Treatment of Young Boys with Duchenne Muscular Dystrophy with the NF-κB Inhibitor Edasalonexent Showed a Slowing of Disease Progression as Assessed by MRI and Functional Measures

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Abstract O.42, World Muscle Society, Copenhagen, October, 2019
The clinical trial was sponsored by Catabasis Pharmaceuticals, Inc.


Maria Mancini, James MacDougall, Pradeep Bista, Andrew Nichols, Angelika Fretzen and Joanne Donovan are employees or consultants of Catabasis and may hold stock in Catabasis.

Edasalonexent is an investigational agent that is not approved in any territory.
Activation of NF-κB in Duchenne Muscular Dystrophy is a Key Factor in Disease Progression in Skeletal and Cardiac Muscle

No Dystrophin + Mechanical Stress

Activated NF-κB

Degeneration

Cross section of mid-thigh muscle in 12-14 YO boys

MuRF1/MAFbx

Control

DMD

Inflammation in Infancy

Fibrosis

Inflammation

Cytokines

Fiorillo et al., Physiol Genomics 2018 50:735

Regeneration

Satellite Cell

Myoblasts

Myotube

Dystrophin and Membrane Stability

NF-κB decreases dystrophin production, suggesting inhibition could increase dystrophin with dystrophin-targeted therapies

Cyclin D1

MMP-9

β-Dystroglycan

MMP-9

miRNA

NF-κB decreases dystrophin production, suggesting inhibition could increase dystrophin with dystrophin-targeted therapies

MyoD

MuRF1/MAFbx

Chen et al., Neurology 2005 65: 826

Fiorillo et al., Physiol Genomics 2018 50:735

Kumar et al., FASEB J 2003 17:386

Akima et al., Neuromuscul Disord 2012 22: 16
Edasalonexent Inhibits NF-κB, A Key Driver of Muscle Disease in DMD

- Edasalonexent is an orally-administered small molecule that is not a steroid
- Inhibiting NF-κB slowed disease progression in animal models of DMD
  - Oral administration of edasalonexent analog (CAT-1041) reduced muscle inflammation and improved function in mdx mice and GRMD dog
- Being developed as foundational therapy for patients with DMD regardless of mutation, both as monotherapy and potentially to be combined with dystrophin-targeted therapies

![Edasalonexent Chemical Structure]

![Reduced Inflammation in mdx Graph]

- Reduced Inflammation in mdx

<table>
<thead>
<tr>
<th>Protein</th>
<th>Control</th>
<th>CAT-1041</th>
<th>p-value</th>
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<tbody>
<tr>
<td>OPN</td>
<td>2.0</td>
<td>1.5</td>
<td>0.02</td>
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<tr>
<td>IL-6</td>
<td>1.5</td>
<td>1.0</td>
<td>0.01</td>
</tr>
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<td>IL-4</td>
<td>1.0</td>
<td>0.5</td>
<td>0.04</td>
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</table>

![Increased Diaphragm Specific Force in mdx Graph]

- Increased Diaphragm Specific Force in mdx

<table>
<thead>
<tr>
<th>Specific Force (N/cm²)</th>
<th>Control</th>
<th>CAT-1041</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>5.0</td>
<td>7.0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Hammers, et al. JCI Insight 2016 1(21): e90341
Means + SEM
Design of MoveDMD, a Phase 1/2 Trial with Open-Label Extension

- **Study Objectives**
  - Safety and PK in pediatric patients with DMD
  - Proof of concept using MRI to assess changes in muscle health
  - Long-term safety and effects on age-appropriate functional measures to enable design of Phase 3 study

- **Study Population**
  - Age 4 up to 8th birthday not currently being treated with corticosteroids
  - Able to perform timed function tests and MRI

- **Design**
  - Phase 1: 1-week open-label to assess safety and PK, with initial assessments of function and MRI
  - Off-treatment period of ~6 months prior to Phase 2
  - Phase 2: 12-week placebo-controlled period of 67 mg/kg and 100 mg/kg doses of edasalonexent
  - Open-label extension >72 weeks

- **Prespecified Analysis Plan**
  - 12-week placebo controlled period evaluated MRI, T2, North Star Ambulatory Assessment, timed-function tests, and safety
  - Additional comparison of rates of change during off-treatment control period versus on edasalonexent treatment
In Phase 2 MoveDMD Trial and Open-Label Extension:

Range of Endpoints to Demonstrate Proof of Concept and Support Design of Phase 3

<table>
<thead>
<tr>
<th>NF-κB Target Engagement</th>
<th>Biomarkers</th>
<th>Muscle MRI</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of NF-κB targeted gene set in peripheral blood</td>
<td>CRP, biomarker of inflammation</td>
<td>MRI T2 of upper and lower leg</td>
<td>North Star Ambulatory Assessment and Timed Function Tests</td>
</tr>
<tr>
<td></td>
<td>Muscle enzymes</td>
<td>MRS muscle fat</td>
<td></td>
</tr>
</tbody>
</table>

NCT02439216
Edasalonexent Inhibits NF-κB Target Genes in DMD Boys

- In MoveDMD trial, during the off-treatment control period, levels of NF-κB target genes were increased
  - Consistent with increased NF-κB activity during disease progression in DMD

- Treatment with edasalonexent decreased the levels of individual NF-κB target genes in the blood
  - Demonstrates target engagement

- Changes in aggregated NF-κB target gene-sets (HALLMARK and BIOCARTA) were also seen with treatment
  - Expression of genes in these sets were increased during off-treatment control period and decreased after edasalonexent treatment

**Mean fold change in NF-κB target gene abundance in blood (relative to start of treatment)**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Off-treatment period</th>
<th>100 mg/kg edasaloxent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFKB2</td>
<td>4.60</td>
<td>0.74</td>
</tr>
<tr>
<td>NFKBIA</td>
<td>2.50</td>
<td>0.97</td>
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</tbody>
</table>
In Phase 2 MoveDMD Trial and Open-Label Extension:

**Muscle Enzymes Significantly Decreased on Edasalonexent, Supporting a Positive Drug Effect**

- Early and sustained biomarker response

Plasma muscle enzymes are elevated 10 to 100 fold in DMD, indicative of leakage from damaged myocytes.

Means ± SEM shown; * p<0.05 for mean change from baseline after 12 weeks
Both Functional Decline and MRI Disease Progression Were Similar in Untreated Patients in MoveDMD and ImagingDMD Natural History Studies

- Off-treatment, steroid-naïve patients enrolled in the MoveDMD study with same data collection protocols had declines consistent with observations in the ImagingDMD natural history study.
  - Declines in function in natural history study at ages 4-7 were similar to those observed in the MoveDMD trial off-treatment.
  - Decreases in function correlate with increases in 5 composite lower leg MRI T2 as well as muscle fat fraction.

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Means ± SEM; side by side comparison from ImagingDMD and MoveDMD datasets.
Finkel et al., World Muscle Society, 2018; Vandenbourne et al., World Muscle Society, 2018.
In Phase 2 MoveDMD Trial and Open-Label Extension:

**Edasalonexent Improved Rate of Change of MRI T2 Compared to Off-Treatment Control Period**

- MRI T2 is tightly correlated with fat fraction and functional measures.
- Composite of 5 lower leg muscles MRI T2 (soleus, gastrocnemius, anterior and posterior tibialis, peroneals) used to encompass muscles at various stages of disease progression and minimize variability.
- Following 72 weeks of edasalonexent, the rate of increase in the composite MRI T2 decreased as compared to the rate of increase during the off-treatment control period.
- Early and sustained response in annualized rate of change.

**Means ± SEM; mixed model comparison with off-treatment period**

- Week 12: p=0.002, n=16; Week 24: p=0.004, n=14; Week 36: p=0.032, n=13; Week 48: p=0.018, n=12; Week 72: p=0.052, n=9
In Phase 2 MoveDMD Trial and Open-Label Extension:

**All Assessments of Function Stabilized on Edasalonexent Compared to Off-Treatment Control**

- **Sustained stabilization through 72 weeks on edasalonexent**

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Means ± SEM shown. Includes data of all boys initially started on 100 mg/kg dose (n=16) with 11 boys participating through 72 weeks.
NF-κB Inhibition Showed Potential for Cardiac Benefits in DMD

- Elevated resting heart rate is initial manifestation of cardiac disease in DMD
  - Cardiac failure is a leading cause of mortality in DMD
  - Elevated heart rate triples the risk of cardiomyopathy several years later

- Edasalonexent analog had positive effects on fibrosis in *mdx* and GRMD models

Inhibiting NF-κB reduces cardiac fibrosis in *mdx* mice and GRMD dog

- On edasalonexent, mean resting heart rate significantly decreased, approaching age-normative heart rate ~92 beats per minute
  - Decreases in heart rate noted to be more pronounced in patients with higher resting heart rates

In Phase 2 MoveDMD Trial and Open-Label Extension:

**Heart Rate: Change from Baseline**

- Baseline 99 beats/min

<table>
<thead>
<tr>
<th>Weeks on Edasalonexent</th>
<th>Beats per minute</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>-5</td>
</tr>
<tr>
<td>40</td>
<td>-10</td>
</tr>
<tr>
<td>60</td>
<td>-15</td>
</tr>
<tr>
<td>80</td>
<td>-20</td>
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</tbody>
</table>

p<0.01


Means ± SEM shown;
In Phase 2 MoveDMD Trial and Open-Label Extension:

**Safety: Edasalonexent was Well-Tolerated**

- **55+ patient years of exposure**
- **Well tolerated, with majority of adverse events mild in nature**
  - Most common related adverse event was diarrhea, generally mild and transient
  - No serious adverse events on treatment (one on placebo)
  - No adverse trends in chemistry, hematology, or measures of adrenal function (cortisol and ACTH)

<table>
<thead>
<tr>
<th>System Organ Class/ Preferred Term</th>
<th>Treatment-Related Adverse Events &gt;5%</th>
<th>Edasalonexent Overall (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16 (51.6%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>7 (22.6%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (9.7%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (9.7%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Faecal incontinence</td>
<td>2 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Faeces soft</td>
<td>2 (6.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4 (12.9%)</td>
<td></td>
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</tbody>
</table>
Boys on edasalonexent grew similarly to growth curves for unaffected boys
- Weight increased by mean 1.3 kg/year
- Height increased by mean 5.3 cm/year
- BMI decreased toward 50th percentile

**Percentiles Compared to CDC Growth Charts**

Means ± SEM shown
Comparison with CDC growth charts: https://www.cdc.gov/growthcharts/clinical_charts.htm
Conclusions from Phase 2 MoveDMD Trial and Open-Label Extension:
Edasalonexent Substantially Slowed DMD Disease Progression on Edasalonexent

- Edasalonexent, an oral NF-κB inhibitor, showed:
  - Clinically meaningful slowing of disease progression on edasalonexent compared to off-treatment control period
    - North Star Ambulatory Assessment and all timed function tests stabilized
  - MRI measures supportive of positive edasalonexent treatment effects
    - Muscle MRI T2 rate of change improved with edasalonexent treatment versus off-treatment control period progression
  - Well tolerated

- Supportive of Phase 3 clinical trial – PolarisDMD is fully enrolled at 40 sites globally

- Enrollment: 4 to 7 year-old (up to 8th birthday) boys not on steroids for 6 months
- Primary endpoint NSAA, secondary timed function tests
- Additional assessments of growth, cardiac and bone