Edasalonexent, an NF-κB Inhibitor In Development as a Potential Disease-Modifying Therapy for Duchenne Muscular Dystrophy

Andrew Nichols, Catabasis Pharmaceuticals

New Directions in Biology and Disease of Skeletal Muscle Conference

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Forward Looking Statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995, including statements regarding our expectations and beliefs about our business, future financial and operating performance, product development plans and prospects, including statements about future clinical trial plans including, among other things, statements about our plans to commence a single global Phase 3 trial in Duchenne muscular dystrophy, or DMD, to evaluate the efficacy and safety of edasalonexent for registration purposes, and our plans to continue to evaluate data from the open-label extension of our MoveDMD® clinical trial of edasalonexent for the treatment of DMD. The words “believe”, “anticipate”, “plans,” “expect”, “could”, “should”, “will”, “would”, “may”, “intend” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements contained in this presentation and in remarks made during this presentation and the following Q&A session are subject to important risks and uncertainties that may cause actual events or results to differ materially from our current expectations and beliefs, including: uncertainties inherent in the initiation and completion of preclinical studies and clinical trials and clinical development of our product candidates, including the final trial design of our planned Phase 3 trial in DMD; availability and timing of results from preclinical studies and clinical trials; whether interim results from a clinical trial will be predictive of the final results of the trial or the results of future trials; expectations for regulatory approvals to conduct trials or to market products, including our expected target product profile for edasalonexent in DMD; our ability to obtain financing on acceptable terms and in a timely manner to fund our planned Phase 3 trial in DMD to evaluate the efficacy and safety of edasalonexent for registration purposes; availability of funding sufficient for our foreseeable and unforeseeable operating expenses and capital expenditure requirements; other matters that could affect the availability or commercial potential of our product candidates; and general economic and market conditions and other factors discussed in the “Risk Factors” section of our Quarterly Report on Form 10-Q for the quarter ended March 31, 2018, which is on file with the Securities and Exchange Commission, and in other filings that we may make with the Securities and Exchange Commission in the future. In addition, the forward-looking statements included in this presentation represent our views as of the date of this presentation. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we specifically disclaim any obligation to do so. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.
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DMD Progresses Through a Predictable Cascade of Discrete Losses of Function and Mobility Milestones to Disablement and Death

Typical DMD Disease Progression and Goal of Edasalonexent Therapy

- Impaired ability to hop run jump
- Loss of rise from floor
- Loss of stair climb
- Loss of ambulation
- Loss of upper limb function
- Ventilation
- Death

Edasalonexent goal: Slow rate of decline

Natural oss of mobility and function

0  5  10  15  20  25  30
DMD Patient Age, Years

Adapted from presentation by Dr. Craig McDonald, UC Davis NeuroNEXT Program Director, University of California
NF-κB: The Key Driver of Muscle Inflammation, Damage and Fibrosis in DMD is Activated Early in Disease Before Onset of Symptoms

Activated NF-κB (p65) in DMD muscle biopsy

Early activation of inflammatory genes in DMD muscle

Modified from:
Early onset of inflammation and later involvement of TGFbeta in Duchenne muscular dystrophy
Chen et al., Neurology 65:826-834, 2005
Central Role of NF-κB: Lack of Dystrophin is Necessary but Not Sufficient for DMD Disease Progression

Mechanical stress activates NF-κB in mouse diaphragm

Replacement of muscle with fat and fibrosis

Muscles with no dystrophin but less mechanical stress are protected from degradation

“The absence of dystrophin alone is necessary but not sufficient to cause the patterned fibrosis, inflammation and failure of muscle regeneration characteristic of dystrophinopathy” – John Porter, past CEO, Parent Project Muscular Dystrophy

Kumar et al FASEB J 2003 17:386
Akima et al Neuromuscul Disord 2012 22(1):16-25
Inhibition of NF-κB by 50% (p65+/−) Reduces Muscle Inflammation, Damage and Fibrosis in mdx Mice

Modified from:
Genetic ablation of P65 subunit of NF-κB in mdx mice to improve muscle physiological function
Yin et al., Muscle Nerve 56:759-767, 2017
Pathogenic Role of Activated NF-κB in Muscle Diseases
Duchenne muscular dystrophy, Becker muscular dystrophy, others

Sarcolemma Function
- 8-Dystroglycan
- Dystrophin
- Actin

Inflammation + Fibrosis
- Inflammation
- Cytokines
- Fibrosis

MMP-9
miRNA

NF-κB

Satellite Cell
- Cyclin D1
- MyoD
- Myoblasts

Regeneration

Degeneration
- MuRF1/MAFbx

Degeneration

Myotube
The Catabasis SMART Linker Technology: A New Approach to Difficult Problems

- **Catabasis-amassed IP, technology, and know-how**
  - Conjugation engineering know-how
  - Library of proprietary “SMART linkers”
  - Bioactives can be ‘GRAS’ molecules, Rx or OTC drugs, food ingredients

- **Targeted delivery of bioactives**
  - Conjugates inactive in circulation but actively taken up by cells
  - Bioactives released inside cells by enzymatic cleavage of linkers
  - Bioactives interact with targets for desired activity

- **New IP**
  - Conjugates have composition of matter and method of use patents
Edasalonexent (CAT-1004) and CAT-1041 are Novel Inhibitors of NF-κB

CAT-1004 synergistically inhibits NF-κB (p65) in LPS-stimulated RAW Macrophages

CAT-1041 synergistically inhibits NF-κB (p65) in LPS-stimulated RAW Macrophages

CAT-1041 was used in some preclinical experiments as a proxy for CAT-1004

Hammers, et al. JCI Insight 2016 1(21): e90341
Inhibition of NF-κB, Slows Muscle Degeneration, Stimulates Muscle Regeneration and Improves Function

Inhibiting NF-κB reduces muscle inflammation and fibrosis and improves muscle mass and function in *mdx* mice

**NF-κB Inhibition**

**Reduced Inflammation**

**Reduced Fibrosis**

**More Muscle**

**Improved Strength**

**Increased Activity**

*mdx* mice treated with CAT-1041 at 0.75% in diet for 6 months

Hammers, et al. JCI Insight 2016 1(21): e90341

Edasalonexent positively impacts human myocyte growth and differentiation

Blue = Nucleus  
Green = Myosin heavy chain  
Human myotube formation

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

- Inhibition of NF-κB strongly reduces cardiac fibrosis and reduces cardiac hypertrophy in models of DMD
- Edasalonexent has the potential to reduce cardiomyopathy, the leading cause of mortality, in DMD

Hammers, et al. JCI Insight 2016 1(21): e90341
Edasalonexent Increases Dystrophin Expression in Combination with Exon-Skipping in *mdx* Mice

- Inhibition of NF-κB by edasalonexent enhances dystrophin production with sarcolemmal localization in combination with exon skipping therapy in *mdx* mice
- Edasalonexent may enhance dystrophin expression in combination with dystrophin-targeted therapies in DMD and as monotherapy in BMD

M23D: exon skipping specific for *mdx*
Edasalonexent administered at 1% in diet
Edasalonexent Clinical Development Program: From First-in-Human to Efficacy in MoveDMD®

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT-1004-102</td>
<td>Multiple ascending-dose, randomized, double-blind, placebo-controlled</td>
<td>Adults (N=44)</td>
<td>14 days</td>
<td>Positive safety and NF-kB inhibition data</td>
</tr>
<tr>
<td>CAT-1004-103</td>
<td>Single-dose biomarker study comparing edasalonexent to equimolar ratio of component bioactives</td>
<td>Adults (N=9)</td>
<td>Single-dose</td>
<td>Demonstrated NF-kB inhibition with single dose</td>
</tr>
<tr>
<td>CAT-1004-201</td>
<td><strong>Phase 1:</strong> Multiple ascending-dose, open-label</td>
<td>DMD Boys (N=17)</td>
<td>7 days</td>
<td>Positive PK and safety in patients</td>
</tr>
<tr>
<td></td>
<td>Off-treatment control period</td>
<td>DMD Boys (n=23)</td>
<td>3-13 months</td>
<td>Demonstrated disease progression during control period for boys in MoveDMD trial</td>
</tr>
<tr>
<td></td>
<td><strong>Phase 2:</strong> Randomized, double-blind, placebo-controlled</td>
<td>DMD Boys (N=31)</td>
<td>12 weeks</td>
<td>Numerical improvement in functional assessments and MRI at 100 mg/kg</td>
</tr>
<tr>
<td></td>
<td><strong>Open-Label Extension</strong></td>
<td>DMD Boys (N=31)</td>
<td>&gt;60 weeks</td>
<td>Long term safety and slowing of disease progression observed. Statistically significant reductions in muscle enzymes and C-reactive protein</td>
</tr>
</tbody>
</table>
MoveDMD Trial Was Designed to Enable Phase 3

Phase 1

- 31 Boys Ages 4 to 7 with DMD not on corticosteroids randomized

- Integrated multi-part trial design
  - Supports evaluation of efficacy, safety/tolerability, target engagement, and dose response

- Off-treatment control period measurements between Phase 1 and commencement of dosing in Phase 2/open-label extension
  - Provides internal control for pre-specified MoveDMD analyses
  - To confirm consistency of patient off-treatment control period disease progression with available natural history data

- Open-label extension
  - Enables assessment of safety and efficacy following longer term treatment
Edasalonexent produces dose-related reductions in NF-κB regulated and inflammation-related gene transcripts

- $C_{\text{trough}}$ and time over threshold is a driver of efficacy in preclinical models and in the clinic
- Preclinical efficacy studies and clinical PK/PD analysis support a TID dosing regimen for edasalonexent
MoveDMD Trial Incorporated Multiple Measures of Physical Function and Biomarkers

Assessments of Physical Function

<table>
<thead>
<tr>
<th>North Star Ambulatory Assessment</th>
<th>3 Timed Function Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 assessments, each scored 0-2. Maximum score: 34</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NSAA Sore</th>
<th>Perform</th>
<th>Perform with difficulty</th>
<th>Unable to perform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most Difficult Lost Early</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hop right leg</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hop left leg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stand on heels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise from floor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jump</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lift head</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descend box step right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descend box step left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climb box step right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climb box step left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stand on one leg right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stand on one leg left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Get to sitting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise from chair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least Difficult Lost Late</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stand</td>
<td></td>
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</tbody>
</table>

Patient with Function

Complete Loss of Function

Non-Effort Based Assessments

MRI T2 and Fat Fraction
Muscle Enzymes
C-Reactive Protein
Boys in the MoveDMD Trial Were Declining in Function Prior to Treatment Similar to Those in Natural History of DMD

- The ImagingDMD natural history study (Willcocks et al., 2014) performed annual timed function tests in young boys with DMD.

- Boys enrolled in the MoveDMD study under same data collection protocols generally had declines consistent with observations in the ImagingDMD natural history study.

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- Boys enrolled in the MoveDMD study under same data collection protocols generally had declines consistent with observations in the ImagingDMD natural history study.

- Boys (ages 5-8.5 yo) not on corticosteroids (n=28)
- Rate of change in MoveDMD off-treatment (n=23)

The ImagingDMD natural history study (Willcocks et al., 2014) performed annual timed function tests in young boys with DMD.

Boys enrolled in the MoveDMD study under same data collection protocols generally had declines consistent with observations in the ImagingDMD natural history study.
NF-κB-Regulated Transcripts in Whole Blood Increased During the Off-Treatment Control Period But Were Decreased by Edasalonexent Treatment for 24 Weeks

Significant Increase in NF-κB Transcript Gene Sets During Off-Treatment Period

Significant Decrease in NF-κB Transcript Gene Sets With Edasalonexent Treatment

Patient Level NF-κB Transcripts Increased During Off-Treatment and Decreased With Edasalonexent Treatment

Data analyzed for 8 boys who participated in Phase 1 and were treated with 100 mg/kg Edasalonexent in Phase 2
North Star Ambulatory Assessment Score, a Measure of Overall Function in Young Boys, Was Stabilized with Edasalonexent Treatment

Disease progression on edasalonexent improved compared with rate of change during off-treatment control period.

Includes data of all boys initially started on 100 mg/kg dose (n=16)
All Timed Function Tests Speed Stabilized with Edasalonexent Treatment, Consistent with Effect on NSAA Mean ± SEM shown includes data of all boys initially started on 100 mg/kg dose (n=16)

- Disease progression on edasalonexent improved compared with rate of change during off-treatment control period
C-reactive protein (CRP) is a well-characterized blood test marker that provides a global assessment of inflammation.

CRP is elevated in DMD - CRP is approximately 3-fold higher in boys affected by DMD compared to unaffected boys†

In MoveDMD, there was a statistically significant CRP reduction from baseline through 48 weeks of 100 mg/kg edasalonexent treatment.

Means ± SEM shown; * p≤0.05, ** p≤0.001 for comparison with pre-treatment baseline measurement

† Anderson et al, 2017, Pediatric Cardiology
MRI Is a Non-Invasive Approach to Assess Disease Progression in DMD

- **MRI T2 and MRS fat fraction in DMD**
  - Magnetic resonance can be used to assess inflammation and fat fraction
  - MRI T2 is elevated and increases with age
  - Fat fraction increases with age

- **MoveDMD incorporated both MRI and MRS**
  - Composite MRI T2 of 5 lower leg muscles was the primary MRI assessment
  - Fat fraction and MRS T2 also measured in lower (soleus) and upper leg (vastus lateralis)

- **Changes in MRI T2 and fat fraction correlate with changes in function**
  - Increases in both measures strongly correlate with worse performance on timed function tests and predict future loss of functional abilities

Edasalonexent Produced Statistically Significant Improvement in Rate of Change of MRI T2

MRI T2: Composite of 5 Lower Leg Muscles

- On edasalonexent, the rate of change for the MRI T2 composite of the 5 lower leg muscles improved significantly compared to the rate of change during the off-treatment control period (p<0.05 for 12, 24, 36 and 48 weeks)

- Stabilization of MRI T2 is consistent with slowing of disease progression also observed in function assessments

Means ± SEM shown; * p<0.05 for mixed model comparison with off-treatment period
Changes in Fat Fraction On Edasalonexent Consistent with Slowing of Disease Progression

MR Spectroscopy
Change in Fat Fraction from Baseline

<table>
<thead>
<tr>
<th>Muscle</th>
<th>MoveDMD Off-Treatment Control Period Annualized Rate</th>
<th>MoveDMD 48 weeks on Edasalonexent</th>
<th>ImagingDMD Natural History Study* 1 Year Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soleus</td>
<td>2.6%</td>
<td>0.85%</td>
<td>3%</td>
</tr>
<tr>
<td>Vastus lateralis</td>
<td>10.4%</td>
<td>5.9%</td>
<td>7%</td>
</tr>
</tbody>
</table>

- Following 48 weeks of edasalonexent treatment the rate of increase in fat fraction of the soleus and vastus lateralis was substantially decreased as compared to the off-treatment control period.

- In ImagingDMD natural history study, boys were largely on chronic steroids.

- At 48 weeks, MRS T2, reflecting inflammation only, decreased by -1.1 and -1.2 msec for the soleus and VL, respectively.

Baseline fat fraction in the soleus was 9.3% and in the VL 13.1%.

Statistically Significant Reduction in Muscle Enzymes on Edasalonexent Treatment

- Plasma muscle enzymes are elevated 10 to 100 fold in DMD, indicative of leakage from damaged myocytes.
- Decrease is consistent with positive impact on muscle health and supportive of an edasalonexent benefit.

Means ± SEM shown; * p<0.05 for change from baseline after 12 weeks.
Edasalonexent Has Been Well Tolerated with No Safety Signals; Normal Growth Observed

- No safety signals to date
- Well tolerated, with majority of adverse events being mild in nature, mostly gastrointestinal
- No adverse trends in hematology, chemistry, renal or adrenal function, calcium and phosphate
- Growth: Age-appropriate increases in weight and height
  - Favorably differentiated from typical profile associated with corticosteroid standard of care, which includes weight gain and curtailed growth

**BMI Compared to CDC Growth Charts**

![Graph showing BMI percentile over weeks on Edasalonexent](chart.png)
Cardiac failure is a leading cause of mortality in DMD.

In young boys, tachycardia is the first manifestation of cardiac disease in patients with DMD.

In MoveDMD trial, ECG heart rate decreased toward age-normative values.

In DMD, fibrosis leads to cardiac dysfunction.
- In *mdx* mouse and GRMD dog, edasalonexent reduces cardiac fibrosis.

**Edasalonexent Has Potential to Have Positive Effects on Cardiomyopathy in DMD**
Positive MoveDMD Data Support the Planned Global Phase 3 Registration Trial for Edasalonexent

Key Phase 3 trial components, including patient population and endpoints, previously evaluated in MoveDMD trial

Enrollment of approximately 125 boys, 2:1 randomization, accounting for dropouts

Study Population
- Anticipated to be all mutations, age 4 to 7, steroid naïve or off steroids for ≥6 months

Endpoints consistent with FDA guidance
- At 12 months
  - Primary: Change in North Star Ambulatory Assessment
  - Key secondary: Age-appropriate timed function tests
  - Additional assessments planned to include cardiac and bone measures

Preparing for Phase 3 clinical trial
MoveDMD® Open-Label Extension Results: Edasalonexent Preserved Muscle Function and Slowed DMD Disease Progression

- Clinically meaningful slowing of disease progression on edasalonexent compared to off-treatment control period through more than 1 year of treatment
  - North Star Ambulatory Assessment stabilized
  - Timed function tests stabilized (10-meter walk/run, 4-stair climb and time to stand)

- Additional measures of muscle health support positive edasalonexent effects
  - Statistically significant improvement in muscle MRI T2 versus off-treatment control period
  - Statistically significant decrease in muscle enzymes compared to baseline
  - Statistically significant decrease in CRP, a marker of systemic inflammation, compared to baseline

- No safety signal and well tolerated
  - Height, weight and BMI growth patterns similar to unaffected boys
Edasalonexent: A Potential Disease-Modifying Foundational Therapy in DMD

- **Disease-modifying non-steroid oral therapy**
  - Intended for all patients, regardless of mutation type
  - Inhibit muscle degeneration, enhance regeneration
  - Benefits in skeletal muscle, diaphragm and heart

- **Preparing for single Phase 3 trial for registration**
  - In MoveDMD® trial, edasalonexent preserved muscle function and slowed disease progression

- **Potential foundational therapy**
  - Initiate upon diagnosis
  - Potential as monotherapy and may enhance efficacy of dystrophin upregulation approaches

- Favorably differentiated tolerability profile from standard of care

- Strong IP position and wholly owned