

Defining Becker Muscular Dystrophy

Defining by age at loss of ambulation, which varies broadly

DMD: Era before steroids:
Age 10 (Range 7-13)

Current era:
Age 16
No Steroids

Current era:
Age 18
On Steroid
Defining Becker Muscular Dystrophy: Clinical Trial Criteria

Edgewise:

Adults (aged ≥ 18 years) with a documented dystrophin mutation and phenotype consistent with BMD, and history of being ambulatory beyond 16 years of age without steroids OR history of being ambulatory beyond 18 years of age with steroids
Classical Definition - Becker Muscular Dystrophy Arises from In-Frame Mutation of the Dystrophin Protein

A Normal

- Translation start: 1-79
- Dystrophin transcript is translated into dystrophin protein

B Duchenne muscular dystrophy

- Frameshifting mutation:
  - Incorporation aberrant amino acids after deletion and generally premature truncation of translation
- Nonsense mutation:
  - Premature truncation of protein translation (reading frame is not affected)

C Becker muscular dystrophy

- In-frame mutation:
  - Translation continues until natural translation stop, shorter, partially functional dystrophin generated

- In-frame mutation of the dystrophin gene results in a truncated form of the protein

- Incidence: >1 in 18,450 male live births

- The 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
Investigating the Effects of Very Low Dystrophin Levels on Muscular Dystrophy Disease Phenotype

Study objective: Determine whether a low residual quantity of dystrophin protein is associated with delayed clinical milestones in patients with DMD mutations.

Objective: This study was undertaken to determine whether a low residual quantity of dystrophin protein is associated with delayed clinical milestones in patients with DMD mutations.

Methods: We performed a retrospective multicentric cohort study by using molecular and clinical data from patients with DMD mutations registered in the Universal Mutation Database–DMD France database. Patients with intronic, splice site, or nonsense DMD mutations, with available muscle biopsy Western blot data, were included irrespective of whether they presented with severe Duchenne muscular dystrophy (DMD) or milder Becker muscular dystrophy (BMD). Patients were separated into 3 groups based on dystrophin protein levels. Clinical outcomes were ages at appearance of first symptoms; loss of ambulation; fall in vital capacity and left ventricular ejection fraction; interventions such as tracheostomy, and noninvasive ventilation; and death.

Results: Of 3,880 patients with DMD mutations, 90 with mutations of interest were included. Forty-two patients expressed no dystrophin (group A), and 31 of 42 (74%) developed DMD. Thirty-four patients had dystrophin quantities < 5% (group B), and 21 of 34 (61%) developed BMD. Fourteen patients had dystrophin quantities ≥ 5% (group C), and all but 4 who lost ambulation before 24 years of age were ambulant. Dystrophin quantities of <5%, as low as <0.5%, were associated with milder phenotype for most of the evaluated clinical outcomes, including age at loss of ambulation (p < 0.001).

Interpretation: Very low residual dystrophin protein quantity can cause a shift in disease phenotype from DMD toward BMD.

ANN NEUROL 2021;89:280-292
Clinical Outcomes

- Age at first symptoms and loss of ambulation
- Medication data
- Age of drop in VC to <50% and <20%
- Age of drop in LVEF to <55% and <30%
- Age at start of noninvasive ventilation, tracheostomy, spinal fusion surgery, and death
Patient Mutations and Disease Severity Varied by Dystrophin Quantity

<table>
<thead>
<tr>
<th>Group A: No Dystrophin (n=42)</th>
<th>Group B: &gt;0% and &lt;5% of normal dystrophin (n=34)</th>
<th>Group C: ≥5% of normal dystrophin (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease phenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>74% of patients had DMD</td>
<td>18% of patients had DMD</td>
<td>0% of patients had DMD</td>
</tr>
<tr>
<td>10% had IMD</td>
<td>3% had IMD</td>
<td>0% had IMD</td>
</tr>
<tr>
<td>2% had BMD</td>
<td>61% had BMD</td>
<td>57% had BMD</td>
</tr>
<tr>
<td>14% had an undefined phenotype</td>
<td>18% had an undefined phenotype</td>
<td>43% had an undefined phenotype</td>
</tr>
</tbody>
</table>

Rate of DMD and BMD differed by group (both $P<0.001$)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment rates were higher in patients with lower dystrophin (steroid $P=0.053$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% corticosteroids</td>
<td></td>
</tr>
<tr>
<td>26% corticosteroids</td>
<td></td>
</tr>
<tr>
<td>1% corticosteroids</td>
<td></td>
</tr>
</tbody>
</table>
Impact of Residual Dystrophin on Time to LoA

Patients with <5% dystrophin showed delay in LoA

- HR 0.16 (95% CI 0.09–0.30), P<0.001

Patients with ≥0.5% dystrophin (subgroup B")

- No further delay in loss of ambulation was seen in patients with ≥0.5% dystrophin (subgroup B")

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Loss of Ambulation (Group A, B, C)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>0-5%</td>
<td>≥5%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0-5%</td>
<td>≥5%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0-5%</td>
<td>≥5%</td>
</tr>
</tbody>
</table>

Loss of Ambulation (Group B’, B”)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group B’</th>
<th>Group B”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>0-5%</td>
<td>0-0.5%</td>
<td>0.5-5%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0-5%</td>
<td>0-0.5%</td>
<td>0.5-5%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0-5%</td>
<td>0-0.5%</td>
<td>0.5-5%</td>
</tr>
</tbody>
</table>

Number at risk:

- A: No dystrophin
- B: <5% dystrophin
- C: ≥5% dystrophin

Cum Survival

AGE (years)

0 5 10 15 20 25 30

0 20 40 60 80 100

P<0.01 P<0.01 NS
Impact of Residual Dystrophin on Survival, and Cardiac and Respiratory Function

Patients with low residual dystrophin (>0%) had a significant delay in markers of disease progression, including decline in vital capacity, cardiac function (LVEF <55%), and improved survival compared to patients with no dystrophin.
Becker Muscular Dystrophy Manifests with Progressive, Debilitating Weakness

- BMD is extremely 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 loss of ambulation variable but after the age of 16
- The most common cause of death is heart failure from cardiomyopathy
  - Onset 28.7 ± 7.1 years

Heart Rhythm 2012; 9: 1890-1895
Discordance of Cardiomyopathy and Skeletal Myopathy

Key Considerations:

• There may be a discordance with skeletal myopathy and cardiomyopathy

• Highly functional BMD patients in young adulthood may present with severe cardiomyopathy

• Severe cardiomyopathy leading to destination VAD and/or cardiac transplantation

Use of Assistive Devices for Mobility is Common in Becker Adults

<table>
<thead>
<tr>
<th>Status</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)
One Year Longitudinal Changes in BMD

Conclusions:

- Patients with “del x-51” or “del 48” mutations have mild or asymptomatic BMD,
- “del 45-x” and “other” mutations cause comparatively severe weakness, and functional deterioration in 1 year.
Proportion of patients continuing to walk

Proportion of patients continuing to run

(Usually 10 meter run/walk of approx. ≤ 3 sec)
Ambulatory Function Shows a Steady Decline Once Function Becomes Compromised

• 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**.

<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>

Source: Data on file; Data presented by Luca Bello at MDA (2022); van de Velde NM et. al., Neurology, 2021
### Table 1 Change in Functional Assessments Between Baseline and After 24 Months

<table>
<thead>
<tr>
<th>Test</th>
<th>Median at baseline</th>
<th>Median change follow-up vs baseline (range)</th>
<th>p Value</th>
<th>SRM</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAA, points</td>
<td>18 (5 to 34)</td>
<td>-2.5 (-12.0 to 1.0)</td>
<td>0.002</td>
<td>-0.81</td>
<td>98</td>
</tr>
<tr>
<td>TMRv, m/s</td>
<td>1.45 (0.26 to 4.17)</td>
<td>-0.22 (-1.4 to 0.25)</td>
<td>0.014</td>
<td>-0.68</td>
<td>138</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>385 (0 to 650)</td>
<td>-12.6 (-151.9 to 33.0)</td>
<td>0.063</td>
<td>-0.46</td>
<td>310</td>
</tr>
<tr>
<td>KE, kg</td>
<td>8.56 (2.9 to 54.5)</td>
<td>-1.3 (-11.1 to 3.8)</td>
<td>0.114</td>
<td>-0.49</td>
<td>264</td>
</tr>
<tr>
<td>KF, kg</td>
<td>8.19 (2.4 to 29.7)</td>
<td>-1.4 (-7.1 to 2.8)</td>
<td>0.040</td>
<td>-0.71</td>
<td>126</td>
</tr>
</tbody>
</table>

Abbreviations: 6MWT = 6-minute walk test; KE = knee extension; KF = knee flexion; NSAA = North Star Ambulatory Assessment; SRM = standardized response mean; SS = sample size; TMRv = 10-meter run velocity.
Findings: Correlations of Outcome Values at Baseline (minors: left panel; adults: right panel)

<table>
<thead>
<tr>
<th>Age</th>
<th>Stand velocity</th>
<th>Climb velocity</th>
<th>Run/Walk velocity</th>
<th>6MWD</th>
<th>NSAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.47</td>
<td>0.53</td>
<td>0.44</td>
<td>0.49</td>
<td>0.55</td>
<td>0.58</td>
</tr>
<tr>
<td>-0.33</td>
<td>0.48</td>
<td>0.29</td>
<td>0.49</td>
<td>0.55</td>
<td>0.58</td>
</tr>
<tr>
<td>0.03</td>
<td>0.44</td>
<td>0.29</td>
<td>0.49</td>
<td>0.55</td>
<td>0.58</td>
</tr>
<tr>
<td>0.07</td>
<td>0.44</td>
<td>0.29</td>
<td>0.49</td>
<td>0.55</td>
<td>0.58</td>
</tr>
<tr>
<td>0.08</td>
<td>0.25</td>
<td>0.35</td>
<td>0.55</td>
<td>0.58</td>
<td>NSAA</td>
</tr>
<tr>
<td>0.08</td>
<td>0.25</td>
<td>0.35</td>
<td>0.55</td>
<td>0.58</td>
<td>NSAA</td>
</tr>
</tbody>
</table>

- Spearman correlations between baseline outcomes similar to previously published.
- Correlation magnitudes stronger in adults suggesting more heterogeneity in outcome capabilities in minors.
- Outcomes less associated with age compared to other outcomes
  - Compared to using only age for eligibility criteria, likely better to use functional outcome window in adults.
Findings: Who Became Non-ambulatory?

- Two participants became non-ambulatory during the course of the study:
  - one at age 35, and
  - another at age 46.

- Last ambulatory measurements in red.
Baseline Factor Likely Predictive of Disease Progression

Age 10 meter R/W

5 sec
Weakness Develops as a Result of Localized Muscle Loss

- Focal muscle loss in the thighs, shoulders and arms
- Focal loss results in greater fat accumulation in select muscles compared to Duchenne for a given functional status
- Thigh fat correlates with Northstar score

Total Steps per Day
Adult NMD (BMD n = 12)
Steps at High Activity Level
(>30 steps/min)

All NMD groups are significantly different from control group.
Exercise Training in BMD
Sveen et al; Brain, 2008

Endurance training improves fitness and strength in patients with Becker muscular dystrophy

Marie Louise Sveen,¹ Tina D. Jeppesen,¹ Simon Hauerslev,¹ Lars Køber,² Thomas O. Krag¹ and John Vissing¹

¹Department of Neurology, Neuromuscular Research Unit, The Copenhagen Muscle Research Centre and
²Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

- 11 gene + BMD patients age 18-55; 7 nl controls
- 12 weeks of 65% VO2 max aerobic exercise on bicycle ergometer; 30 min; 5x per week (50 sessions)
  - 6 pts continued protocol for 12 months at 3x/week
- Muscle biopsies done pre/post-exercise in 6
- CK, QOL, monitored
Exercise in BMD
Sveen et al, 2008

- VO2 max up by 47 ± 11%
  - 16% in normals
- W max work up 80± 19%
- Strength up by 13-40%
- Most “showed improvement” in QOL
- No change in HR, CK, histology, central nuclei
- Improvements maintained at one year in six patients
- “Our studies support a more active approach to …patients with BMD.”
Conclusions

• Low levels of dystrophin result in intermediate dystrophinopathy and Becker muscular dystrophy with ambulation past the age of 16 (without steroids and > 18 (with steroids)

• Variability, frame-shift rule does not always apply and patients with “del x-51” or “del 48” mutations have mild or asymptomatic BMD

• Traditional dystrophinopathy endpoints characterize disease progression and are likely prognostic in BMD

• Functional outcome criteria will be important for trials (baseline NSAA < 32)
• MRI is a promising biomarker in BMD
• Cardiomyopathy discordant from skeletal myopathy in BMD
• Community activity monitoring promising in BMD
• Formal exercise and activity may impact functional deterioration in trials
Clinical Development of EDG-5506 in Duchenne and Becker Muscular Dystrophy

Joanne Donovan, M.D., Ph.D.
Chief Medical Officer
Edgewise Therapeutics
BMD and Duchenne Muscular Dystrophy (DMD) Represent Severe Dystrophinopathies

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>Serum Creatinine (mean, mg/dL)</td>
<td>0.58</td>
<td>0.92 - 1.16</td>
</tr>
<tr>
<td>Serum Creatine Kinase (mean CK, U/L)</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>
<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>

<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**

<table>
<thead>
<tr>
<th>Daily Dose</th>
<th>Muscle (ng/g)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>5,155**</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

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

** BMD Biomarkers Change From Baseline After 14 Days

<table>
<thead>
<tr>
<th></th>
<th>Control (Healthy+EDG-5506)</th>
<th>Placebo</th>
<th>EDG-5506</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine Kinase</td>
<td>ns</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>Fast Troponin</td>
<td>****</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

Source: Data on file

* EDG-5506 20 mg
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

**Screening**
Biomarkers, NSAA, NSAD, Timed Function Tests

**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

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>-</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>

- No dose reductions or adjustments
- No treatment discontinuations due to AEs

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

- 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)

Patient Step Count

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

Creatine Kinase

Fast Skeletal Muscle Troponin I (TNNI2)

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

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

Source: Data on file for month 4 (n=10) or 6 (n=2) as available

*p<0.001

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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)
  o 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
  o 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.

**Baseline NSAA Score** | **Estimate of Yearly Change** | **Standard Error** | **P-value**
--- | --- | --- | ---
10-32 | **-1.22** | 0.07 | <0.0001

Source: Data presented by Luca Bello at MDA (2022); van de Velde NM et. al., Neurology, 2021
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

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
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

PLoS ONE 14(2): e0212437, 2019
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>
<th>Status Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1 OL Study (BMD) (NCT05160415)</strong></td>
<td>Fully Enrolled</td>
<td>Steady-state PK, biomarker response and longer-term safety</td>
</tr>
<tr>
<td><strong>Natural History Study in BMD (NCT05257473)</strong></td>
<td>Enrolling</td>
<td>Observational natural history study in BMD adults and adolescents</td>
</tr>
<tr>
<td><strong>Phase 2 BMD (NCT05291091)</strong></td>
<td>Enrolling</td>
<td>Multi-dose</td>
</tr>
<tr>
<td><strong>Phase 2 LGMD 2I, BMD and McArdle Biomarker Study (NCT04349566)</strong></td>
<td>2H22 Start</td>
<td>Multi-dose</td>
</tr>
<tr>
<td><strong>Phase 2 DMD Dose Ranging Study (ambulatory boys, NCT05540860)</strong></td>
<td>2H22 Start</td>
<td>Multi-dose</td>
</tr>
</tbody>
</table>
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
Acknowledgements:

Study Participants and their families

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

Site Personnel:
Emily Murray
Alvin Nguyen
Darwin Nguyen