MoveDMD[SM]: A Clinical Trial of Edasalonexent (CAT-1004) in Boys with Duchenne Muscular Dystrophy

JM Donovan[1], K Vandenborne[2], EL Finanger[3], HL Sweeney[2], G Tennekoon[4], SW Yum[4], MC Mancini[1], RS Finkel[5]

[1]Catabasis Pharmaceuticals*, [2]University of Florida, [3]Oregon Health & Science University, [4]Children's Hospital of Philadelphia, [5]Nemours Children's Hospital, Orlando

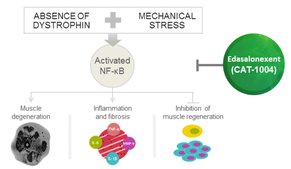
Background

Edasalonexent: Potential Disease-Modifying Oral Therapy for Duchenne Muscular Dystrophy

- Potential disease-modifying agent across age groups and mutations
- Oral agent that targets a pathway central to DMD pathophysiology
- Positive effects on skeletal, respiratory and cardiac muscle observed in pre-clinical models
- NF-κB activity demonstrated in Phase 1 clinical trials in adults and boys with DMD
- Phase 2 MoveDMD trial ongoing

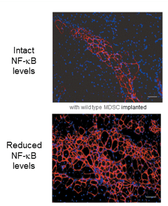
- Why edasalonexent?
  - In DMD, lack of dystrophin and mechanical stress activate NF-κB in muscles, leading to muscle degeneration, inflammation, fibrosis and inhibition of muscle regeneration and ultimately loss of function
  - Steroids suppress inflammation but have significant side effects

Edasalonexent (CAT-1004) Inhibits NF-κB and Shows Disease-Modifying Effects in DMD Preclinical Models



- **Findings for edasalonexent in pre-clinical models:**
  - Reduced muscle degeneration, inflammation and fibrosis, and enhanced muscle regeneration
  - Effects seen in skeletal, diaphragm and cardiac muscle
  - 5-10 fold higher edasalonexent concentration in muscle compared to plasma

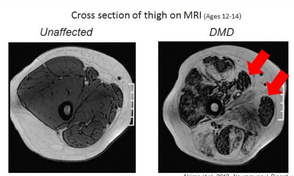
Inhibition of NF-κB Produces Disease-Modifying Effects in Duchenne Muscular Dystrophy



- NF-κB is chronically activated in Duchenne due to lack of dystrophin and elevated NF-κB is seen before the onset of fibrosis
- ~50% reduction in NF-κB observed to have disease-modifying effects
  - Reduced muscle degeneration
  - Enhanced muscle regeneration
  - Improvement in muscle mass and function
- Inhibition of NF-κB seen to have a positive effect on dystrophin-production in models with baseline dystrophin production
- Edasalonexent (CAT-1004) is being developed to target NF-κB in Duchenne muscular dystrophy

Li et al., 2012, Mol. Therapy

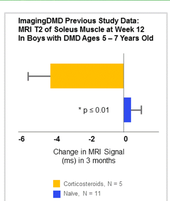
Activated NF-κB – Not Just Absence of Dystrophin – Plays a Central Role in DMD Pathophysiology



- Mechanical stress activates NF-κB in muscles
- Muscles with less mechanical stress (red arrow) are relatively protected – even in the absence of dystrophin

MRI is an Objective, Quantifiable and Sensitive Measure that is Highly Correlated with Function

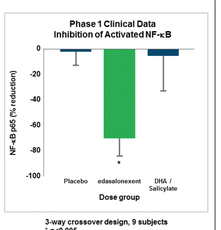
- **MRI T2 signal is a measure of muscle inflammation**
  - Increases continuously with age in boys with DMD vs. unchanged in normal boys
  - Objective, quantifiable and low variability
  - Highly correlated with functional measures
- **Corticosteroids provide proof of biology**
  - Statistically significant changes in MRI T2 of leg muscles in small sample sizes at week 12
  - Trends in timed function tests e.g. 10 meter walk/run, 4-stair climb, time to stand



Source: Arpan et al. Neurology. 2014; 83:1-7

Phase 1 Trials of Edasalonexent (CAT-1004) in Adults: Safety, Tolerability and Inhibition of Activated NF-κB

- **Design:**
  - Three completed Phase 1 trials
    - Single and multiple ascending dose trials
    - Biomarker trial
  - 79 adult subjects treated with edasalonexent (CAT-1004)
- **Results:**
  - No safety signals and good tolerability
  - Significantly reduced expression of NF-κB-target gene set after 14 days of dosing
  - Significant reductions in NF-κB biomarker activity compared to placebo or the co-administration of the bioactives, salicylate and the omega-3 fatty acid, DHA
  - The effect seen with edasalonexent is not seen when salicylate and the omega-3 DHA are taken at the same time

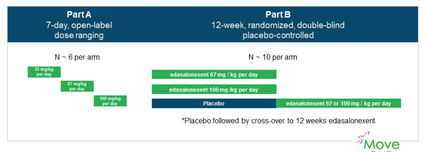


Part A Results

Edasalonexent (CAT-1004) MoveDMD Trial Objectives and Design

Part A (1 week of treatment):
- Assess the safety and PK of edasalonexent in ~18 boys with Duchenne aged 4-7
- Identify doses of edasalonexent that have plasma exposures known to have effects on NF-κB

Part B (12 weeks of treatment):
- Assess the safety of edasalonexent in ~30 boys with Duchenne over 12 weeks
- Measure the efficacy of edasalonexent versus placebo on MRI, timed functional tests (10 meter walk/run, 4 step climb, time to stand), North Star, PODCI, muscle strength



*Placebo followed by cross-over to 12 weeks edasalonexent

MoveDMD: Part A Safety and Tolerability

- Generally well tolerated
  - No serious adverse events, no discontinuations
  - All patients able to take edasalonexent capsules
  - Adverse events (AE) predominantly mild, most common AE was diarrhea
- Assessments:
  - Laboratory: no trends or safety issues in liver, renal, hematology
  - Physical exam, EKG, vitals: no safety issues
- Adverse events (7 days):

	33 mg/kg n=5	67 mg/kg n=6	100 mg/kg n=6	Total n=17
Diarrhea	0	0	4	4
Fecessoft	1	1	1	3
Abdominal pain upper	1	0	1	2

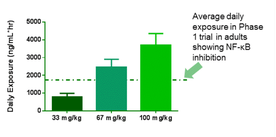
MoveDMD Part A Results: Positive NF-κB Biomarker Results and Sufficient Exposure at Top Two Doses

- At top two doses in Part A, statistically significant decrease in NF-κB target gene expression, consistent with NF-κB findings in adults
- Dose-dependent exposure in boys affected by DMD

Total Daily Dose

33 mg/kg	67 mg/kg	100 mg/kg
-	✓	✓

Statistically significant reduction in NF-κB target gene expression



Average daily exposure in Phase 1 trial in adults showing NF-κB inhibition

Part B Design

MoveDMD Study Population

Initial approach is to assess safety, pharmacokinetics and MRI as a biomarker of inflammation in young boys not on steroids

Inclusion Criteria
- Diagnosis of DMD based on a clinical phenotype with increased serum CK and the presence of a mutation in the dystrophin gene known to be associated with a DMD phenotype
- Ambulatory
- Age ≥4 years and <8 years
- Adequate immunization for varicella and influenza

Exclusion Criteria
- Use of corticosteroids within prior 6 months to treatment initiation or planning to initiate steroid therapy within the next 6 months
- Abnormal GGT, creatinine, hemoglobin <10.5 g/dL
- Ongoing immunosuppressive therapy

MoveDMD Endpoints: Assessments of Disease

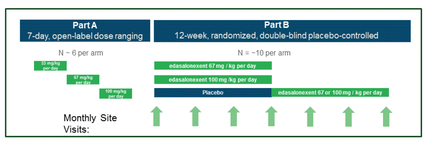
- MRI assessments (primary endpoint):
  - T2 as measure of muscle damage
    - Prior to initiation of Part A
    - Baseline and endpoint of Part B: 12-week edasalonexent vs PBO
- Functional assessments
  - Timed functional tests:
    - 10 meter walk / run, 4-step climb, time to stand
  - North Star Ambulatory Assessment
  - PODCI
  - Limited muscle strength testing
- Timing
  - Prior to initiation of Part A / Part B dosing
  - At baseline, monthly and endpoint of 12-week edasalonexent vs PBO

MRI is an Exciting New Tool in Drug Development for DMD

From Vandenborne K, ImagingDMD

- Magnetic Resonance Imaging (MRI) allows investigators to understand more about the natural history of DMD, to assess muscle health, and to assess potential effects of investigational drugs on muscle without need for biopsy
  - There is no radiation exposure or injections involved
  - Done at the ImagingDMD centers, who are expert in MRI in DMD

Design of MoveDMD Part B



Inclusion/Exclusion: Similar to Part A

Safety: Monitored by investigators, Sponsor and Data Safety and Monitoring Committee

Sites: University of Florida; Shriners, Portland OR; CHOP, Philadelphia PA; Nemours Children's Hospital, Orlando FL; UCLA, CA

Key Endpoints: Changes in Magnetic Resonance Imaging (MRI) of leg muscles at 12 weeks
- Changes in appropriate Timed Function Tests (10 meter walk/run, 4 step climb, time to stand), North Star, PODCI, muscle strength at 12 weeks
- Assess safety, tolerability and pharmacokinetics

Summary

Edasalonexent: Potential Disease-Modifying Oral Therapy for Duchenne Muscular Dystrophy

- No safety signals and generally well tolerated at all 3 doses tested
- Plasma exposure levels consistent with those previously observed in adults at which inhibition of NF-κB was observed, and which are higher than exposure levels in animal models at which disease modifying effects were seen.
- MoveDMD is an ongoing 12-week, double-blind, placebo-controlled Phase 2 efficacy trial of 67 mg / kg and 100 mg / kg edasalonexent in approximately 30 boys aged 4 – 7 with confirmed DMD.
- Based on inhibition of activated NF-κB, edasalonexent may reduce inflammation and muscle degeneration with potentially positive longer-term effects on muscle regeneration and function in DMD patients regardless of mutation type

Thank You!

- Patients and families
- Patient advocacy groups
- ImagingDMD Investigators and Staff
- Thanks to our partners for grant support for patient travel:

Part A: Parent Project Muscular Dystrophy – LEADING THE FIGHT TO END DUCHENNE

Part B: MDA Fighting Muscle Disease; Jerry Lewis Foundation; Cure Duchenne

For questions: Email our Chief Medical Officer, Joanne Donovan, M.D., Ph.D. and the Clinical Team: **joanne.donovan@catabasis.com**

Disclosures:

* Edasalonexent (CAT-1004) is an investigational agent being developed for the treatment of Duchenne muscular dystrophy, and not approved for treatment.

* Dr. Joanne Donovan is an employee of Catabasis Pharmaceuticals, Inc.