Edasalonexent, an Oral NF-κB Inhibitor, in Development for Treatment of Duchenne Muscular Dystrophy: the Phase 3 PolarisDMD Study Design

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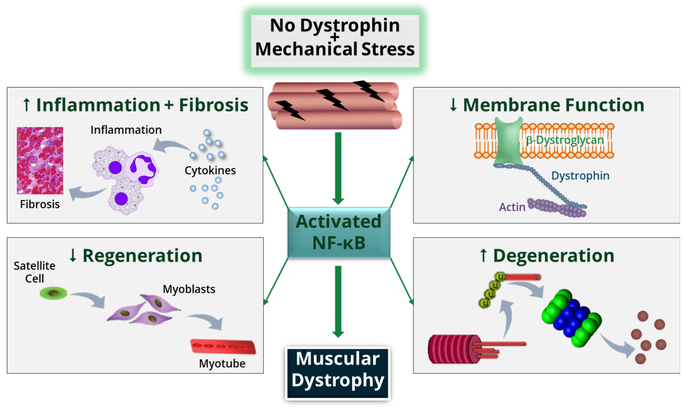
BACKGROUND: NF-kB is Central to DMD Disease Pathogenesis

Role of NF-κB mediated muscle damage in DMD

- **In DMD, NF-κB is activated in early infancy** as seen by nuclear NF-kB and upregulation of NF-kB regulated genes in muscle biopsies *(Chen, et. al., Neurology, 2005)*
- **NF-κB promotes muscle inflammation and fibrosis in DMD** *(Acharyya, et. al., JCI, 2007)*
- **NF-κB drives muscle degeneration and suppresses muscle regeneration** *(Acharyya, et. al., JCI, 2007)*

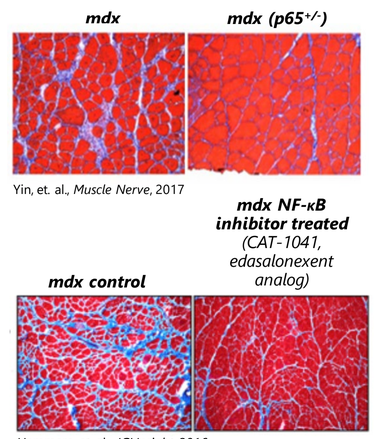


NF-κB also regulates

- cardiac muscle pathology in DMD *(Peterson, et. al., 2018)*
- miRNAs that affect dystrophin levels in muscle *(Fiorillo, et. al., 2015)*

Inhibiting NF-κB in DMD for functional benefit

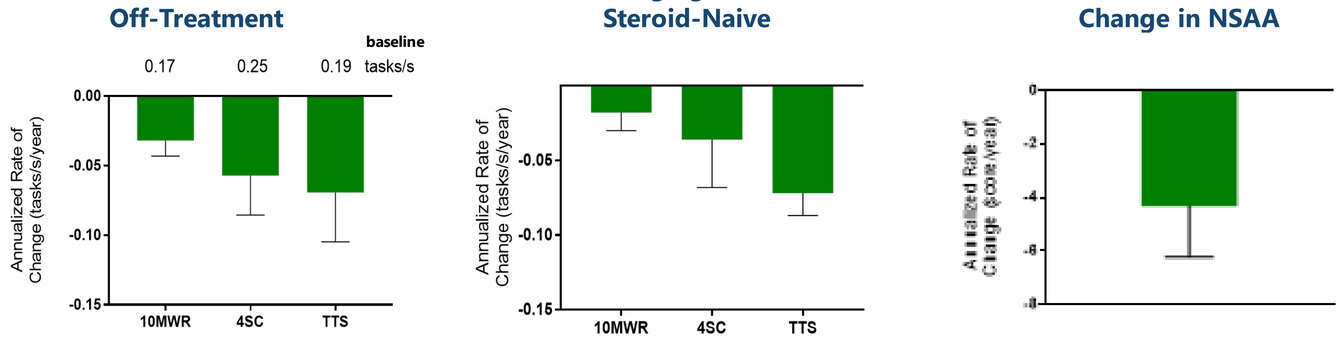
- Genetic **disruption of NF-κB** in *mdx* mice (p65 haploinsufficient, or deletion of IKKβ in muscle) **improves muscle health**
- **Pharmacological inhibition of NF-κB** in *mdx* mice (NEMO binding peptide, or edasalonexent/CAT-1041**) improves muscle health** and provides functional benefit
- **Treatment of DMD boys with edasalonexent** reduced NF-κB activity and **provided functional benefit** in MoveDMD trial



STUDY DESIGN: Rationale for Patient Population

- We are enrolling 125 4-7 year old boys (up to 8th birthday) in a 2:1 ratio because we believe early intervention offers potential to have greatest benefits and is important to developing a new standard of care starting treatment shortly after diagnosis.
- In the US almost 40% of diagnosed boys in this age range are currently not on steroids (data from The Duchenne Registry, Cowen et al, WMS 2017)
- Boys with DMD in this age group who are not on steroids are experiencing declines in timed function tests and NSAA
- In the 23 boys in MoveDMD who had an off-treatment period and in 9 steroid-naïve boys in the ImagingDMD natural history study, average annualized decreases in the TFT's are shown:

Functional Decline in 4-7 Year Old Boys Off-Treatment

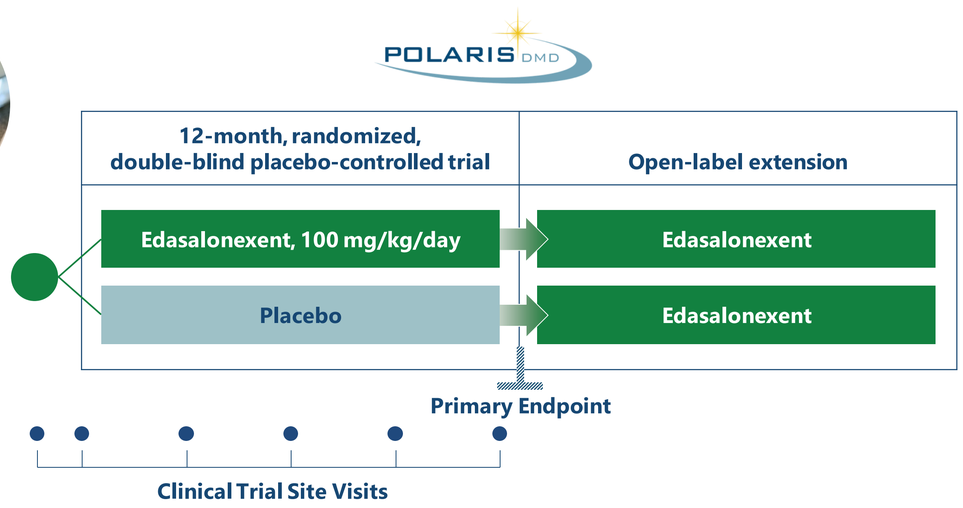


STUDY DESIGN: Developing a New Foundational Therapy

Objective: A registration study to comprehensively define the benefit/risk profile for edasalonexent that has the potential to lead to a new standard of care

Patients and Dose

125 boys will take 100 mg/kg/day of edasalonexent or placebo in a 2:1 ratio, orally administered in three divided doses with meals



Cardiac Measures

- In *mdx* mouse and GRMD dog, inhibiting NF-kB reduces cardiac fibrosis.
- 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, and heart rates in the upper quartile are associated with later cardiomyopathy.
- In the MoveDMD trial, ECG heart rate decreased toward age-normative values

- In the PolarisDMD trial, boys will be monitored with a single-lead ECG monitor at baseline, 6 and 12 months. Continuous ECG will be analyzed for changes in heart rate as well as heart rate variability, which is known to be decreased in DMD as in other cardiomyopathies.

Functional Assessment

- Change in North Star Ambulatory Assessment Score, a comprehensive assessment of multiple functions, at 52 weeks will be the primary endpoint
- Age-appropriate timed functional tests will be secondary endpoints:

Bone Health

Recently updated care guidelines stress the importance of monitoring bone health in Duchenne. Vertebral fractures can occur at a young age, particularly after initiating steroid treatment, and can be asymptomatic. Further, they are predictive of future fractures. As part of the standard of care, a lateral thoracolumbar spine radiograph and spine bone mineral density by DXA is recommended at baseline in boys with Duchenne.

Lateral thoracolumbar spine radiograph will be collected at the baseline visit and after one year of treatment. Additionally, bone mineral density by DXA will be collected at the baseline visit and after one year of treatment. In the planned open-label extension, both measures will continue to be followed.

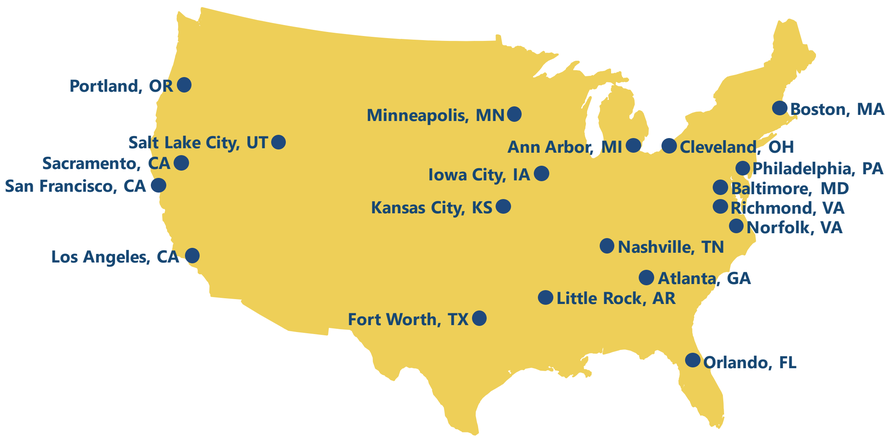
Inclusion Criteria

- Diagnosis of DMD based on a clinical phenotype and genetic confirmation
- Male sex by birth
- Age ≥4.0 to <8.0 years
- Able to perform stand from supine without assistance in ≤ 10 seconds, as well as the 10MWR and 4-stair climb

Exclusion Criteria

- Use of corticosteroids within 24 weeks
- Use of an investigational drug, idebenone, or dystrophin-focused therapy within 4 weeks or a period of 5 half-lives duration prior to Day 1. Patients who have received at least 24 weeks of a stable dose of eteplirsen prior to Day 1, and expected to continue treatment, will be eligible.
- Recent use of the following within 4 weeks prior to Day 1: immunosuppressive therapy, warfarin, phenytoin, human growth hormone
- Hemoglobin <10.5 g/dL or GGT > ULN
- Other prior or ongoing medical conditions that could impair the assessment of study results

Expected PolarisDMD Clinical Trial Sites



Sites also anticipated in Canada, Europe, Israel and Australia

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