Edasalonexent (CAT-1004), an Oral Agent Targeting NF-κB: MoveDMD® Part A Results in Duchenne Muscular Dystrophy

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Disclosure information: J Donovan, M Mancini, J Danis, P Bista, and A Nichols are/were employees of Catabasis Pharmaceuticals and has stocks or other ownership interest in Catabasis Pharmaceuticals

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Background

- In DMD, muscle NF-κB is activated from infancy, driving inflammation, muscle degeneration and inhibiting muscle regeneration.[1]
- Edasalonexent (CAT-1004) is an oral small molecule that inhibits NF-κB and improves muscle degeneration, regeneration, function and exercise endurance in preclinical models.[2]
- In Phase 1 trials in adults, edasalonexent was generally well tolerated without safety signals and evidence of NF-κB inhibition was seen after single and multiple doses.
- Since MRI (T2) in DMD demonstrates leg muscle inflammation that is reduced with steroid therapy,[3] a proof-of-concept study of edasalonexent with MRI endpoints was designed.

1. Chen, YW, et. al., *Neurology* 2005; 65:826-834
2. Milne, J, et. al., *Neuromuscul Disord* 2014; 24:825-
3. Arpan, I, et. al., *Neurology* 2014; 83:974-980, and Willcocks, RJ, et. al., *Neuromuscul Disord* 2015; 24:393-401

Background: MRI Able to Identify Early Changes in Muscle Pathology in Small Patient Numbers in an Objective and Quantitative Manner

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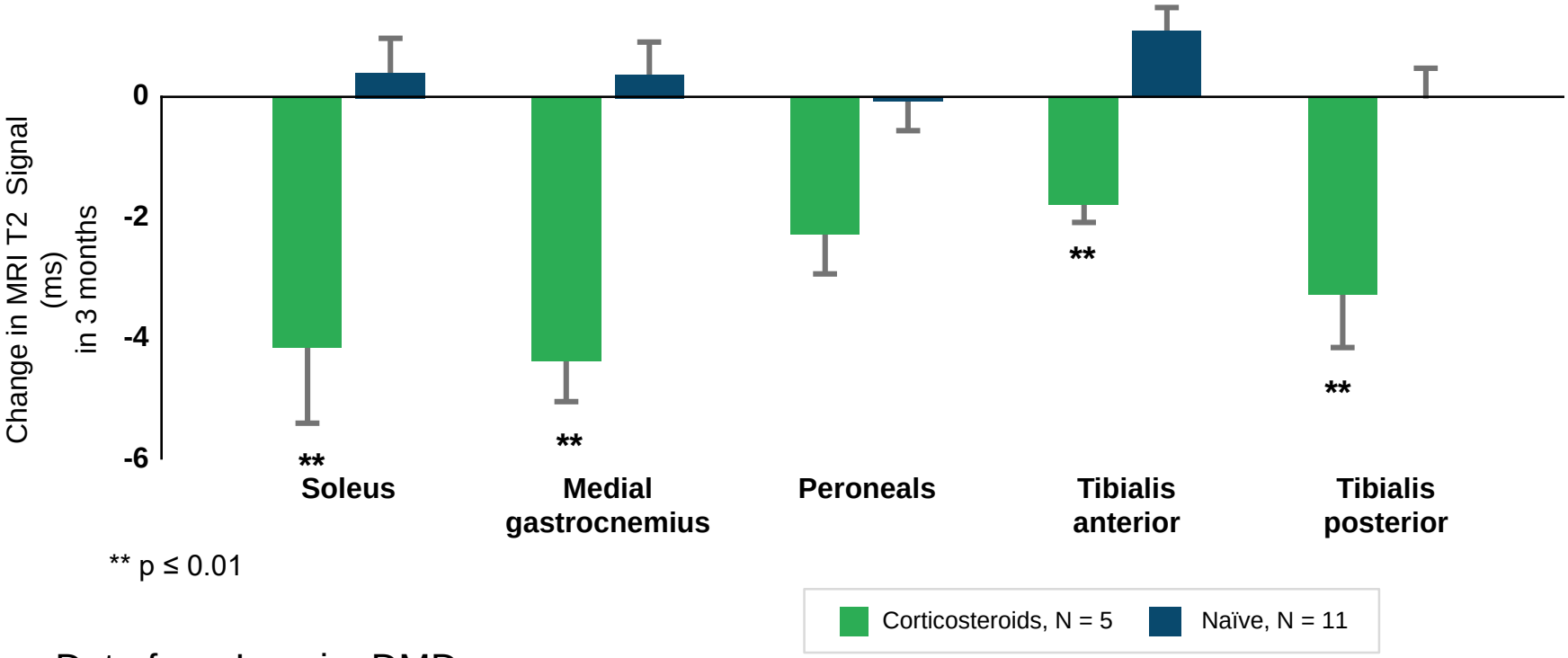
Comparison of MRI in Lower Leg Muscles in Corticosteroid-Naïve vs. Corticosteroid-Treated Boys with DMD Ages 5 – 7 Years Old



- Data from ImagingDMD
  - MRI T2 signal correlates with functional measures
  - MRI T2 signal increases continuously with age

Arpan et al Neurology 2014 83:1-7

Overview of 3-Part MoveDMD Trial in Boys with DMD

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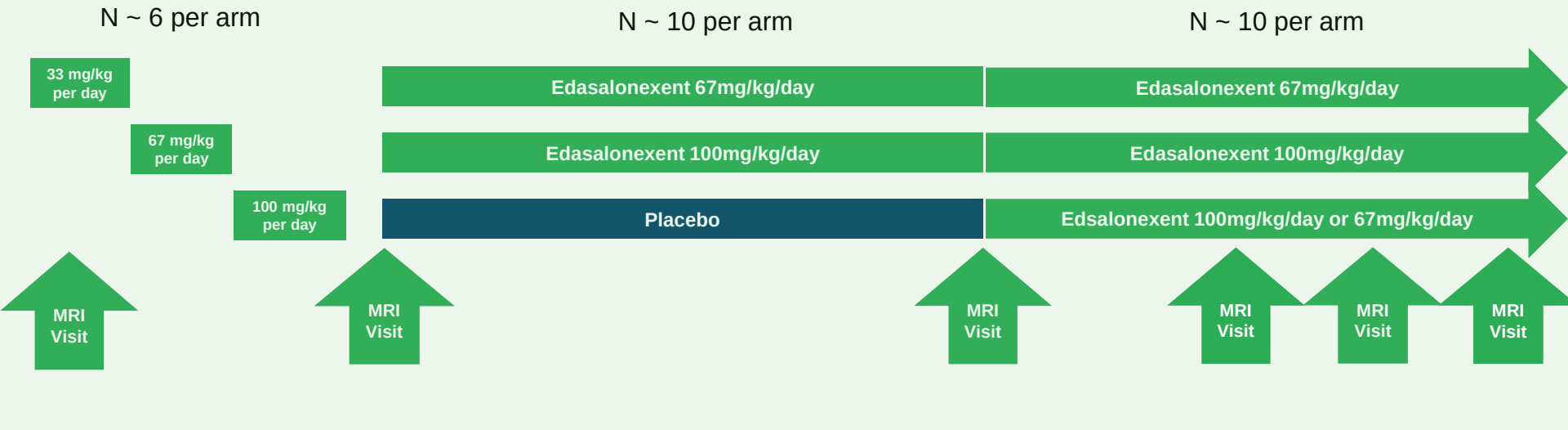
Part A
7-day, open-label dose ranging trial

Part B
12-week, randomized, double-blind placebo-controlled trial

Part C
36-week, open-label treatment period



Endpoints:
safety, tolerability, pharmacokinetics and biomarker

Primary endpoint:
T2 of lower leg muscles
Other measures:
safety and tolerability
timed function tests – 10MWRT, 4SC, time-to-stand; NSAA, muscle strength, PODCI

Additional safety and functional assessments

MRI T2 and fat fraction

MoveDMD Trial Part A: Initial Assessment of Safety and Pharmacokinetics in DMD

- Key objectives:
  - Assess safety in 3 cohorts of boys age 4 -7 with Duchenne
    - Cohort 1 – 33 mg/kg per day
    - Cohort 2 – 67 mg/kg per day
    - Cohort 3 – 100 mg/kg per day
  - Measure pharmacokinetics in pediatric patients under various dietary conditions
    - On Day 1 and Day 7 single doses administered with high or low-fat diet in random sequence
  - Determine whether pediatric exposures are similar to those at which NF-κB inhibition was observed in adults
  - Assess effect on NF-κB gene expression after 7 days of dosing

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

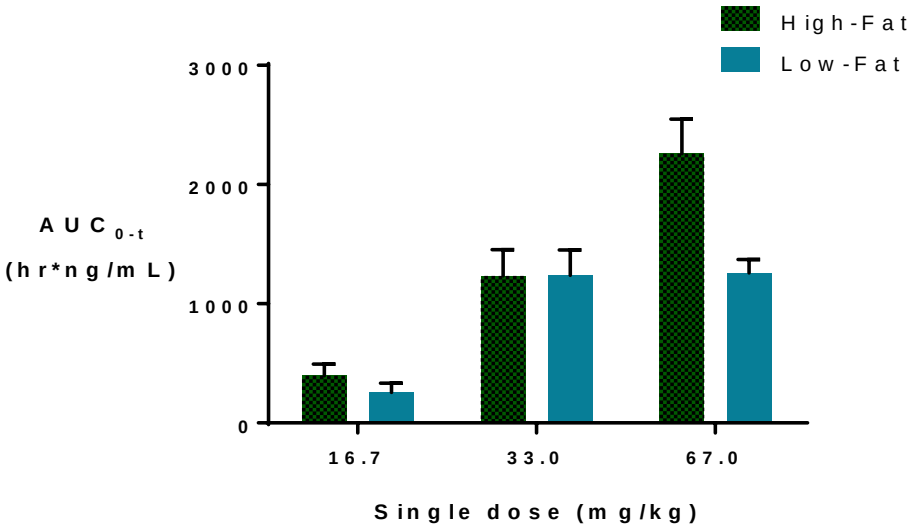
Results: Safety and Tolerability

- Generally well tolerated
  - No serious adverse events, no discontinuations
  - All patients able to take 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):

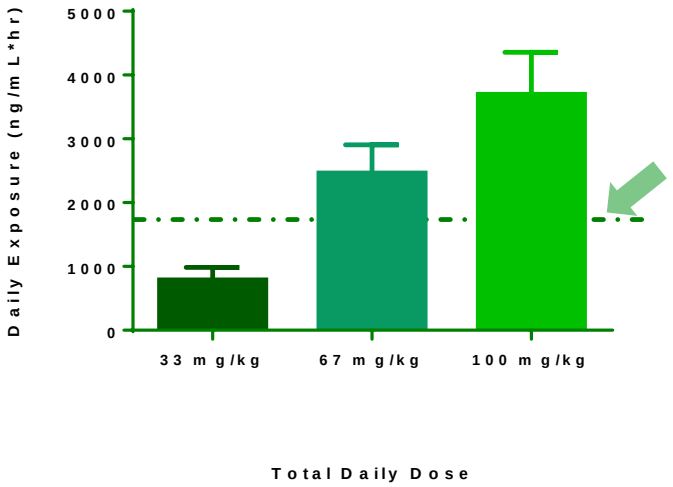
	33 mg/kg n=5	67 mg/kg n=6	100 mg/kg n=6	Total n=17
Diarrhea	0	0	4	4
Feces soft	1	1	1	3
Abdominal pain upper	1	0	1	2

Pharmacokinetics: Dose-Dependent Increases in Exposure, with Modest Effect of Meal Composition

Exposure: AUC at single doses



Predicted Daily Exposure

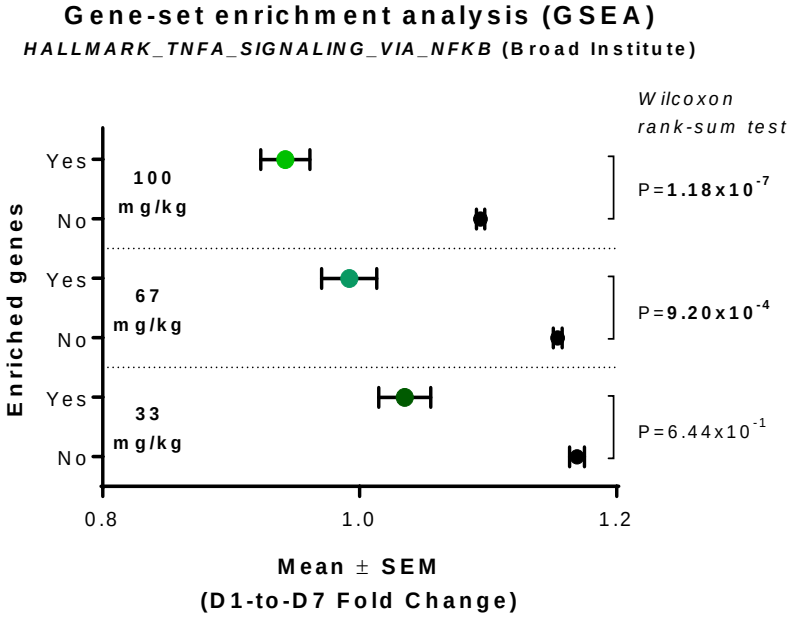


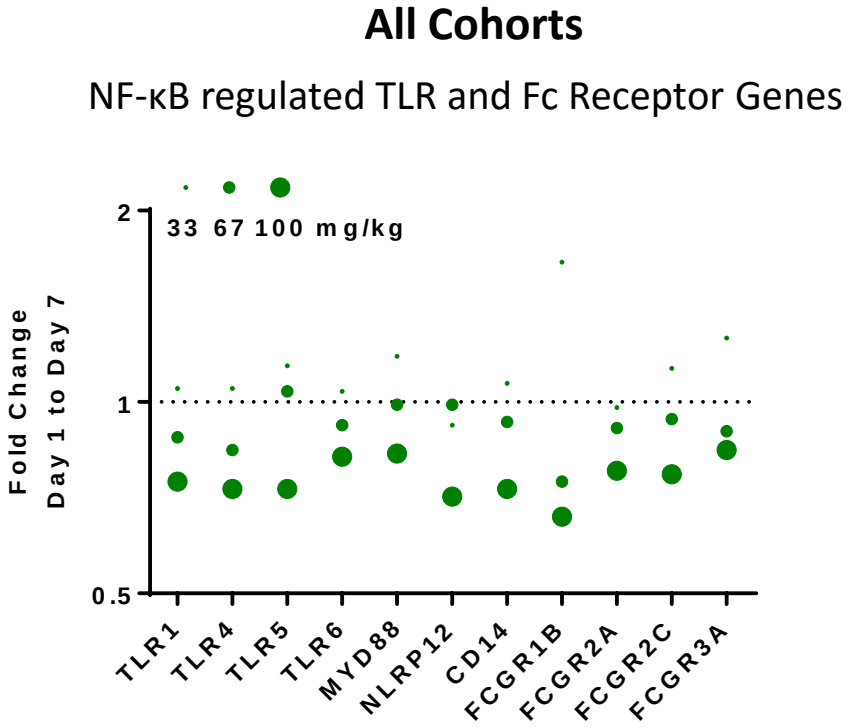
Average Daily Exposure in Phase 1 in Adults Showing NF-κB Inhibition

- With single doses of 33 mg/kg there were minimal differences in AUC or C_{max} when edasalonexent was administered either with a high-fat or a low-fat meal
- Phase 2 dose: A total daily dose of 67 or 100 mg/kg administered as 33 mg/kg either 2 or 3 times daily with low- or high-fat meal

MoveDMD Part A: Edasalonexent Reduced the NF-κB Gene Signature in DMD Blood after 1 Week of Treatment

- Genes enriched for NF-κB targets were assessed in whole blood mRNA after one week on edasalonexent. Compared with baseline, NF-κB gene-set was significantly inhibited with the two higher doses.
- Broad Institute curated HALLMARK NF-κB gene-set (comprises 200 NF-κB regulated genes) was significantly decreased when compared to all other genes
- Dose-proportional decrease seen in the two higher dose groups with this gene-set. TLR and Fc-receptor genes showed a dose-dependent reduction in whole blood





Conclusions

- In MoveDMD Part A, edasalonexent was found to be generally well-tolerated. AUC and C_{max} were approximately dose-proportional.
- After one-week of dosing, NF-κB gene-set was significantly inhibited in whole blood mRNA with the two higher doses. IL-12 and osteopontin protein levels in serum were also reduced.
- These results support the ongoing Part B of the trial, a 12-week, double-blind, placebo-controlled efficacy trial with MRI and functional endpoints.
- By reducing inflammation and muscle degeneration with potentially positive longer-term effects on muscle regeneration and function, edasalonexent may have the potential to be disease-modifying in DMD patients regardless of mutation type.

Thank You!

- Patients and families
- Patient 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