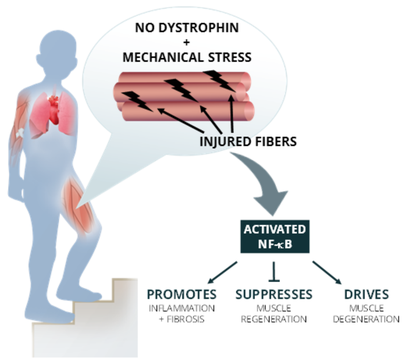
Edasalonexent, an NF-κB Inhibitor, Slows Disease Progression Compared to Control Period in 4 to 7-Year Old Patients with Duchenne Muscular Dystrophy

Richard Finkel, MD[1]; Krista Vandenborne, PT, PhD. for the ImagingDMD Consortium [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], Sean C Forbes, PhD [2], Glenn Walters, PhD [2], William Rooney, PhD[3], William T. Triplett, BSc [2], Sabrina S. Yum, MD [4], Maria Mancini, MHP [6], Pradeep Bista, PhD [6] Angelika Fretzen, 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,

Background

NF-κB Is a Fundamental Component of Duchenne Muscular Dystrophy Disease Progression

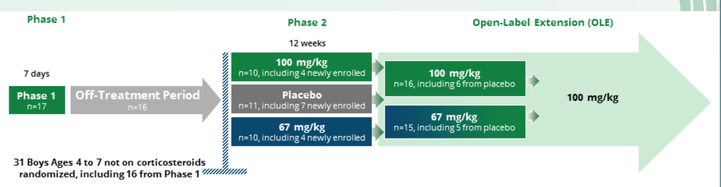


- NF-κB pathway is the key link between loss of dystrophin and disease manifestation and progression in DMD
- Lack of dystrophin combined with mechanical stress activates NF-κB early in life, which promotes muscle degeneration and suppresses muscle regeneration
- Edasalonexent is an oral small molecule that inhibits NF-κB, which improves skeletal, diaphragm and cardiac disease in mouse and dog models of DMD

Kumar, et al. FASEB J 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.

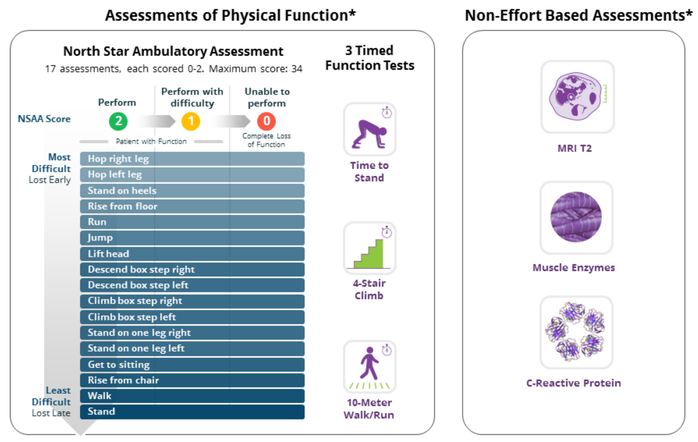
Design

MoveDMD Trial of Edasalonexent



- **Integrated 3-part trial design to evaluate efficacy, safety, tolerability**
  - Phase 1: 7 days of dosing at 33, 67 and 100 mg/kg demonstrated safety and acceptable pharmacokinetics; effects on NF-kB targeted genes observed at doses of 67 and 100 mg/kg
- **Muscle function measures and MRI at beginning of Phase 1 enabled an off-treatment control period for planned comparison to on-treatment period (n=16)**
  - Of the 15 boys newly enrolled in Phase 2, 7 were randomized to placebo so had an off-treatment period, for a total of 23 boys with a control off-treatment period
- **Phase 2 showed trends towards slowing of disease progression after 12 weeks without safety issues, allowing dose escalation from 67 to 100 mg/kg after average 36 weeks in OLE**
- **Open-label extension enables assessment of safety and efficacy following treatment to 48 weeks and longer**
- **Current analyses focus on identified dose of 100 mg/kg**

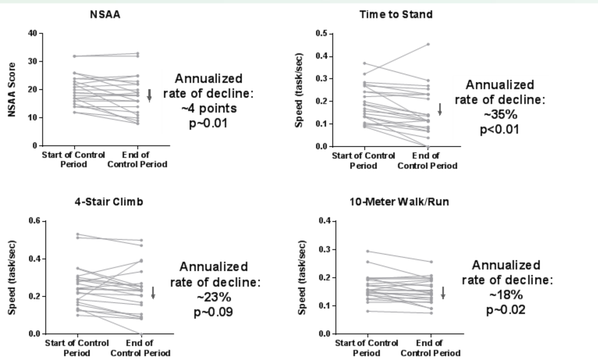
MoveDMD Trial Incorporated Multiple Measures of Physical Function and Biomarkers



*Assessed every 12 weeks during open-label extension

Baseline Observations

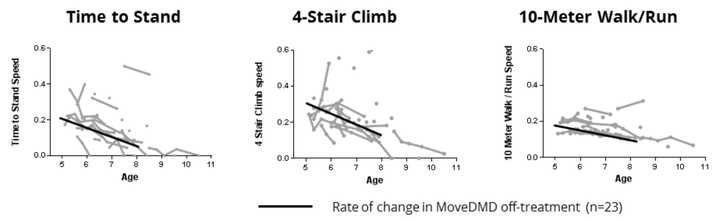
Observations During Off-Treatment Control Period: Declines in Speed of Timed Function Tests and NSAA



- Because the off-treatment control period varied from 3 to 13 months, the rate of decline for each boy was determined to obtain an average rate of change (n=23)
- There were clinically meaningful annual rates of decline across all measures of muscle function for boys in the MoveDMD trial over an off-treatment control period

p-values for baseline to endpoint comparison

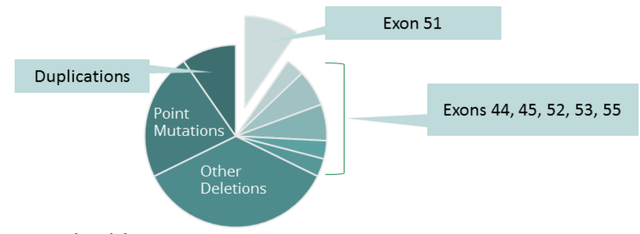
Natural History of Boys not on Corticosteroids Showed Declines Similar to Those Seen in the MoveDMD Study



- In the ImagingDMD natural history study, annual timed function tests were performed (Willcocks et al., 2014). Gray lines and symbols are assessments in boys initially from 5 to 8.5 years not on corticosteroids (n=28).
- ImagingDMD natural history study and MoveDMD study were performed at the same sites with the same guidelines.
- Black line shows average rate of change for boys in MoveDMD study (n=23).
- Boys enrolled in the MoveDMD study generally had absolute functional abilities and declines consistent with observations in the ImagingDMD natural history study.

MoveDMD Population Reflects Broad Range of Mutations and Established Disease

- **26 Distinct Dystrophin Mutations in Boys Enrolled**



- **Average Age in Trial**

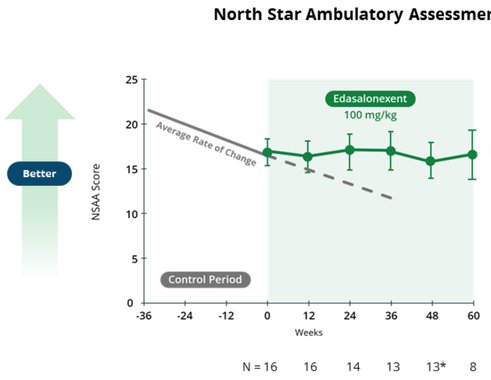
At beginning of control period	6.0 years (range 4.5-8.1)
At beginning of active treatment	6.2 years (range 4.8-8.2)
As of data cut	7.5 years (range 5.8-9.5)

- **Functional Status at initiation of active treatment**

NSAA	18.7 out of maximum 34
Time to stand	9.6 s vs ~2 s for unaffected boys
4-stair climb	6.1 s vs ~3 s for unaffected boys
10-meter walk/run	6.9 s vs ~2 s for unaffected boys

Results

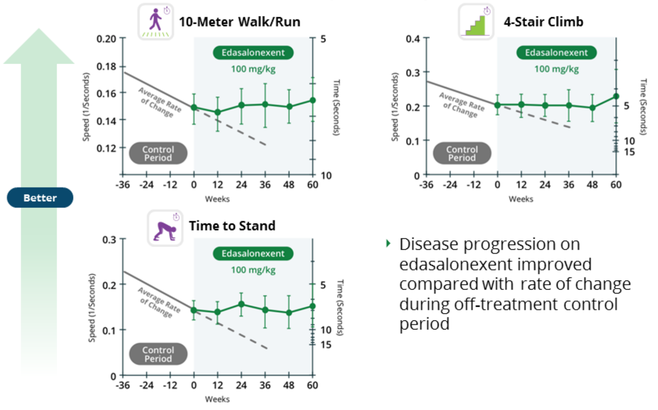
North Star Ambulatory Assessment Score Stabilized with Edasalonexent Treatment



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

*3 discontinued for steroid use (n=2) or no reason given (n=1): all patient completed >48 weeks after initiation of therapy, and those who reached 60 weeks as of data cut-off are included
Means ± SEM shown; p NS

All Timed Function Tests Speed Stabilized with Edasalonexent Treatment



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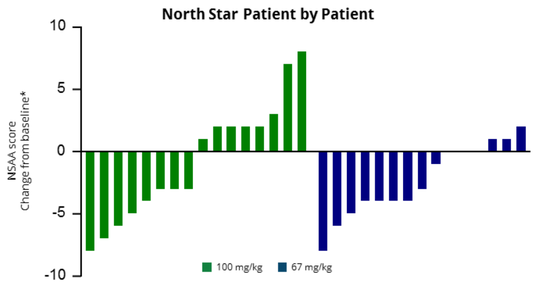
Edasalonexent Treatment Showed a Positive Dose Response

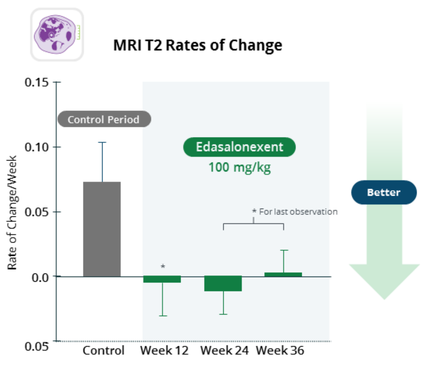


- MoveDMD trial evaluated 33 mg/kg BID (67 mg/kg/day) and 33 mg/kg TID (100 mg/kg/day)
- Overall more favorable response with 100 mg/kg than 67 mg/kg
- Data from preclinical studies support efficacy driven by time above exposure threshold achieved by more frequent dosing rather than total dose¥

*to last treatment visit ¥Presented at the Action Duchenne International Conference, 2017

Edasalonexent Significantly Improved Rate of Change of MRI T2 Compared with Pre-Specified Control Period

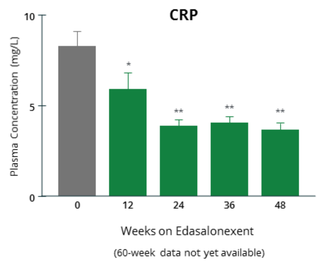
- MRI T2 increases over time in DMD and is highly correlated with worsening timed function tests[ϕ]
- Rate of change for the composite of 5 lower leg muscles MRI T2 on active treatment improved significantly compared to each individual's rate of change during the off-treatment control period
- 12-week Phase 2 MRI T2 primary endpoint for treated boys compared to boys in the placebo group was directionally positive although not statistically significant



Means ± SEM shown; * ps0.05 for comparison with off-treatment period ϕ Willcocks et al, 2016, Ann. Neurol., Willcocks et al, 2014, Ann. Neurol.

Edasalonexent Significantly Reduced Plasma C-Reactive Protein Compared with Pretreatment Baseline

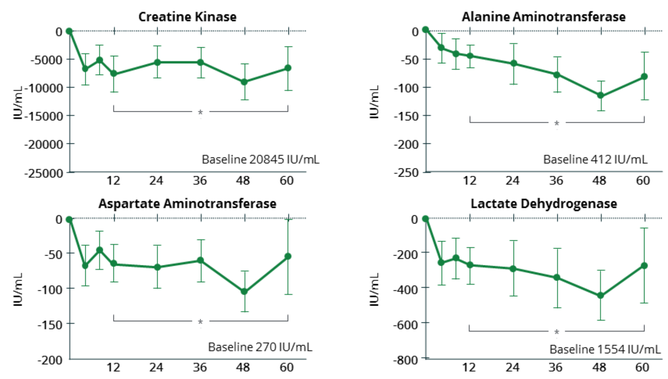
- C-reactive protein (CRP) is a well-characterized blood test marker that provides a global assessment of inflammation
- CRP is elevated in DMD
  - CRP approximately 3-fold higher in boys affected by DMD compared to unaffected boys[†]
- In MoveDMD, CRP significantly decreased from baseline through 48 weeks of 100 mg/kg edasalonexent
  - No change in CRP following 12 weeks of placebo (8.3 ± 0.7 to 9.7 ± 0.8)



Means ± SEM shown; * ps0.05, ** ps0.001 for comparison with pre-treatment baseline measurement
† Anderson et al, 2017, Pediatric Cardiology

Muscle Enzymes Significantly Decreased from Baseline on Edasalonexent

- Plasma muscle enzymes are elevated 10 to 100 fold in DMD, indicative of leakage from damaged myocytes
- Decrease is consistent with positive impact on muscle and supportive of an edasalonexent benefit

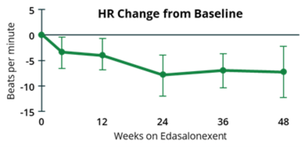


Means ± SEM shown; * p<0.05 for change from baseline after 12 weeks

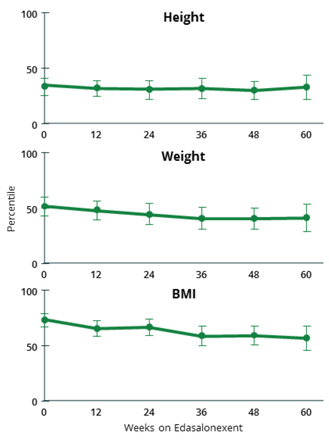
Safety

Edasalonexent Was Well Tolerated with No Safety Signals

- **No safety signals in MoveDMD trial to date**
- **Well tolerated, with majority of adverse events being mild in nature, mostly gastrointestinal**
  - Most common treatment-related adverse events were mild diarrhea
  - No serious treatment-related adverse events or dose reductions
- **No adverse trends in hematology, chemistry, renal or adrenal function, calcium and phosphate**
- **Growth: Age appropriate increases in weight and height**
- **ECG heart rate decreased toward age-normative values**



Percentiles Compared to CDC Growth Charts



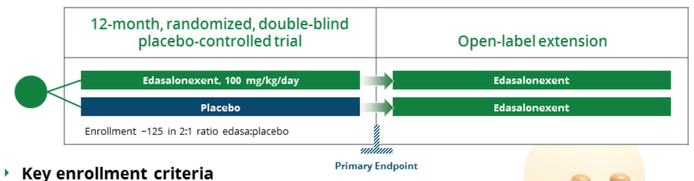
Conclusions

MoveDMD Open-Label Extension: Edasalonexent Substantially Slowed DMD Disease Progression

- **Clinically meaningful slowing of disease progression on edasalonexent compared to off-treatment control period**
  - North Star Ambulatory Assessment stabilized
  - All timed function tests stabilized (10-meter walk/run, 4-stair climb and time to stand)
- **Additional measures of muscle health support positive edasalonexent treatment effects**
  - Muscle MRI T2 significantly improved versus off-treatment control period progression
  - Muscle enzymes significantly decreased compared to baseline
  - CRP, a marker of systemic inflammation, significantly decreased
- **No safety signal and well tolerated**
  - Height, weight and BMI growth patterns continued to be similar to unaffected boys
- **Phase 3 clinical trial initiation planned in H1 2018**

Next Steps

Positive MoveDMD Data Support Planned Global Phase 3 Trial for Edasalonexent



- **Key enrollment criteria**
  - Age 4 to 7th birthday
  - Able to complete timed function tests
  - Not on corticosteroids for at least 6 months
  - Not on other investigational therapies for at least 1 month, can be on stable eteplirsen
- **Visits / key assessments every 3 months**
  - North Star Ambulatory Assessment, Timed Function Tests, Muscle Strength, PODCI
  - Safety measures
  - Assessments of growth, ambulatory heart rate monitoring and bone health
- **Locations: US, Canada, Europe and Australia – specific sites to be determined**

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Conflicts of interest: Joanne Donovan, Maria Mancini, Pradeep Bista and Angelika Fretzen are employees of Catabasis, and the MoveDMD study was funded by Catabasis

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