Targeting NF-κB with Edasalonexent for Muscle and Bone Health in Duchenne Muscular Dystrophy

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Disclosures

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, clinical trial plans, product development plans and prospects, including statements about future clinical trial plans including, among other things, statements about our single global Phase 3 PolarisDMD trial in Duchenne muscular dystrophy, or DMD, to evaluate the efficacy and safety of edasalonexent for registration purposes, our plans to continue to evaluate data from the open-label extension of our MoveDMD® clinical trial of edasalonexent for the treatment of DMD, and our plans to combine edasalonexent treatment with other DMD treatments such as gene therapy and other dystrophin-targeted approaches. 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.

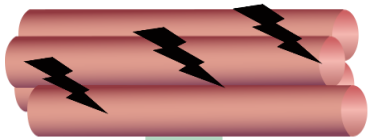
The forward-looking statements contained in this presentation and in remarks made during this presentation and the following Q&A session are subject to important risks and uncertainties that may cause actual events or results to differ materially from our current expectations and beliefs, including: uncertainties inherent in the initiation and completion of preclinical studies and clinical trials and clinical development of our product candidates; 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; 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 Annual Report on Form 10-Q for the period ended March 31, 2019, 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.

Joanne Donovan is an employee of Catabasis Pharmaceuticals, Inc.

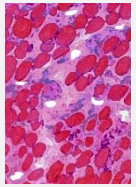
Edasalonexent is an investigational agent that is not approved in any territory.

Activation of NF-κB in Muscular Dystrophy Is a Key Factor in Disease Progression in Skeletal and Cardiac Muscle

No Dystrophin + Mechanical Stress



Inflammation in Infancy



Inflammation

Cytokines

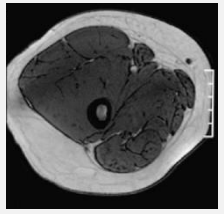
Fibrosis

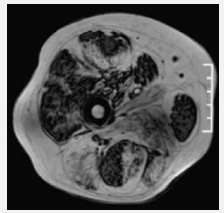
MuRF1/MAFbx

Degeneration

Control

DMD





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

Activated NF-κB

Regeneration

Satellite Cell

Myoblasts

Myotube

Cyclin D1

MyoD

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

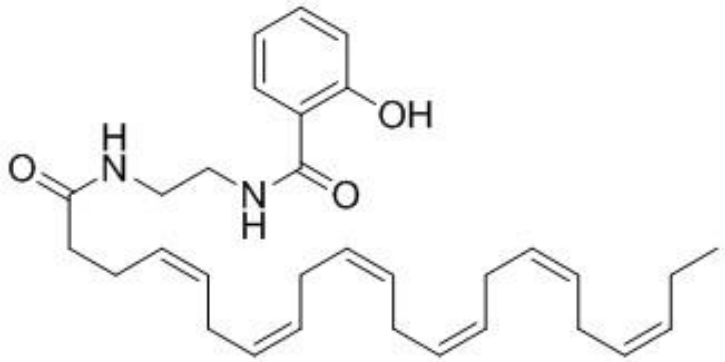
Disease Progression

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

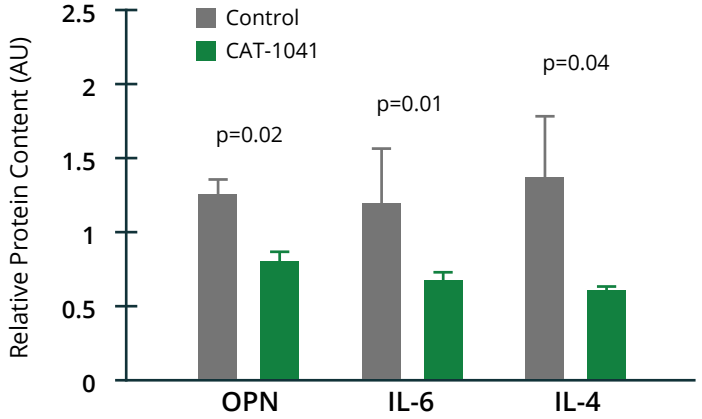
- **Edasalonexent is an orally-administered small molecule that is not a steroid**



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

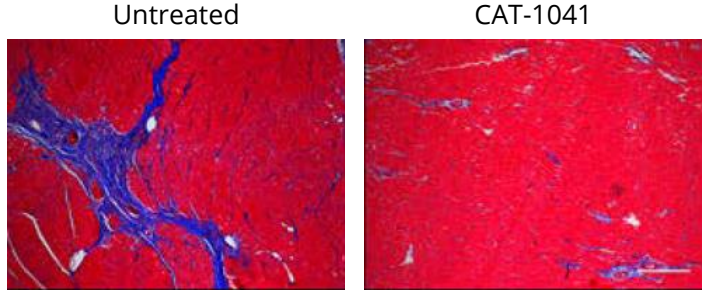
- **Inhibiting NF-κB slows disease progression in animal models of DMD**
  - Oral administration of edasalonexent or analog (CAT-1041) reduces muscle inflammation and improves function in mdx mice and GRMD dog

Reduced Inflammation in *mdx*



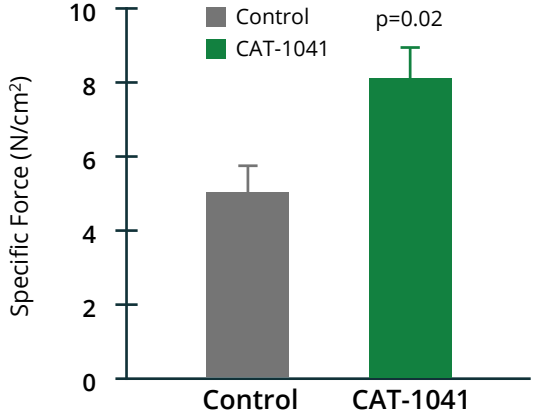
Decreased Cardiac Fibrosis

12 month-old GRMD



Masson's Trichrome Staining

Increased Diaphragm Specific Force in *mdx*

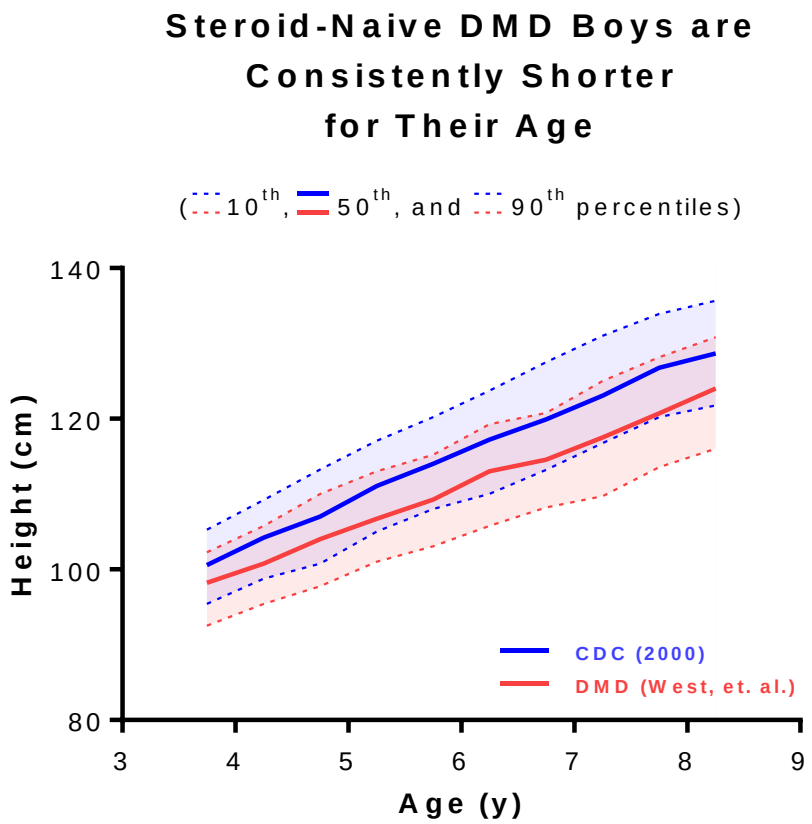


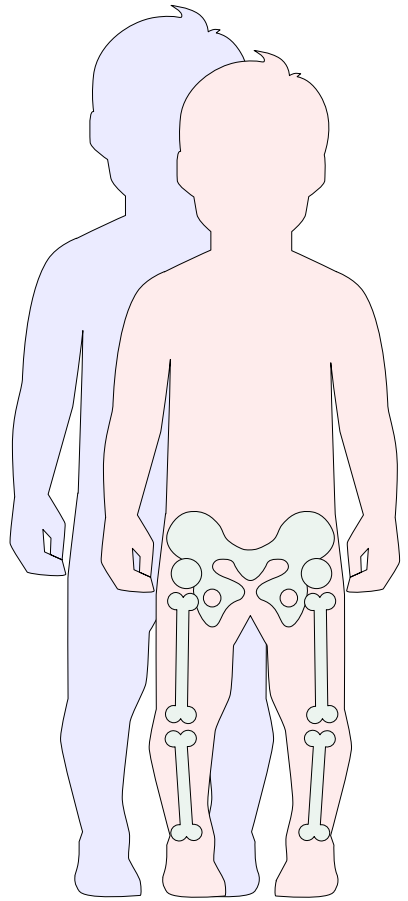
Means + SEM

Hammers et al., 2016 JCI Insight

DMD Boys Are Shorter From an Early Age

- Normal length at birth
- Progressive divergence in the difference in stature (compared to healthy controls)
- ~5% difference in height from healthy controls

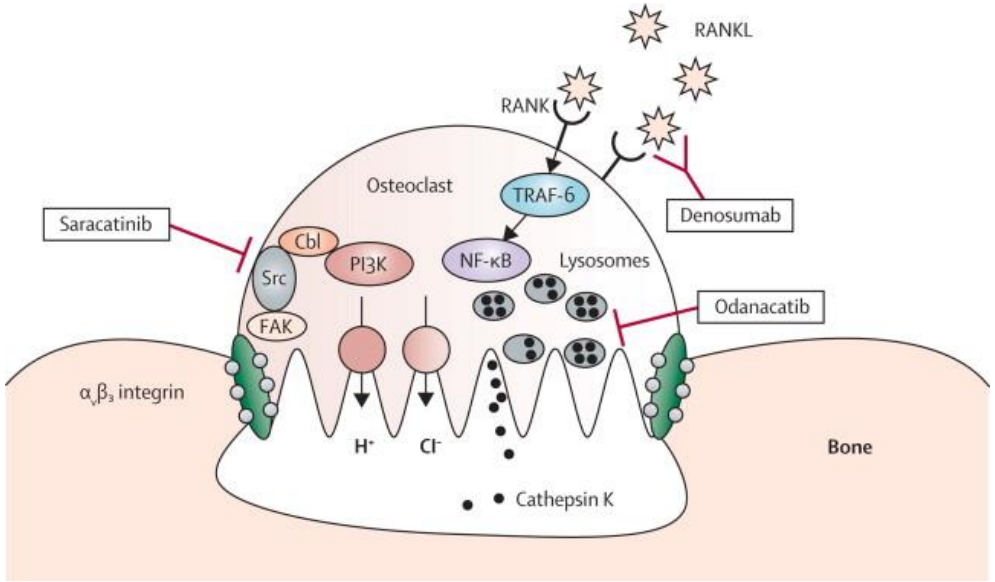




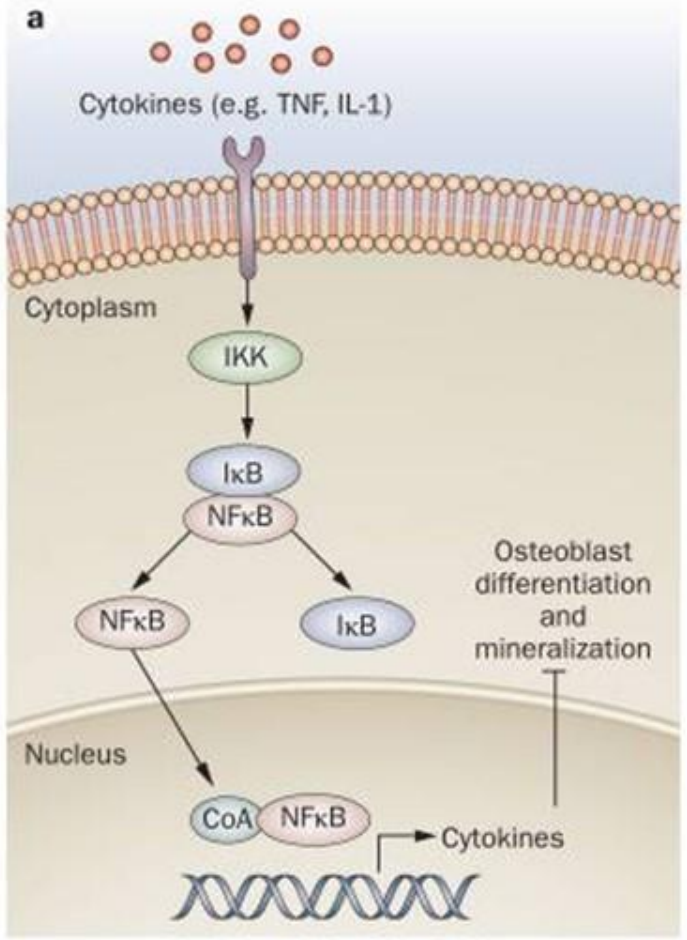
West et al., 2013 J Peds

NF-κB Activity Mediates Inflammation-induced Bone Loss

- **RANK-ligand mediated NF-κB activates osteoclast differentiation and function**
  - Drives bone loss
- **NF-κB activation additionally inhibits osteoblast maturation**
  - Inhibits new bone growth



(Rachner, et. al., *Lancet* **2011**)

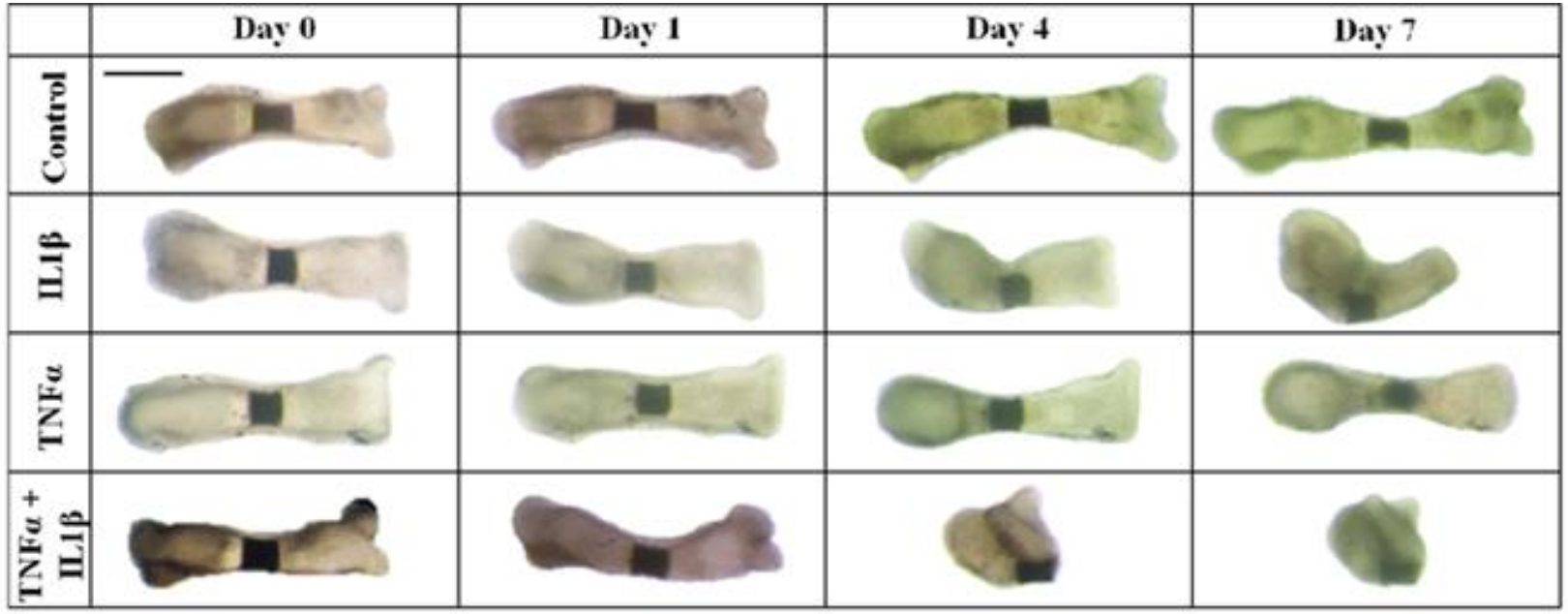


(Krum, et. al., *Nature Rev Rheum* **2010**)

Inhibition of NF-κB has the potential to reduce bone loss and enhance new bone growth in patients affected by DMD

Persistent NF-κB Activation Reduces Bone Length

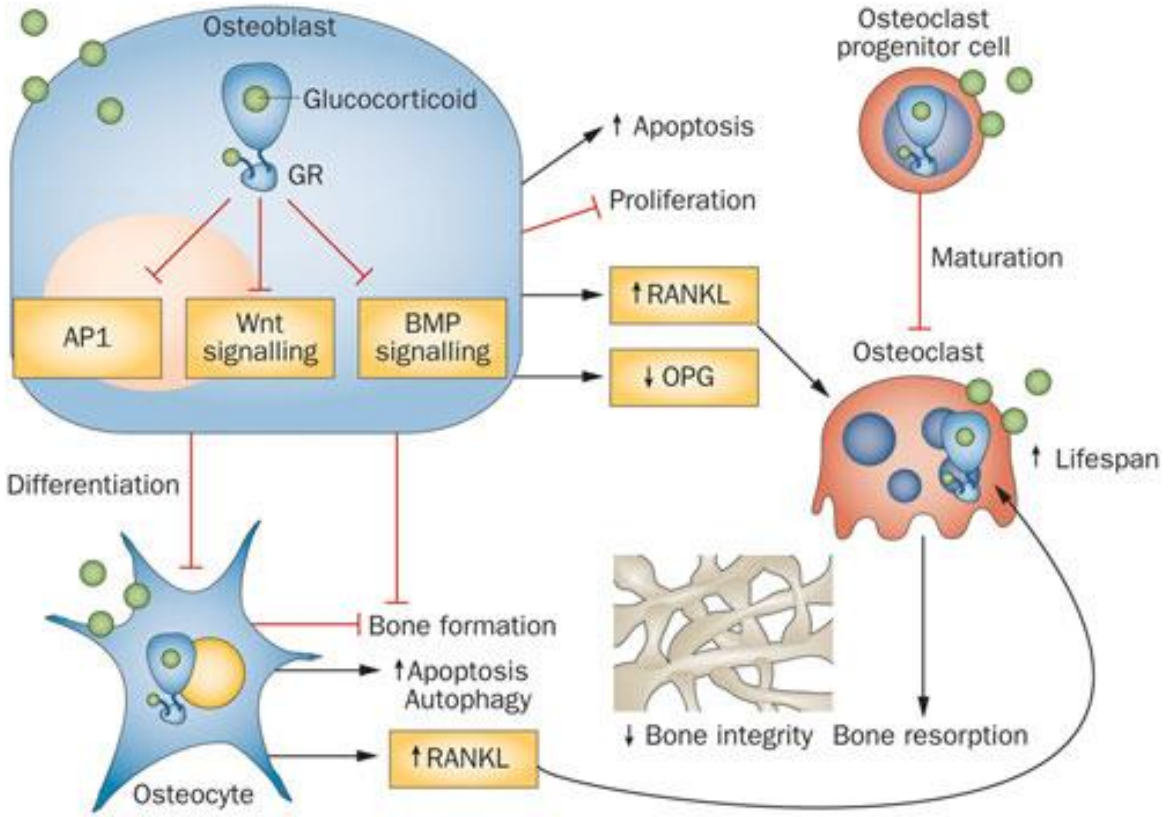
- **Inflammatory stimuli that activate NF-κB cause reduced bone lengths**
  - (*in situ* fetal mouse metatarsals)



Landman, et. al., *Arthritis Research and Therapy* **2013**

Corticosteroid Activity Favors Bone Resorption

- **Corticosteroid molecules enhance osteoblast apoptosis and reduce ossification**
- **Steroid-induced increase in RANK-ligand and decrease in Osteoprotegerin leads to enhanced bone resorption and osteoporosis**



(Baschant et. al., *Nature Rev Rheum* **2012**)

- **Clinical consequence is an increased risk of fractures with minimal mechanical stress**

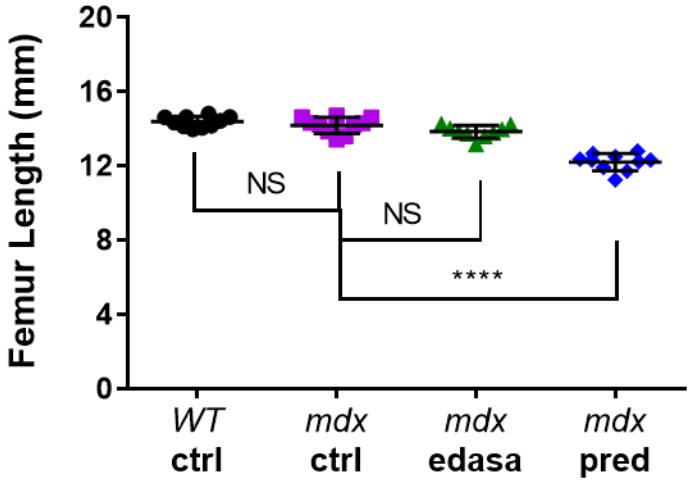
(Joseph et. al., *JAMA Neurology* **2019**)

Bone Sparing Effect of Edasalonexent in *mdx* Mice

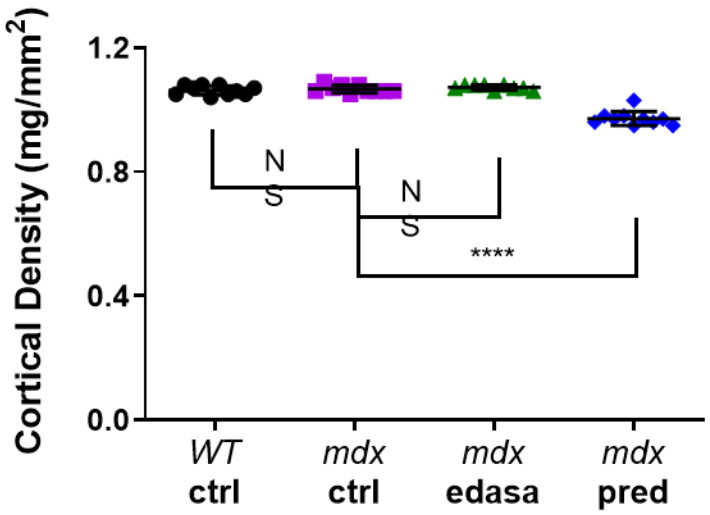
Compared to bone loss seen with prednisolone

- **No bone metabolism defects in young *mdx* mice relative to WT (measured by peripheral quantitative CT)**
- **Prednisolone treatment (5mg/kg daily) for ~6 weeks significantly reduced bone length and density**
- **With edasalonexent treatment bone length and density are normal**

Femur Length



Cortical Density



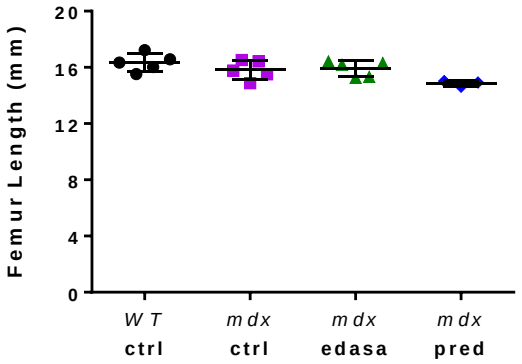
**** P<0.0001 vs *mdx* control

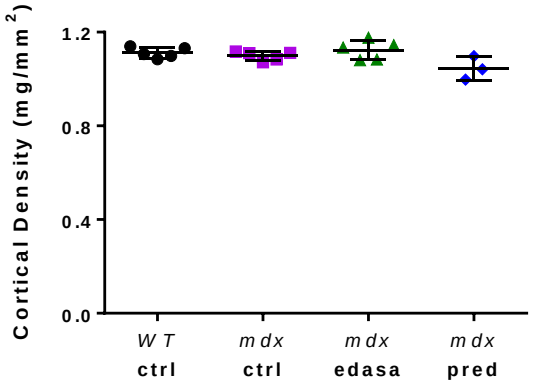
Edasalonexent Maintains Bone Sparing Effect in *mdx* Mice After Long Term Treatment

- **Long-term low dose corticosteroid is sufficient to induce bone loss and reduced femur lengths**

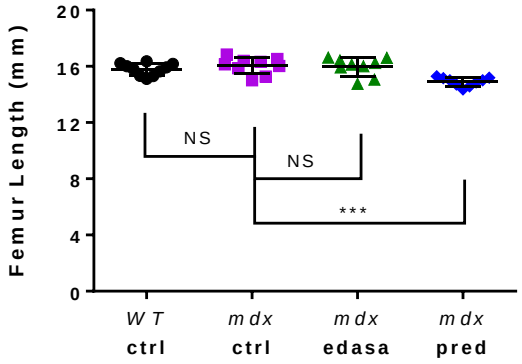
Femur Length | **Cortical Density**

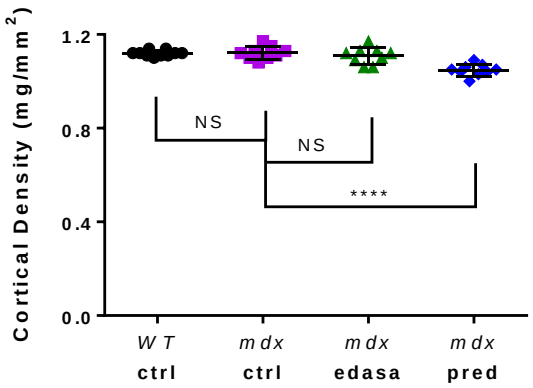
3-month treatment
1 mg/kg Prednisolone





6-month treatment
1 mg/kg Prednisolone

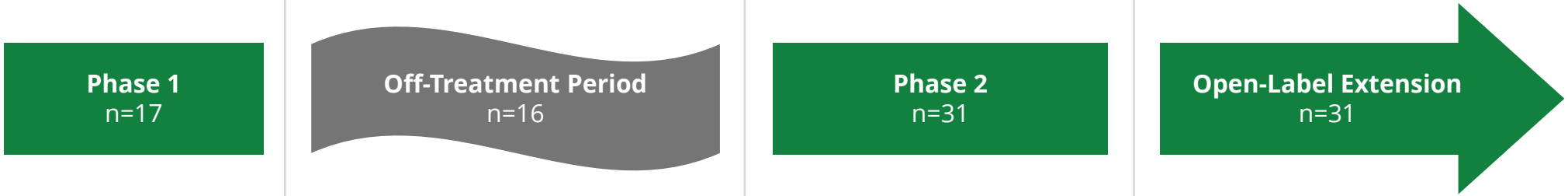




****p<0.0001, ***p<0.005

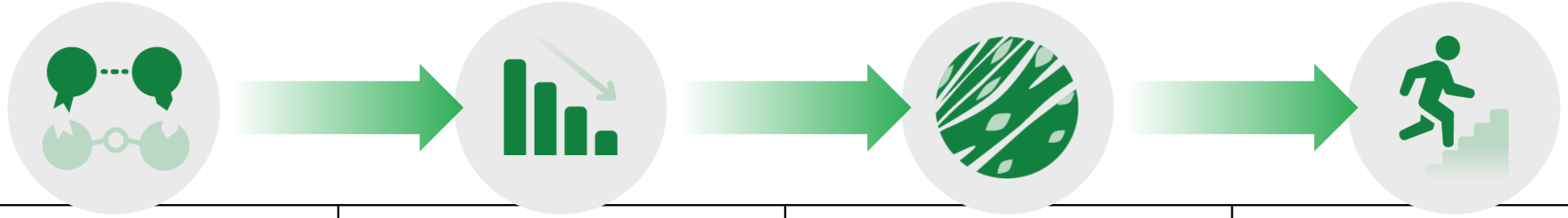
Design of MoveDMD, a Phase 2 Trial with Open-Label Extension

- **Study Objectives**
  - Proof of concept using MRI to assess changes in muscle health
  - Long-term study to enable Phase 3
- **Key Inclusion / Exclusion criteria**
  - Age 4 to 8th birthday not on corticosteroids for at least 24 weeks



- **Analysis Plan**
  - 12-week placebo control period
  - **Compare changes during off-treatment control period with changes after initiation of edasalonexent**

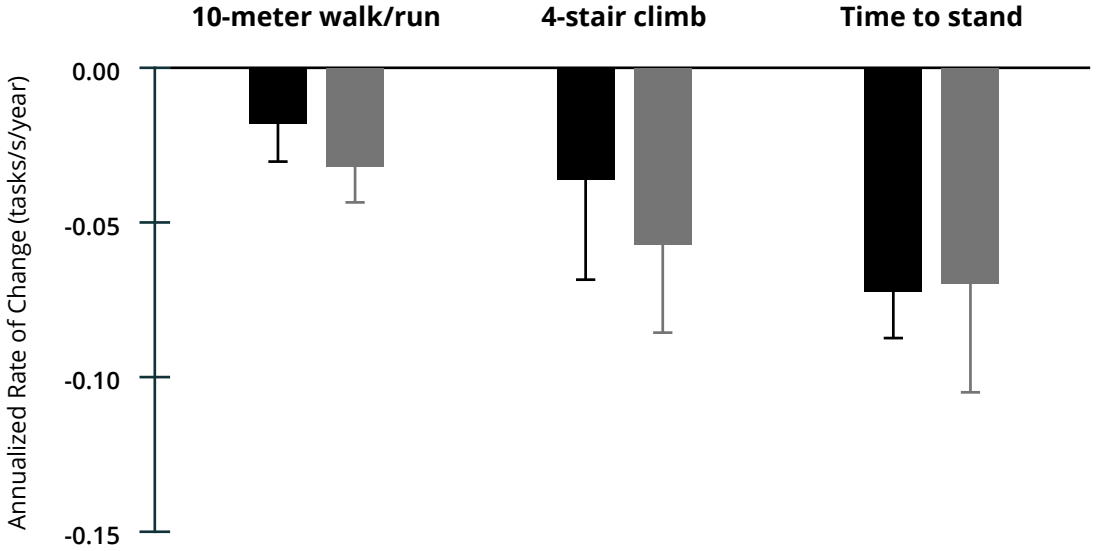
Range of Endpoints to Demonstrate Proof of Concept and Support Design of Phase 3



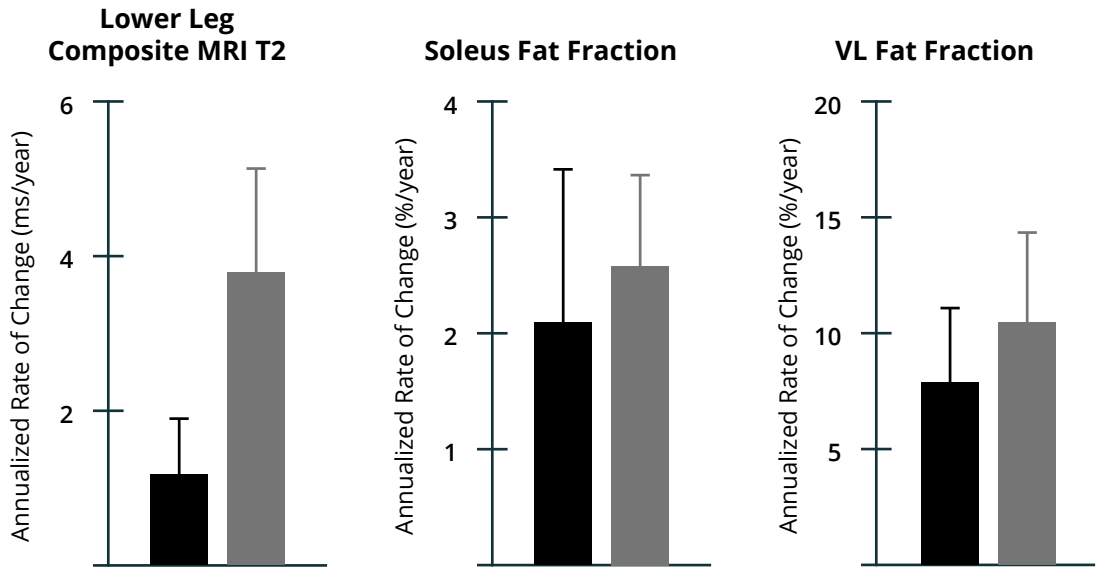
NF-κB Target Engagement	Biomarkers	Muscle MRI	Functional
▸ Inhibition of NF-κB targeted gene set in peripheral blood	▸ CRP, biomarker of inflammation ▸ Muscle enzymes	▸ MRI T2 of upper and lower leg ▸ MRS muscle fat	▸ North Star Ambulatory Assessment and Timed Function Tests

Steroid-Naïve Boys in Age Range 4 to 8th Birthday Are Declining in Function and Progressing on MRI

Functional Decline in Boys Not Receiving Steroids or Edasalonexent



MRI Shows Disease Progression



Natural History: ImagingDMD Prior to treatment: MoveDMD

- Declines in function in natural history study were similar to those observed in the MoveDMD trial off-treatment
- Decreases in function correlate with increases in composite lower leg MRI T2 as well as muscle fat fraction

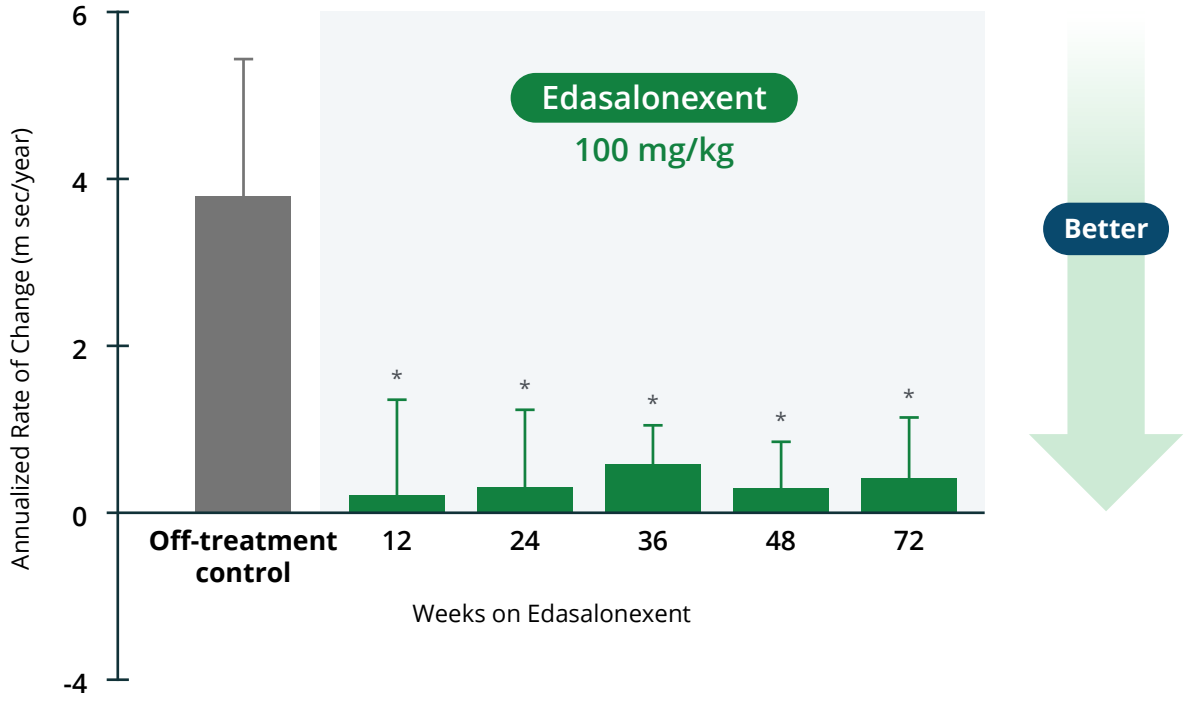
Means + SEM

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: Composite of 5 Lower Leg Muscles

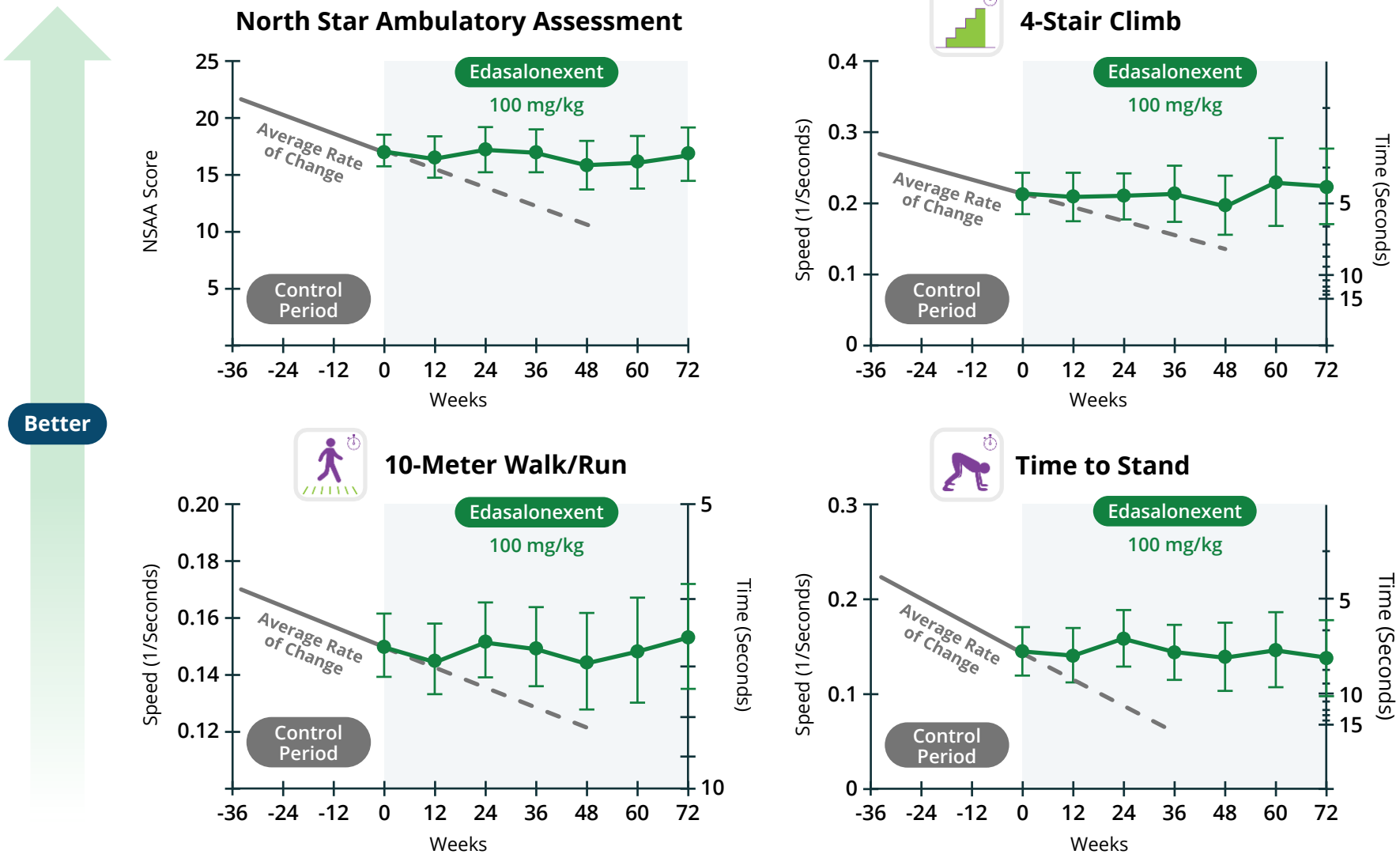


- Composite of 5 lower leg muscles MRI T2 used to encompass muscles at various stages of disease progression and minimize variability
- Following 72 weeks of edasalonexent, the rate of increase in the composite MRI T2 in the five lower leg muscles decreased as compared to the rate of increase during the off-treatment control period

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:

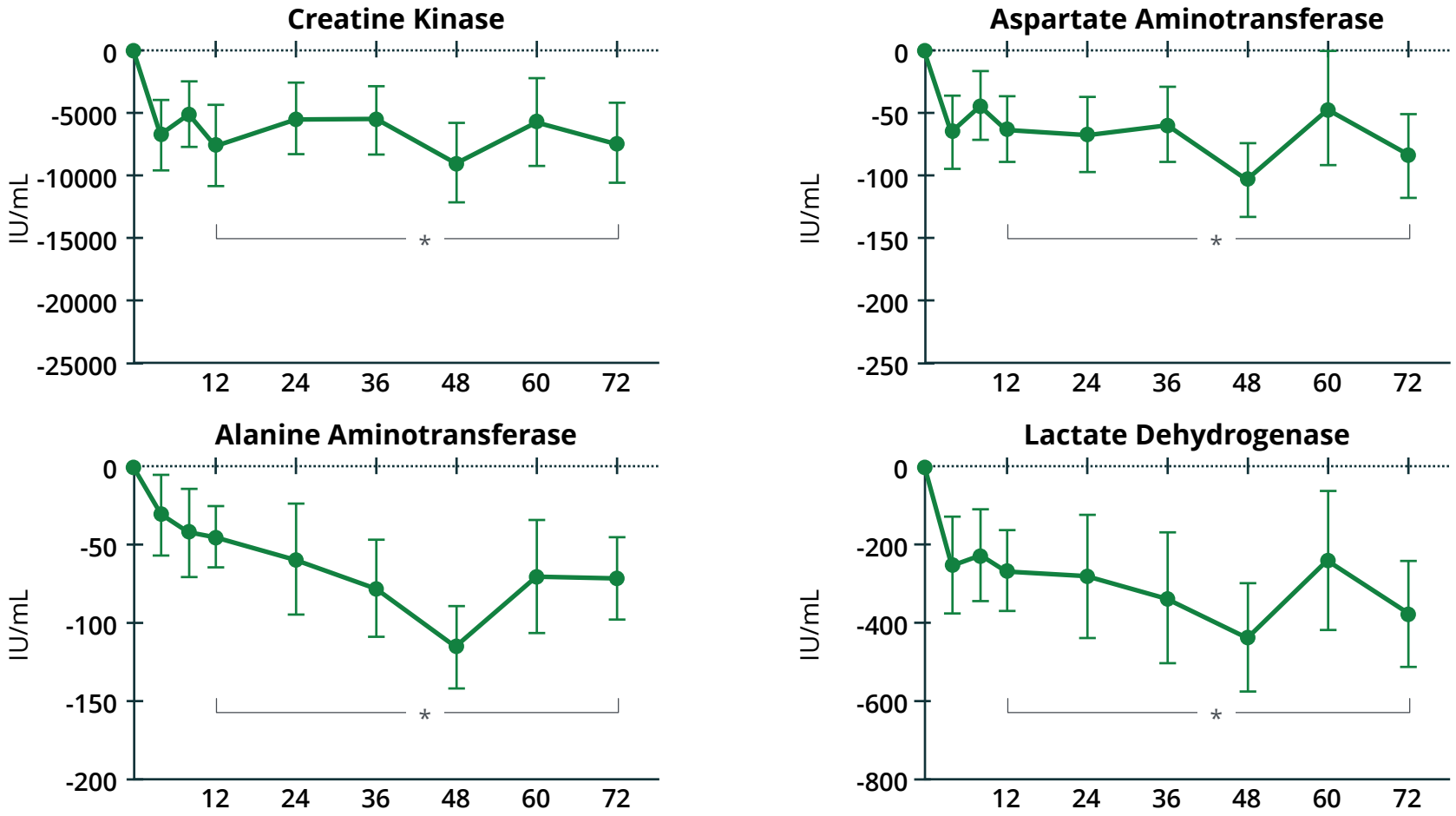
All Assessments of Function Stabilized on Edasalonexent Compared to Off-Treatment Control



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

In Phase 2 MoveDMD Trial and Open-Label Extension:

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

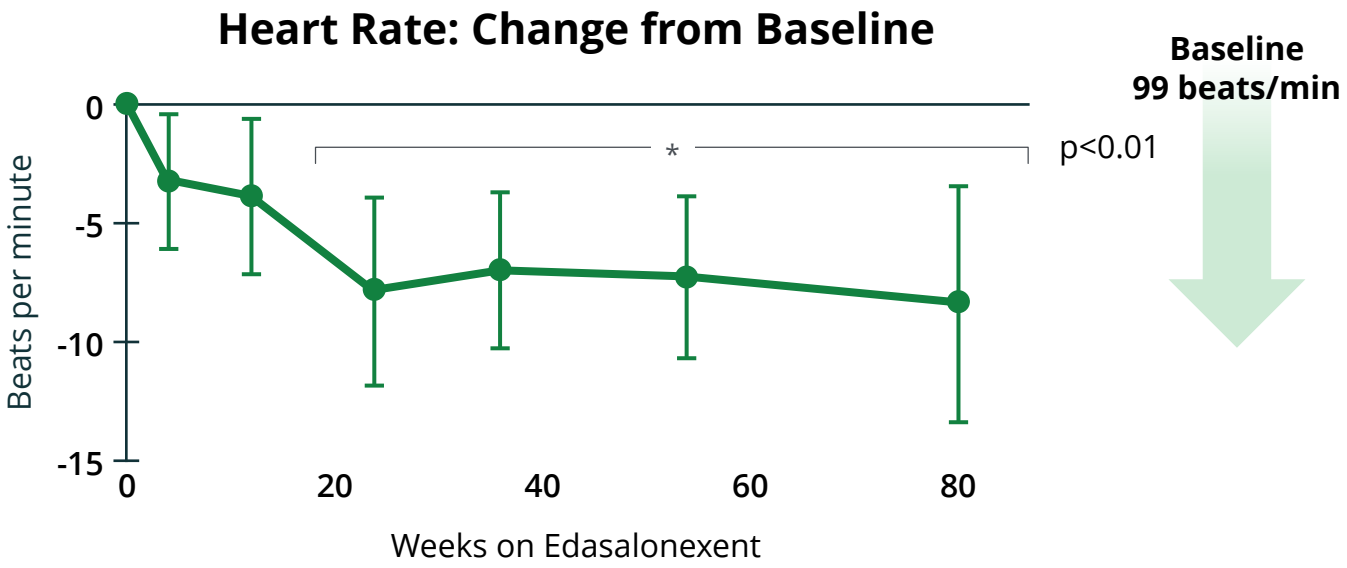


Plasma muscle enzymes are elevated 10 to 100 fold in DMD, indicative of leakage from damaged myocytes

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

In Phase 2 MoveDMD Trial and Open-Label Extension:

Edasalonexent 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**
  - Edasalonexent tissue levels in heart > skeletal muscle
- **In MoveDMD trial, mean resting heart rate significantly decreased, approaching age-normative heart rate ~92 beats per minute**

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

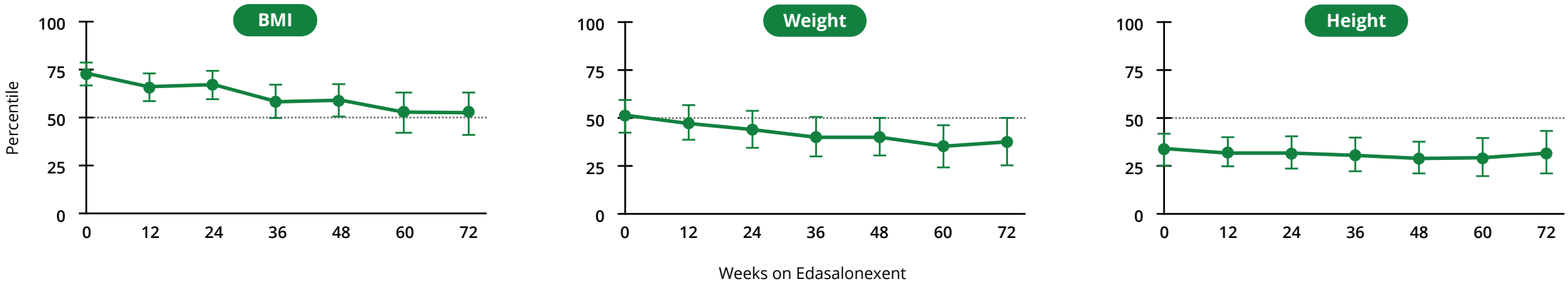
Means ± SEM shown;

In Phase 2 MoveDMD Trial and Open-Label Extension:

Safety: Growth Continues as Expected

- **50+ patient years of exposure**
- **Well tolerated, with majority of adverse events mild in nature**
  - Most common related adverse event was diarrhea, which did not require discontinuation
  - No adverse trends in chemistry, hematology, or measures of adrenal function (cortisol and ACTH)
- **Boys on edasalonexent grew 2.1 inches/ year, similar to unaffected boys**

Percentiles Compared to CDC Growth Charts

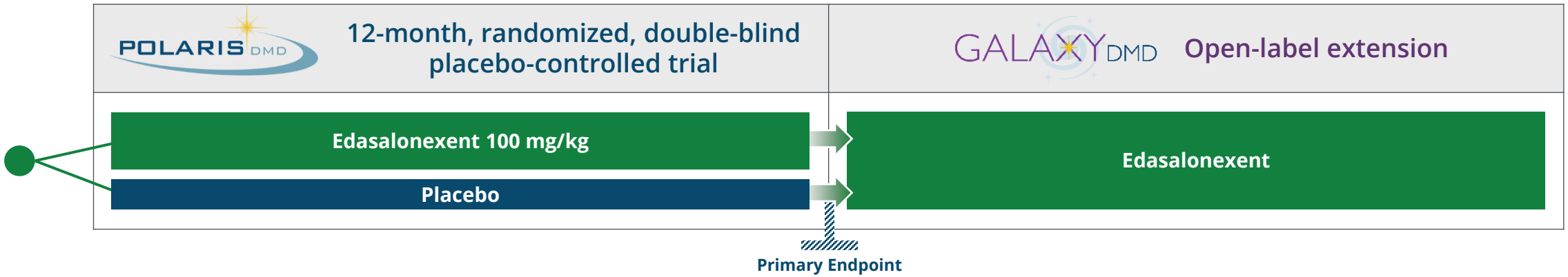


Means ± SEM shown

Targeting NF-κB with Edasalonexent Has Potential for Benefit of Skeletal and Cardiac Muscle as well as Supporting Growth and Bone Health in DMD

- **Preclinical data support potential for NF-κB inhibition to support bone health in DMD**
- **In Phase 2 MoveDMD trial and open-label extension, edasalonexent, an oral NF-κB inhibitor, showed:**
  - 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 with growth along expected growth curves
  - Clinically meaningful slowing of disease progression on edasalonexent compared to off-treatment control period
    - North Star Ambulatory Assessment and all timed function tests stabilized
- **Preclinical and clinical data support design of Phase 3 registration trial**

Phase 3 Polaris Clinical Trial Currently Ongoing



- Enrolling approximately 125 4-to-<8 year-old boys not on steroids for 6 months
- Primary endpoint: NSAA
- Secondary endpoints: age-appropriate timed functional tests

- **Bone-related measures:**
  - Standardized lumbosacral spine films to assess for fractures
  - DXA: bone density and body composition

- **Top-line results anticipated in second half of 2020**

Acknowledgements

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- **Patient groups**
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