Edasalonexent, an NF-κB Inhibitor, Slows Disease Progression Over More Than a Year Compared to Control Period in 4 to 7-Year Old Patients with Duchenne Muscular Dystrophy

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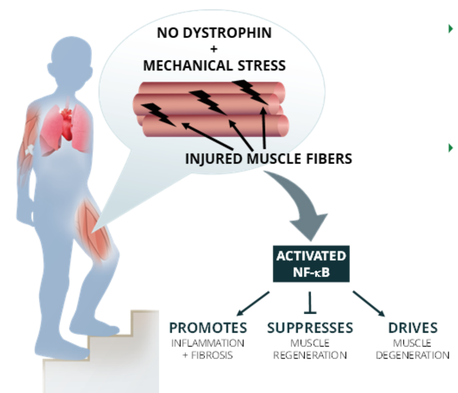
Background

NF-κB is a Fundamental Driver of Disease Progression in DMD

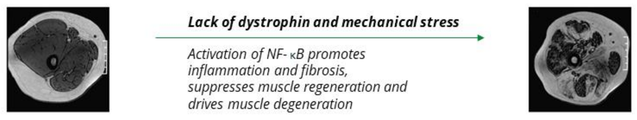


- NF-κB pathway is the key link between loss of dystrophin and disease manifestation and progression in DMD
- Lack of dystrophin combined with mechanical stress activates NF-κB, which promotes muscle degeneration and suppresses muscle regeneration

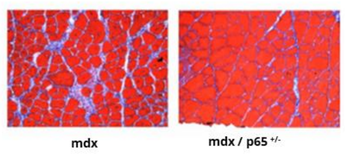
Kumar, et al. FASEBJ 2003 17(3):17: 386-96.
Peterson, et al. Curr Top Dev Bio. 2011; 96: 85-119.
Hammers, et al. JCI Insight 2016;1:e90341.

Edasalonexent Inhibits NF-κB

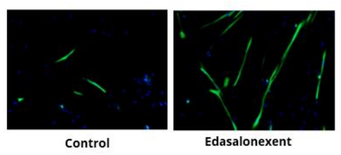
- **NF-κB pathway is the key link between loss of dystrophin and disease manifestation and progression in DMD**



- **Edasalonexent: NF-κB inhibition suppresses inflammation and fibrosis, and decreases muscle degeneration, enhances muscle regeneration**



Inhibition of NF-kB by 50% reduces fibrosis

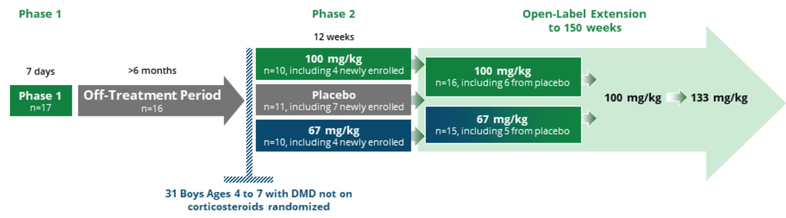


Human myocyte growth and differentiation in the context of inflammation is positively impacted by edasalonexent

Yin, et. al., Muscle Nerve 2017

Study Design

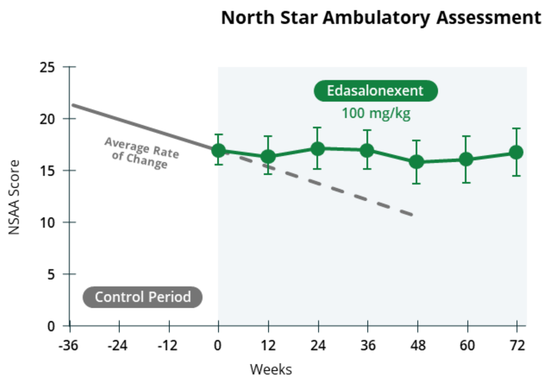
MoveDMD Trial Was Designed to Enable Phase 3



- **Integrated multi-part trial design**
  - Supports evaluation of efficacy, safety/tolerability, target engagement, and dose response
- **Off-treatment control period of > 6 months allowed measurements between Phase 1 and commencement of dosing in Phase 2/open-label extension**
  - Provides internal control for pre-specified MoveDMD analyses
  - To confirm consistency of patient off-treatment control period disease progression with available natural history data
- **Open-label extension**
  - Enables assessment of safety and efficacy following longer term treatment
  - After ~72 weeks patients were increased to 133 mg/kg/day in 3 divided doses (33/33/67)

Results

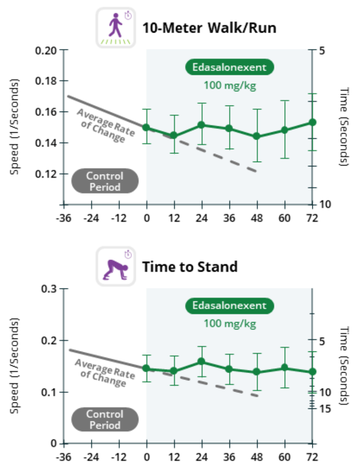
North Star Ambulatory Assessment Score, a Measure of Overall Function in Young Boys, Was Stabilized with Edasalonexent Treatment



- Disease progression on edasalonexent improved compared with rate of change during off-treatment control period

Means ± SEM shown
Includes data of all boys initially started on 100 mg/kg dose (n=16)

Speed on All Timed Function Tests Stabilized with Edasalonexent Treatment, Consistent with Effect on NSAA

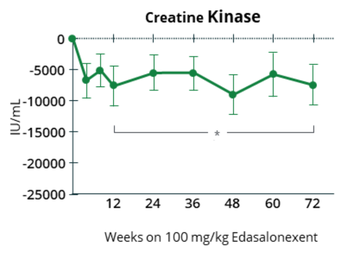


- Disease progression on edasalonexent improved compared with rate of change during off-treatment control period

Week	0	12	24	36	48	60	72
N =	16	16	14	13	13	10	11

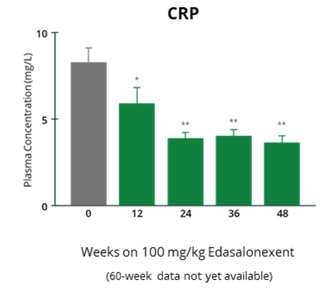
Means ± SEM shown
Includes data of all boys initially started on 100 mg/kg dose (n=16)

Biomarkers Show Significant and Sustained Decrease with Edasalonexent Treatment



- All muscle enzymes (CK, ALT, AST and LDH) show sustained decrease after 12 weeks ($p<0.05$)
- Consistent positive impact on muscle supportive of an edasalonexent benefit

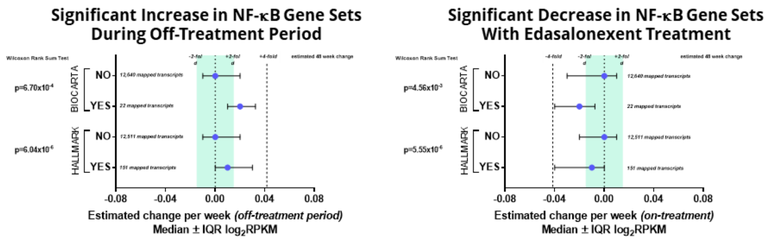
Means ± SEM shown
* p<0.05 for change from baseline after 12 weeks

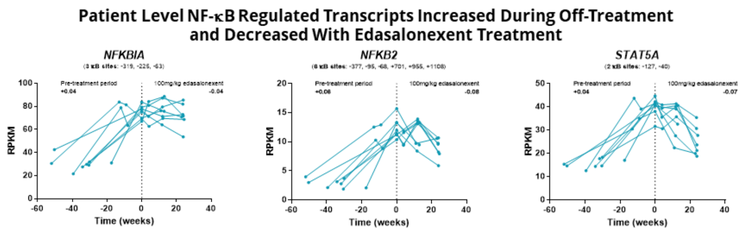


- C-reactive protein (CRP), a well-characterized blood test marker that provides a global assessment of inflammation, is elevated in DMD
- CRP approximately 3-fold higher in boys affected by DMD compared to unaffected boys (Anderson, 2017)
- In MoveDMD, CRP significantly decreased from baseline through 48 weeks of 100 mg/kg edasalonexent

Means ± SEM shown; * p≤0.05, ** p≤0.001 for comparison with pre-treatment baseline measurement
† Anderson et al, 2017, Pediatric Cardiology

NF-κB-Regulated Transcripts in Whole Blood Increased During the Off-Treatment Control Period But Were Decreased by Edasalonexent Treatment for 24 Weeks



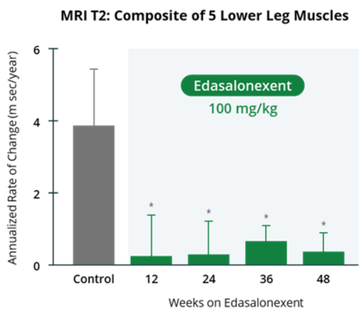


Data analyzed for 8 boys who participated in Phase 1 and were treated with 100 mg/kg Edasalonexent in Phase 2

Edasalonexent Significantly Improved Rate of Change of MRI T2

MRI T2: Composite of 5 Lower Leg Muscles

- On edasalonexent, the rate of change for the MRI T2 composite of the 5 lower leg muscles improved significantly compared to the rate of change during the off-treatment control period ($p<0.05$ for 12, 24, 36 and 48 weeks)
- Stabilization of MRI T2 is consistent with slowing of disease progression also observed in function assessments
- Following 48 weeks of edasalonexent the rate of increase in fat fraction of the soleus and vastus lateralis was also substantially decreased as compared to the rate of increase during the off-treatment control period

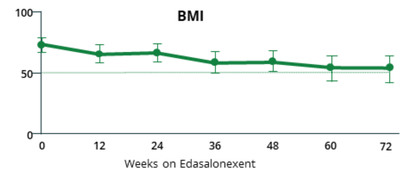


Means ± SEM shown; * p<0.05 for repeated measure mixed model comparison with off-treatment period

Edasalonexent Has Been Well Tolerated with No Safety Signals

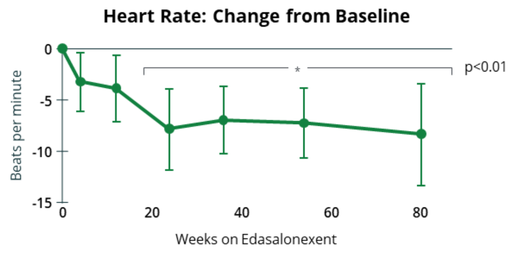
- No safety signals to date in >48 years of patient exposure
  - Safety profile similar at 100 and 133 mg/kg doses (boys transitioned ~72 weeks), although no clear difference in functional trends
- Well tolerated, with majority of adverse events being mild in nature, mostly gastrointestinal
- No adverse trends in hematology, chemistry, renal or adrenal function, calcium and phosphate
- Growth: Age-appropriate increases in weight and height
  - Favorably differentiated from corticosteroids standard of care

Percentiles Compared to CDC Growth Charts



Cardiac Results and Background

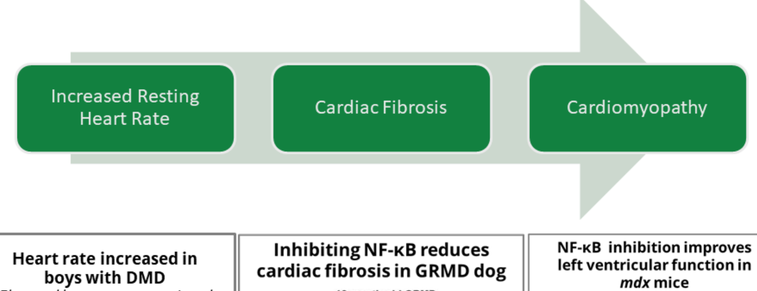
Elevated Resting Heart Rate Characteristic of DMD Decreased to Age-Normative Values

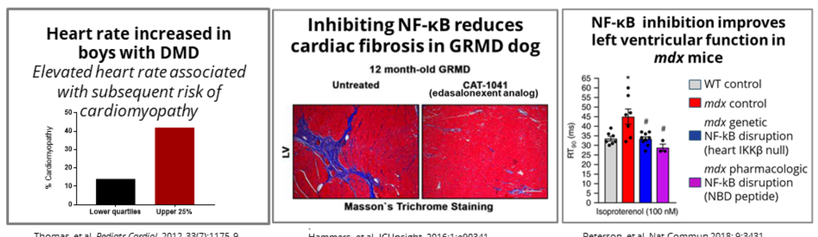


- **In DMD, heart rate does not decrease with age from 6 to 12** *(Thomas, 2012)*
- **Age-normative value is ~92 beats per minute** *(Fleming, 2011)*
- **In MoveDMD ECG heart rate decreased from baseline of 99 to 92 beats per minute**
- **Heart rate by physical examination showed similar trends**
  - No significant changes in systolic or diastolic blood pressure

Thomas, et al. *Pediatr Cardiol.* 2012 33(7):1175-9.

Increased Resting Heart Rate Is the Initial Cardiac Manifestation of DMD





Thomas, et al. *Pediatr Cardiol.* 2012 33(7):1175-9. Hammers, et al. JCI Insight 2016;1:e90341. Peterson, et al. Nat Commun 2018; 9:3431

Conclusion

In MoveDMD Open-Label Extension Edasalonexent Showed Preserved Muscle Function and Slowed DMD Disease Progression

- **Clinically meaningful slowing of disease progression on edasalonexent compared to off-treatment control period through 72 weeks of treatment**
  - North Star Ambulatory Assessment stabilized
  - Timed function tests stabilized (10-meter walk/run, 4-stair climb and time to stand)
- **Additional measures of muscle health support positive edasalonexent effects**
  - Muscle MRI T2 significantly improved versus off-treatment control period
  - Muscle enzymes significantly decreased compared to baseline
  - CRP, a marker of systemic inflammation, significantly decreased
- **Significant decreases in heart rate toward normal support potential cardiac effect**
- **No safety signal and well tolerated**
  - >48 years of patient exposure
  - Height, weight and BMI growth patterns similar to unaffected boys
- **Phase 3 PolarisDMD study underway**

Acknowledgements

Patients and families
Patient groups
ImagingDMD Staff

Site Staff
Catabasis team
Thanks to PPMD and MDA for generous grant support for patient travel

Presented at the 23rd International Congress of the World Muscle Society | October 2-6, 2018 | Mendoza, Argentina