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

Richard Finkel, MD[1]; Krista Vandenborne, PT, PhD[2], H Lee Sweeney, PhD [2], Erika Finanger, MD [3], Gihan Tennekoon, MBBS, MRCS, LCRP [4], Perry Shieh, MD, PhD [5], Rebecca J. Willcocks, PhD [2], Glenn Walter PhD [2], William Rooney PhD [3], Sean C Forbes, PhD [2], William T. Triplett, BSc [2], Sabrina W. Yum, MD [4], Maria Mancini, MHP [6], James MacDougall, PhD [6]; Angelika Fretzen, PhD [6], Pradeep Bista, PhD [6]; Andrew Nichols, PhD [6]; Joanne Donovan, MD, PhD [6]

[1]Nemours Children's Health System, Orlando, FL; [2]University of Florida Health, Gainesville, FL; [3]Oregon Health Sciences University, Portland, OR; [4]The Children's Hospital of Philadelphia, Philadelphia, PA; [5]University of California, Los Angeles, Los Angeles, CA; [6]Catabasis Pharmaceuticals, Cambridge, MA

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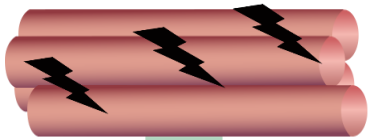
Disclosures

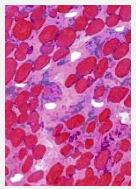
- Richard Finkel received research support and honoraria from Catabasis Pharmaceuticals, Inc.
- The clinical trial was sponsored by Catabasis Pharmaceuticals, Inc.
- Krista Vandenborne, H. Lee Sweeney, Erika Finanger, Gihan Tennekoon, Perry Shieh, Rebecca Willcocks, Sean Forbes, William Triplett, and Sabrina Yum received research support from Catabasis. H. Lee Sweeney, Erika Finanger, and Perry Shieh received honoraria from Catabasis
- 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



Inflammation in Infancy



Inflammation

Cytokines

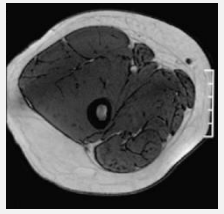
Fibrosis

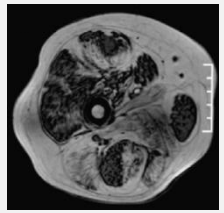
Degeneration

MuRF1/MAFbx

Control

DMD





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

Activated NF-κB

Regeneration

Cyclin D1

Satellite Cell

Myoblasts

MyoD

Myotube

Dystrophin and Membrane Stability

MMP-9

miRNA

β-Dystroglycan

Dystrophin

Actin

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

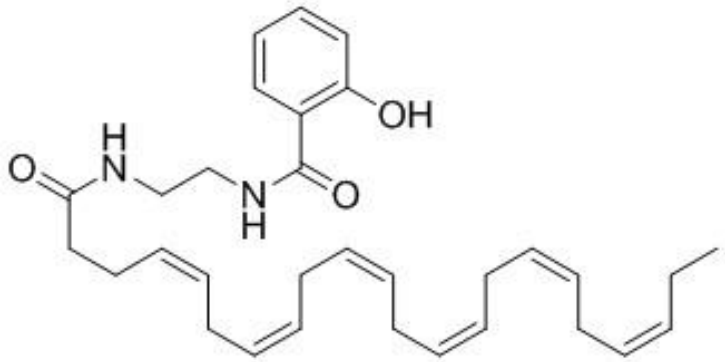
Disease Progression

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

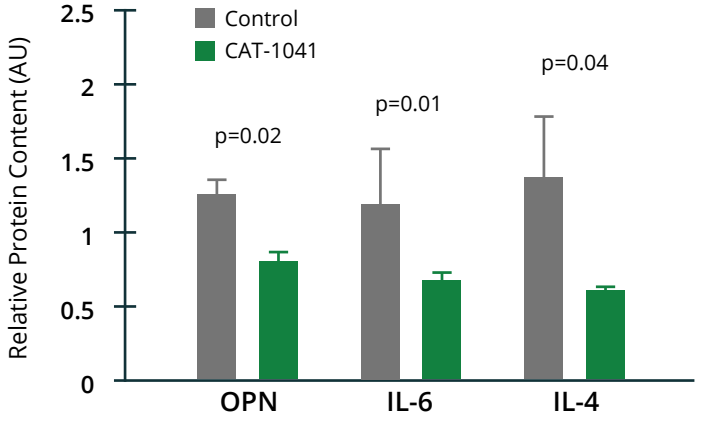
- **Edasalonexent is an orally-administered small molecule that is not a steroid**



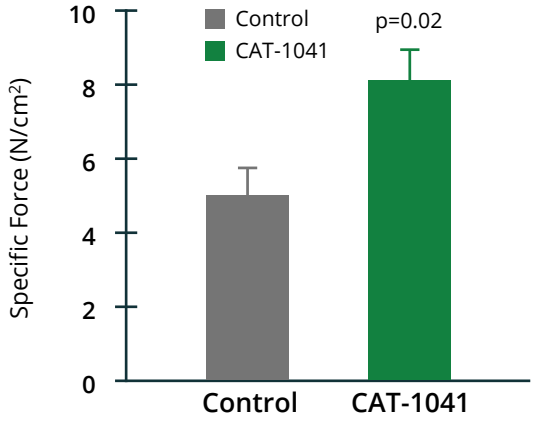
- **Being developed as foundational therapy for patients with DMD regardless of mutation, both as monotherapy and potentially to be combined with dystrophin-targeted therapies**

- **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

Reduced Inflammation in *mdx*



Increased Diaphragm Specific Force in *mdx*



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

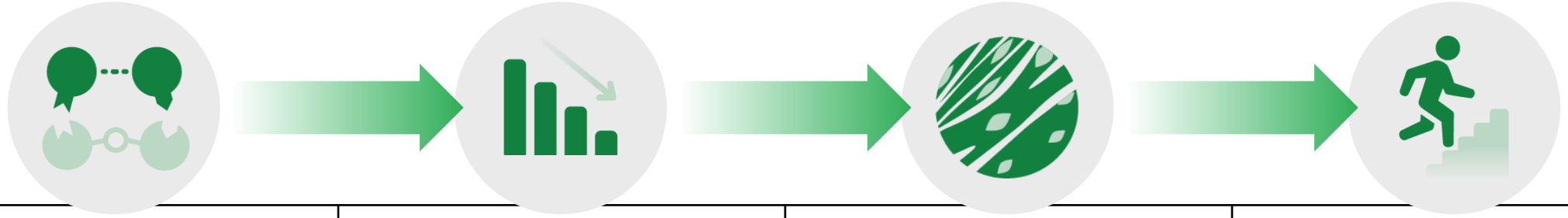
Design of MoveDMD, a Phase 1/2 Trial with Open-Label Extension

- **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

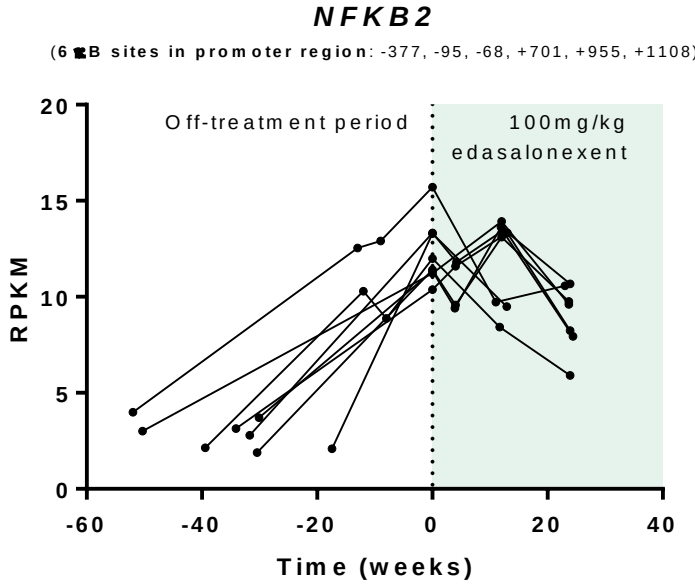


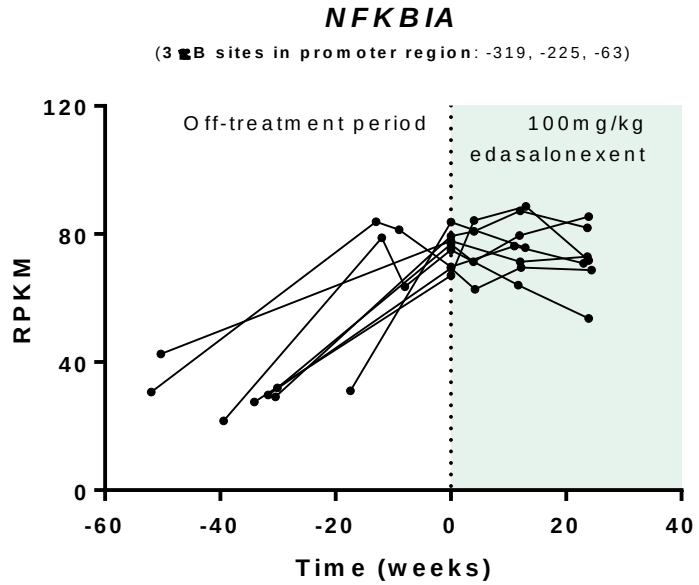
NF-κB Target Engagement	Biomarkers	Muscle MRI	Functional
▸ Inhibition of NF-κB targeted gene set in peripheral blood	▸ CRP, biomarker of inflammation ▸ Muscle enzymes	▸ MRI T2 of upper and lower leg ▸ MRS muscle fat	▸ North Star Ambulatory Assessment and Timed Function Tests

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





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

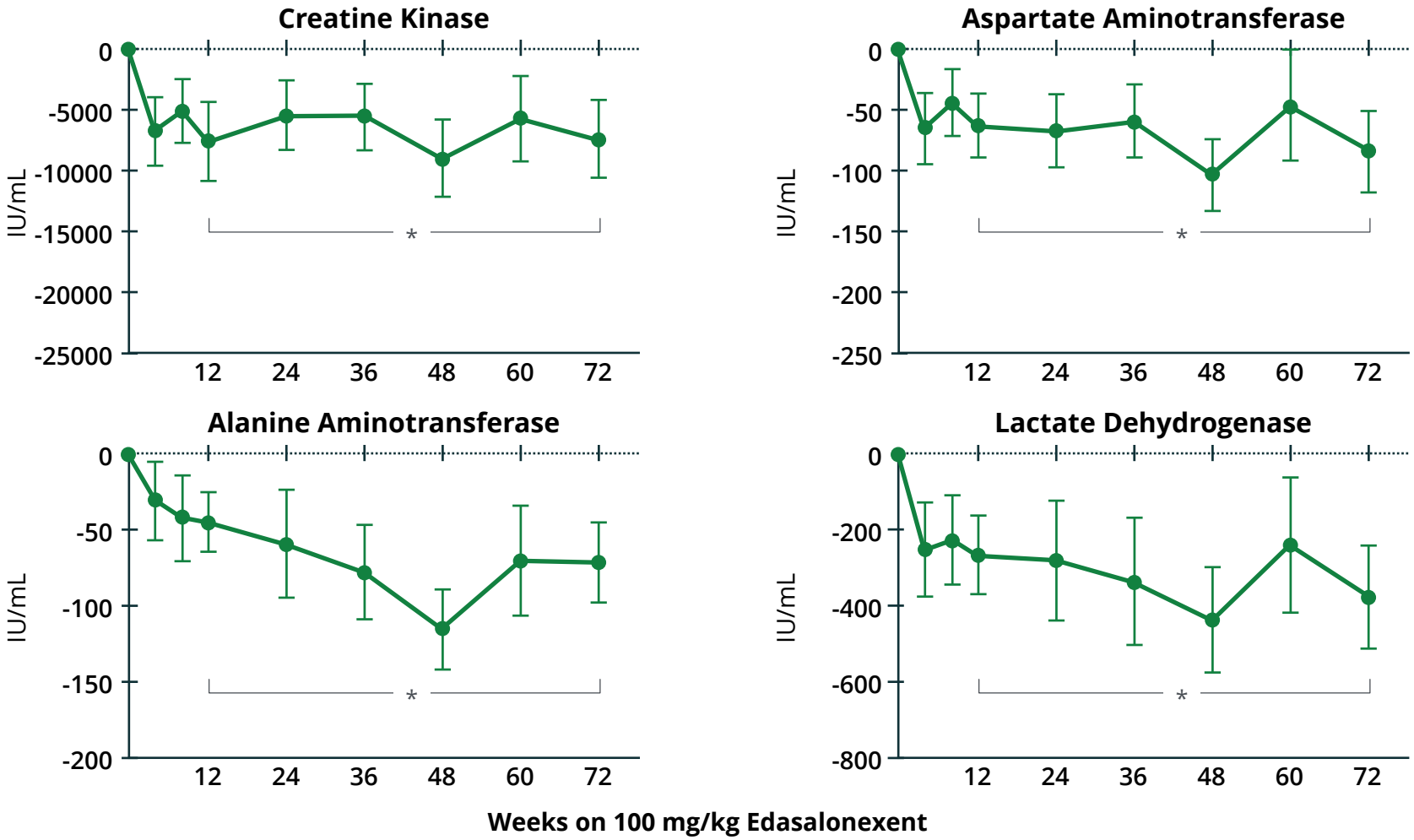
	Off-treatment period	100 mg/kg edasa
NFKB2	4.60	0.74
NFKBIA	2.50	0.97

- **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

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**

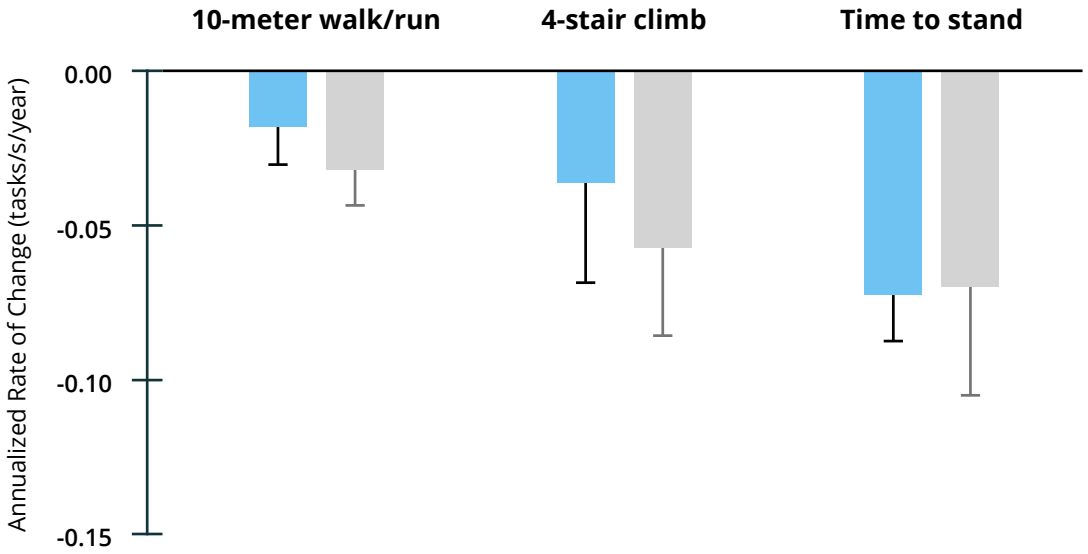


Plasma muscle enzymes are elevated 10 to 100 fold in DMD, indicative of leakage from damaged myocytes

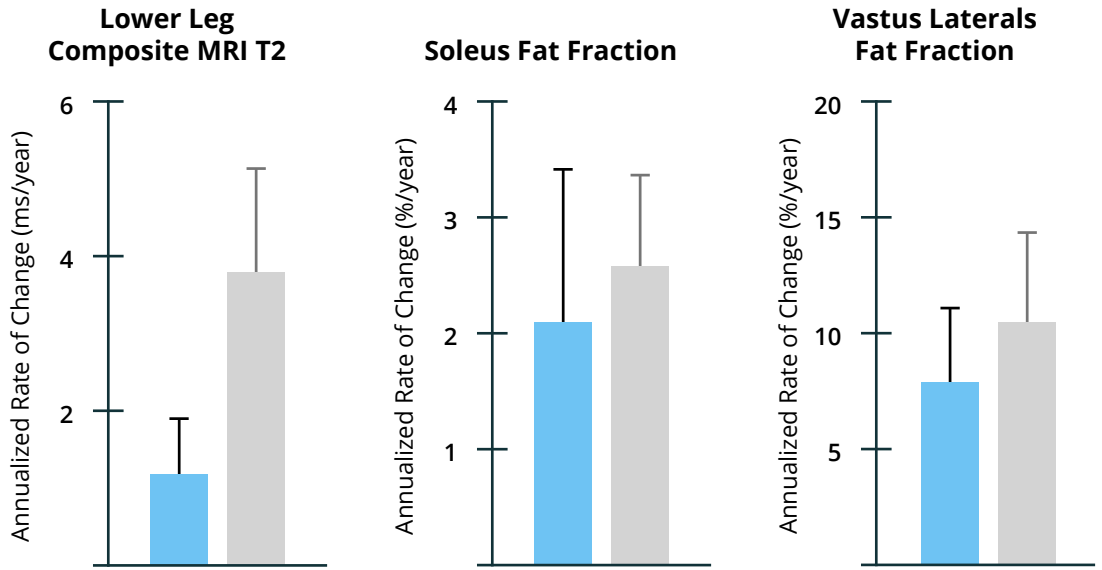
Means ± SEM shown; * p<0.05 for mean change from baseline after 12 weeks

Both Functional Decline and MRI Disease Progression Were Similar in Untreated Patients in MoveDMD and ImagingDMD Natural History Studies

Functional Declines in Velocity for Patients Not Receiving Steroids or Edasalonexent



MRI Shows Disease Progression



Non-Steroid Cohort: Natural History ImagingDMD

Off-treatment: MoveDMD

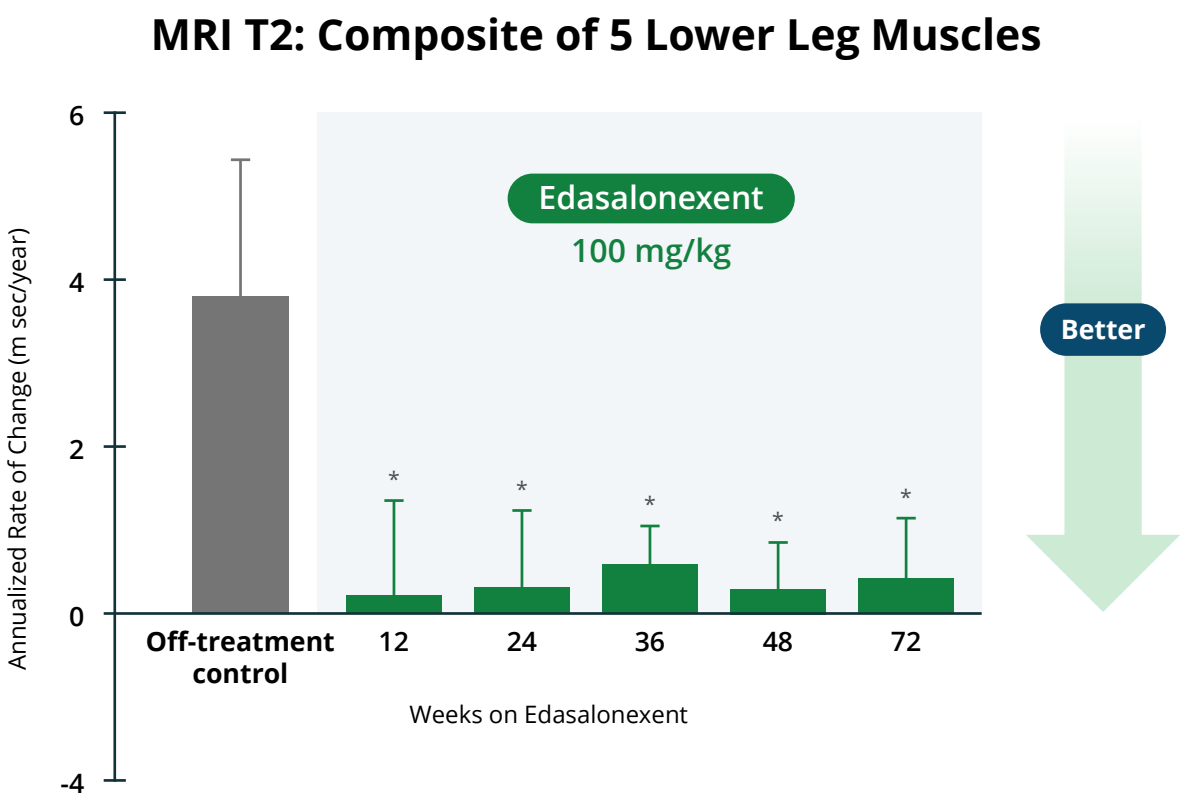
- **Off-treatment, steroid-naïve patients enrolled in the MoveDMD study with same data collection protocols had declines consistent with observations in the ImagingDMD natural history study.**
  - Declines in function in natural history study at ages 4-7 were similar to those observed in the MoveDMD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

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



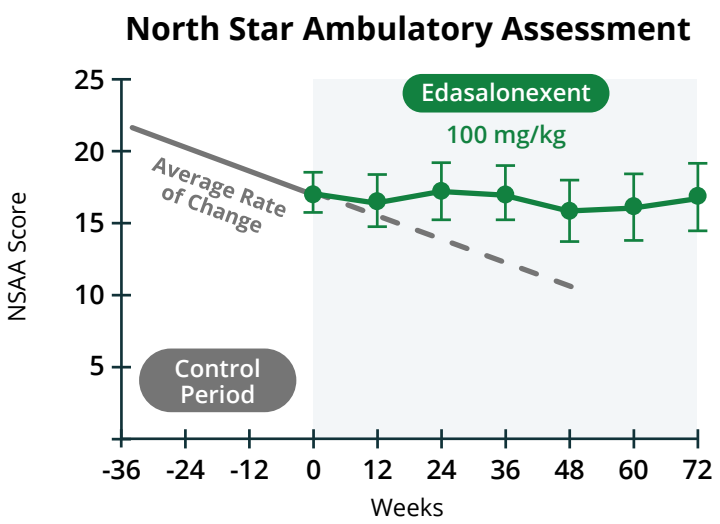
- MRI T2 is tightly correlated with fat fraction and functional measures
- Composite of 5 lower leg muscles MRI T2 (soleus, gastrocnemius, anterior and posterior tibialis, peroneals) used to encompass muscles at various stages of disease progression and minimize variability
- Following 72 weeks of edasalonexent, 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**

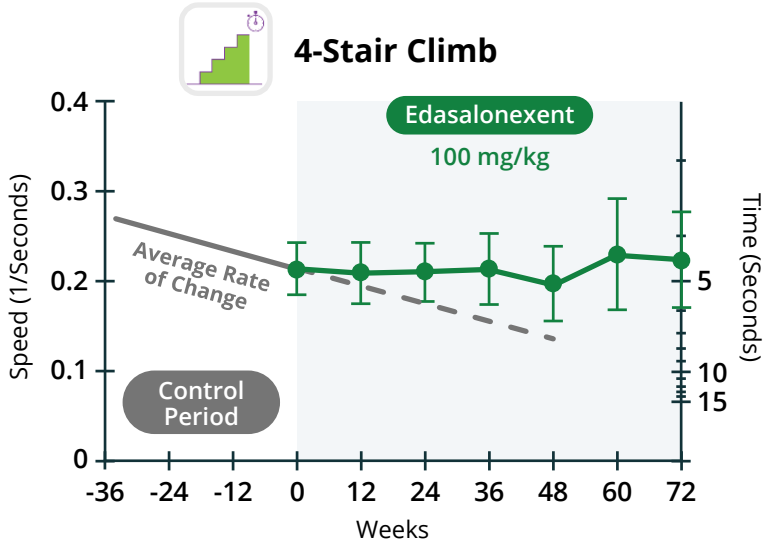
Means + SEM; mixed model comparison with off-treatment period
* Week 12: p=0.002, n=16; Week 24: p=0.004, n=14; Week 36: p=0.032, n=13; Week 48: p=0.018, n=12; Week 72: p=0.052, n=9

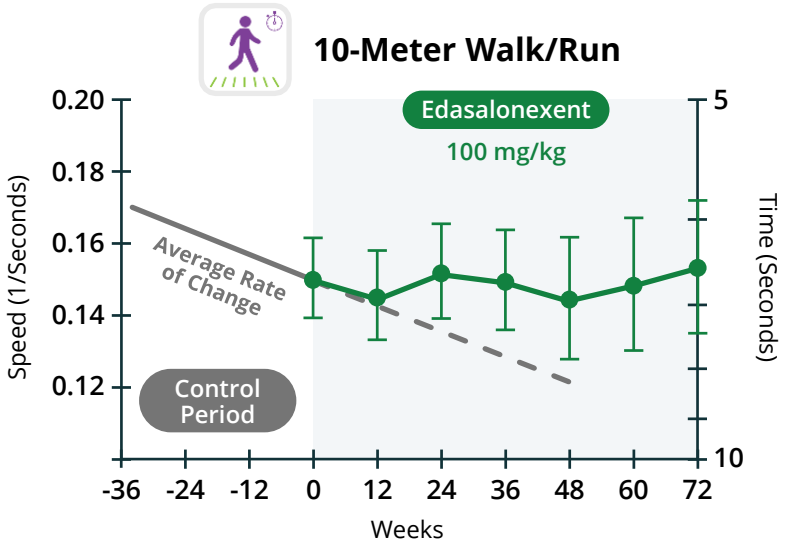
In Phase 2 MoveDMD Trial and Open-Label Extension:

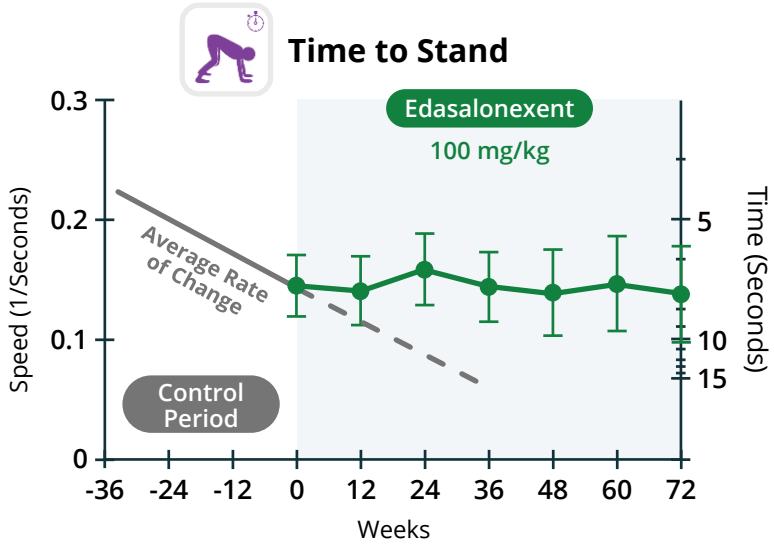
All Assessments of Function Stabilized on Edasalonexent Compared to Off-Treatment Control

- **Sustained stabilization up to 72 weeks on edasalonexent**







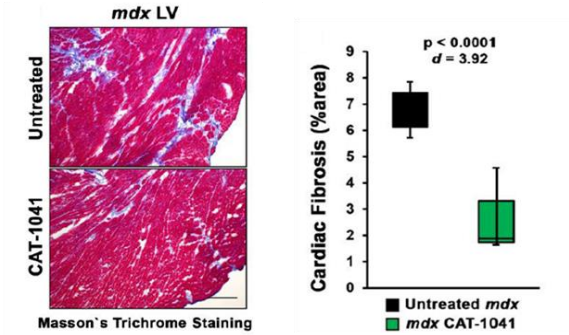


Means ± SEM shown. Includes data of all boys initially started on 100 mg/kg dose (n=16) with 11 boys participating through 72 weeks.

NF-κB Inhibition Showed Potential for Cardiac Benefits in DMD

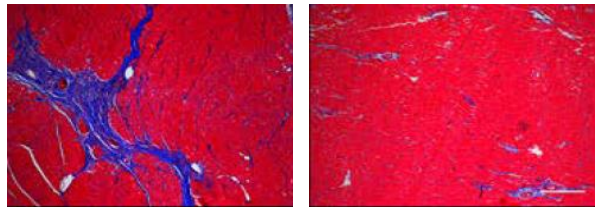
- **Elevated resting heart rate is initial manifestation of cardiac disease in DMD**
  - Cardiac failure is a leading cause of mortality in DMD
  - Elevated heart rate triples the risk of cardiomyopathy several years later
- **Edasalonexent analog had positive effects on fibrosis in *mdx* and GRMD models**

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



12 month-old GRMD

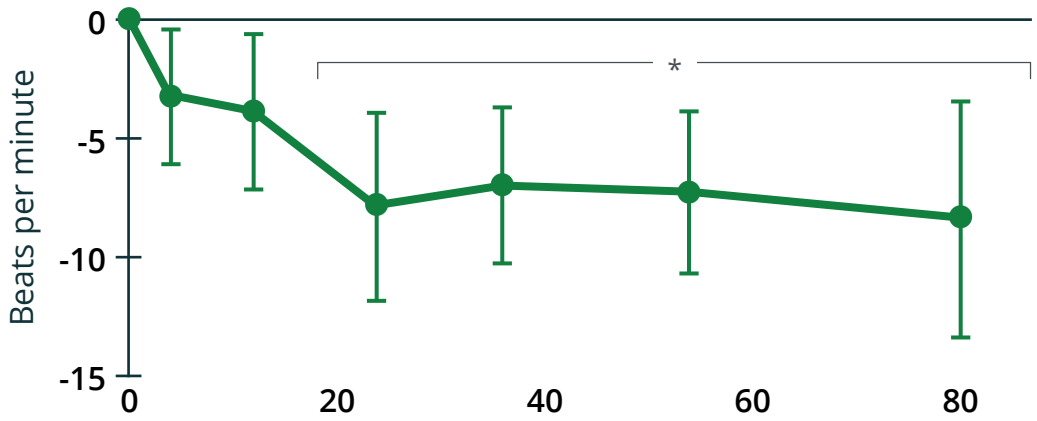
Untreated CAT-1041



Masson's Trichrome Staining

In Phase 2 MoveDMD Trial and Open-Label Extension:

Heart Rate: Change from Baseline



- **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

Thomas, et al. *Pediatr Cardiol.* 2012 33(7):1175-9.
Hammers, et al. *JCI Insight* 2016 1(21): e90341
Fleming, et al., *Lancet* 2011 377: 1011-18
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)

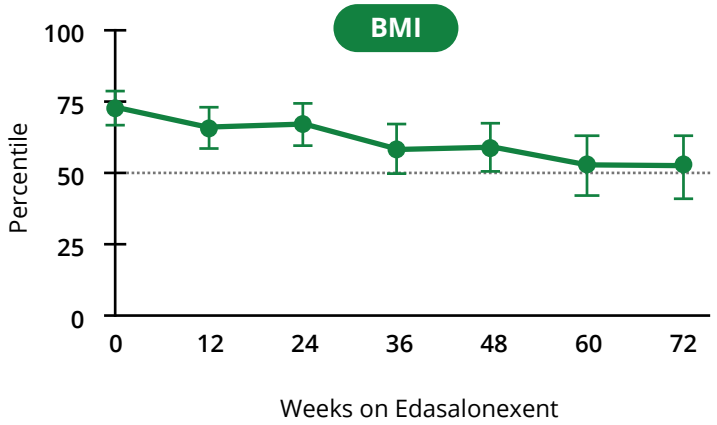
Treatment-Related Adverse Events >5% System Organ Class/ Preferred Term	Edasalonexent Overall (N=31) n %
Gastrointestinal disorders	
Diarrhoea	16 (51.6%)
Abdominal pain upper	7 (22.6%)
Nausea	3 (9.7%)
Vomiting	3 (9.7%)
Abdominal discomfort	2 (6.5%)
Abdominal pain	2 (6.5%)
Faecal incontinence	2 (6.5%)
Faeces soft	2 (6.5%)
Metabolism and nutrition disorders	
Decreased appetite	4 (12.9%)

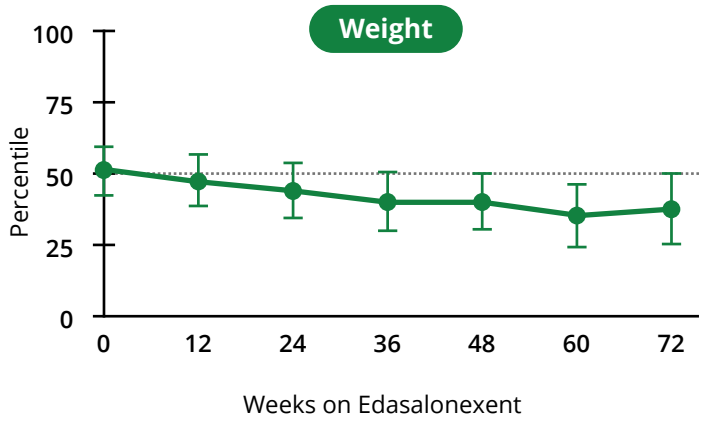
In Phase 2 MoveDMD Trial and Open-Label Extension:

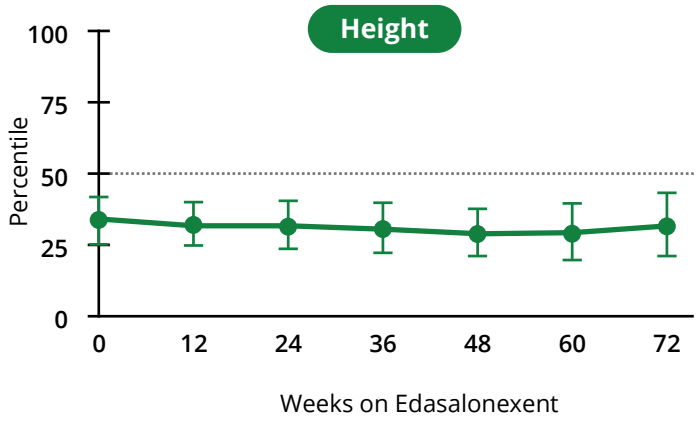
Safety: Growth Continues as Expected Compared to Standard Growth Charts

- **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





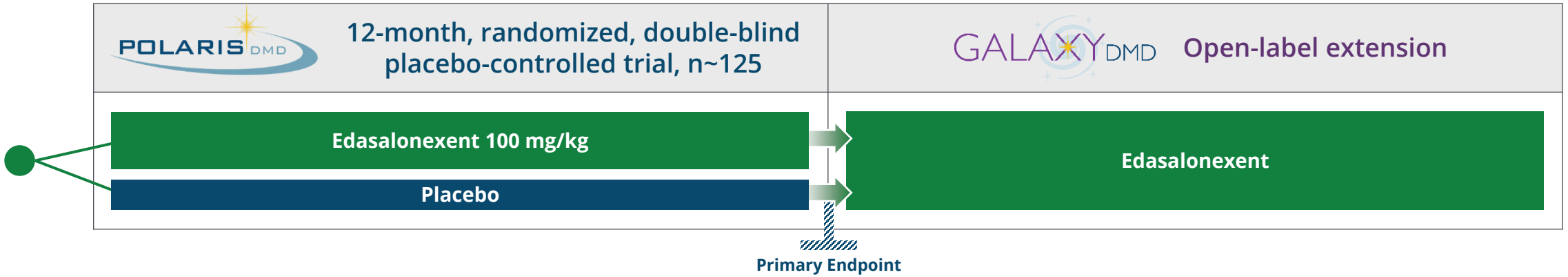


Means ± SEM shown
Comparison with CDC growth charts: https://www.cdc.gov/growthcharts/clinical_charts.htm

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

NCT03703882 and NCT03917719

Acknowledgements

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