MoveDMD Results: Effects of Edasalonexent, an NF-κB Inhibitor, in 4 to 7 Year Old Patients with Duchenne Muscular Dystrophy

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Background

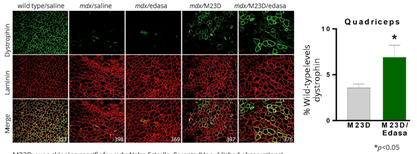
Background and Objectives

- In Duchenne muscular dystrophy (DMD), NF-κB is activated from infancy, driving inflammation, muscle degeneration and inhibiting muscle regeneration.
- Edasalonexent is an oral small molecule that inhibits NF-κB and improves muscle degeneration, regeneration, function and exercise endurance in preclinical models.
- In Phase 1 trials in adults, edasalonexent was generally well tolerated without safety signals and inhibited NF-κB after single and multiple doses.

- Objectives of the three-part MoveDMD study:
  - Assess safety and efficacy of edasalonexent (CAT-1004) in boys with DMD not yet on steroids
  - Assess MRI T2 as primary endpoint, selected as an early biomarker at 12 weeks (Part B)
  - Perform additional assessments in Parts B and C (open-label extension) to provide key information about dose, duration and functional endpoints for future trials

Background: Edasalonexent Increases Dystrophin Expression in Combination with Exon-Skipping

- Dystrophin production in exon-skipping models is inhibited by several miRNA, the levels of which are increased by TNFα. This increase is blocked by inhibition of NF-κB (Fiorillo, 2015), suggesting that NF-κB inhibition could enhance production of dystrophin with dystrophin-focused therapies.
- *mdx* mice were treated for 4 weeks with an exon-skipping agent, edasalonexent or the combination.

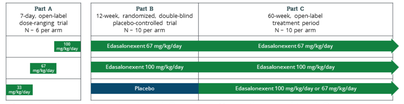


M23D: exon skipping specific for *mdx* Nelsa Estrella, Sarepta (Unpublished observations)

Part B Design

Three-Part Phase 1/2 MoveDMD Trial Design

Study Population: All DMD mutations, ages 4 – 7, steroid naive or off steroids for ≥6 months



- Assess the safety and PK of edasalonexent in ~18 boys with Duchenne
- Showed positive PK, NF-κB biomarker effects, safety and tolerability

- Assess the safety and efficacy of edasalonexent versus placebo
- MRI as an early biomarker
  - Trial powered only for primary endpoint: change from baseline in MRI T2 composite of lower leg muscles
- Secondary measures:
  - Timed function tests (10-meter walk/run, 4-stair climb, time to stand)
  - NSAA
  - PODCI
  - Muscle strength
  - MRI fat fraction

- Measure the same safety and efficacy parameters as in Part B of the trial
  - Assessing treatment effects over a longer time
- Focus on functional changes to plan future trials

Study conducted at 5 sites in US

Analysis Plan: Change from Baseline and Rate of Change Analyses

- **Prespecified analyses:**
  - Placebo-controlled: Comparison of change from Baseline between treatments and placebo during 12-week placebo-controlled Part B
  - Crossover: Comparison of rate of change for off-treatment (Part A baseline to Part B baseline) to Part B active treatment
- **Methodology:**
  - Speed, the reciprocal of the time to perform the function test, used for comparisons to account for boys unable to perform tests
  - Comparison of pooled (n=20) and individual treatment groups (n=10 each) vs. placebo (n=11) during Part B (Placebo-Controlled)
  - For 12 boys in Part A who received edasalonexent in Part B, assess rate of change in functional assessments with edasalonexent compared to the control period (Crossover)
    - Since time periods for the off-treatment period between Part A and Part B and for Part B treatment differ, weekly rates of change are compared
  - The trial was powered for MRI T2, not for functional assessments

Part B Results

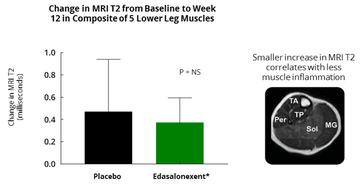
MoveDMD Trial Part B: Baseline Demographics and Values

Treatment Group	Placebo	Edasalonexent 67 mg/kg/day	Edasalonexent 100 mg/kg/day	Overall Edasalonexent
	(n =11)	(n =10)	(n =10)	(n =20)
Age at Week 0 (years)	6.3	6.0	6.0	6.0
Age at Symptom Onset (years)	3.7	3.0	2.0	2.5
Age at Diagnosis (years)	4.6	3.5	3.0	3.3
Weight at randomization (kg)	21.4	22.1	22.0	22.1
10-meter walk/run (10MWR in seconds)	6.9	6.3	6.8	6.6
4-stair climb (4SC in seconds)	5.0	4.5	6.3	5.4
Time to stand (TTS in seconds)	6.5	7.0	12.0	9.4

Values shown are means
Patients were all male and steroid-naive and predominantly Caucasian

- Patient randomization was stratified for baseline age and 10-meter walk/run
- On average, patients in the edasalonexent 100 mg/kg/day group were symptomatic at a younger age and did not perform as well on the 4-stair climb and the time to stand function tests at baseline; characteristics consistent with more advanced disease
- All 31 patients completed Part B and were included in the per protocol population.

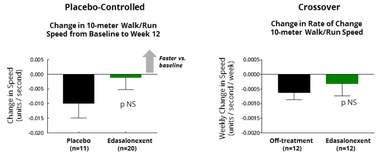
MoveDMD Trial Part B Results Primary Efficacy Endpoint



- No significant change in the primary endpoint, average change from baseline to Week 12 in the MRI T2 measure for a composite of lower leg muscles for the pooled edasalonexent treatment groups vs. placebo.

Error bars in chart denote SEM
Edasalonexent pooled doses: 100 mg/kg (n=10) and 67 mg/kg (n=10), compared with placebo (n=11)

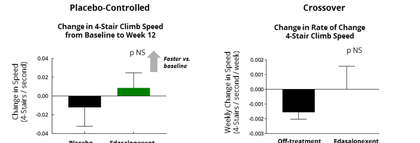
MoveDMD Trial Part B Results 10-meter Walk/Run Speed



- *Placebo-Controlled*:
  - The change in 10-meter walk/run speed was numerically better for edasalonexent than placebo
- *Crossover*:
  - The rate of decline decreased by 50% on edasalonexent

Error bars in chart denote SEM

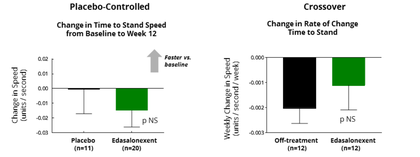
MoveDMD Trial Part B Results: 4-Stair Climb



- *Placebo-Controlled*
  - The change in 4-stair climb speed was numerically better for edasalonexent than placebo
- *Crossover*
  - The rate of change was negative in the off-treatment period but was neutral on edasalonexent

Error bars in chart denote SEM

MoveDMD Trial Part B Results: Time to Stand



- *Placebo-Controlled*:
  - The change in time to stand speed was numerically worse for edasalonexent compared to placebo
- *Crossover*:
  - The rate of decline decreased by 45% on edasalonexent

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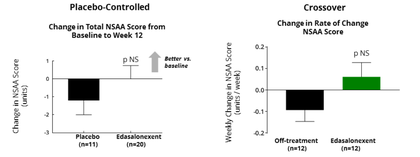
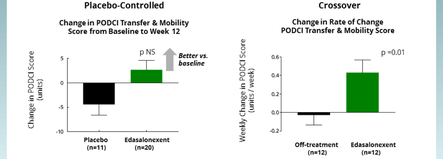
MoveDMD Trial Part B Results North Star Ambulatory Assessment



- *Placebo-Controlled*:
  - The change in North Star Ambulatory Assessment was numerically better for edasalonexent vs. placebo
- *Crossover*:
  - A decline in score was observed off treatment while an improvement in score was observed on treatment

Error bars in chart denote SEM

MoveDMD Trial Part B Results Pediatric Outcomes Data Collection Instrument



- PODCI is a questionnaire for parents that asks about observations of their son's daily activities. Transfer and Basic Mobility Score correlates best with loss of milestones over time (McDonald, 2010)
- *Placebo-Controlled*:
  - Numerical improvement for the treatment groups compared with placebo
- *Crossover*:
  - A decline in score was observed off treatment while an improvement in score was observed on treatment

Error bars in chart denote SEM

MoveDMD Trial Part B Results Adverse Events

- **Well tolerated with majority of adverse events being mild in nature**
- **No discontinuations or dose reductions**

Treatment Group	Placebo	Edasalonexent 67 mg/kg/day	Edasalonexent 100 mg/kg/day	Overall Edasalonexent
Adverse events in >10% of edasalonexent patients	(n =11)	(n =10)	(n =10)	(n =20)
Subjects with any TEAEs	10 (90.9)	9 (90.0)	8 (80.0)	17 (85.0)
Gastrointestinal disorders				
Diarrhea	0 (0.0)	3 (30.0)	4 (40.0)	7 (35.0)
Vomiting	1 (9.1)	1 (10.0)	3 (30.0)	4 (20.0)
Abdominal Pain Upper	0 (0.0)	2 (20.0)	2 (20.0)	4 (20.0)
Nausea	0 (0.0)	1 (10.0)	2 (20.0)	3 (15.0)
General disorders				
Pyrexia	3 (27.3)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications				
Fall*	3 (27.3)	4 (40.0)	2 (20.0)	6 (30.0)
Skin abrasion	0 (0.0)	2 (20.0)	1 (10.0)	3 (15.0)
Metabolism and nutritional disorders				
Decreased appetite	0 (0.0)	1 (10.0)	2 (20.0)	3 (15.0)
Respiratory, thoracic and mediastinal disorders				
Rhinorrhea	1 (9.1)	2 (20.0)	2 (20.0)	4 (20.0)

*Falls were specifically recorded as an exploratory measure.

Part A Results

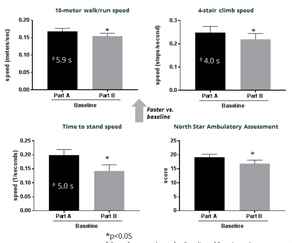
MoveDMD Part A Results Supported Part B Design

- **Safety:**
  - Generally well tolerated, no discontinuations
  - All patients able to take edasalonexent capsules
  - Adverse events (AE) predominantly mild, most common AE was diarrhea
  - AE over 7 days:

	33 mg/kg n=5	67 mg/kg n=6	100 mg/kg n=6	Total n=17
Diarrhea	0	0	4	4
Soft feces	1	1	1	3
Abdominal pain upper	1	0	1	2

- **PK**
  - At the two higher doses, exposures were at or above levels associated with NF-κB inhibition in adults in Phase 1
- **Biomarker**
  - Changes in NF-κB targeted genes at two higher doses
- **Identified doses of 67 and 100 mg/kg for Phase 2 Part B study**

MoveDMD Trial: Observations Prior to Treatment in Part B



- During the approximately 8-month period from the Baseline of Part A to the Baseline of Part B, patients were off-treatment except for the initial week of dosing in Part A.
- Declines in TFTs and NSAA were evident during this control period.
- In pre-specified crossover analysis, rates of change in this control period were compared to those during 12 weeks of edasalonexent treatment in Part B.

*p<0.05
† For reference, shown for Baseline of Part A are the times corresponding to the average speed.

Error bars in chart denote SEM

Summary

MoveDMD Trial Part B Conclusions

- Primary Endpoint: No significant change observed in primary endpoint of change from baseline in MRI T2 of the composite of lower leg muscles for pooled edasalonexent vs. placebo.
- Functional Measures: Edasalonexent treatment groups showed numerical improvement vs. placebo across multiple functional measures, both in the placebo-controlled Part B and the crossover analysis, although the changes were generally not statistically significant.
- Safety: Edasalonexent was well tolerated with an adverse event profile consistent with prior findings.
- Open-Label Extension: Part C of the MoveDMD trial is ongoing to assess effects in patients on edasalonexent over a longer time period.
  - Expect to learn important information about dose, duration and functional endpoints for possible future clinical trials of edasalonexent
  - Focused on the functional assessments going forward as they are known to be clinically meaningful and have precedence as pivotal trial endpoints
- Edasalonexent in DMD: Edasalonexent has potential for treatment of Duchenne, regardless of underlying mutation.

Acknowledgments:
- Patients and Families
- Patient groups
- ImagingDMD Staff
- Catabasis team

Conflict of interest: J Donovan, M Mancini, P Bista and A Nichols are employees of Catabasis
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