Edasalonexent (CAT-1004), an Oral Agent Targeting NF-κB: MoveDMD® Part A Results in Duchenne Muscular Dystrophy

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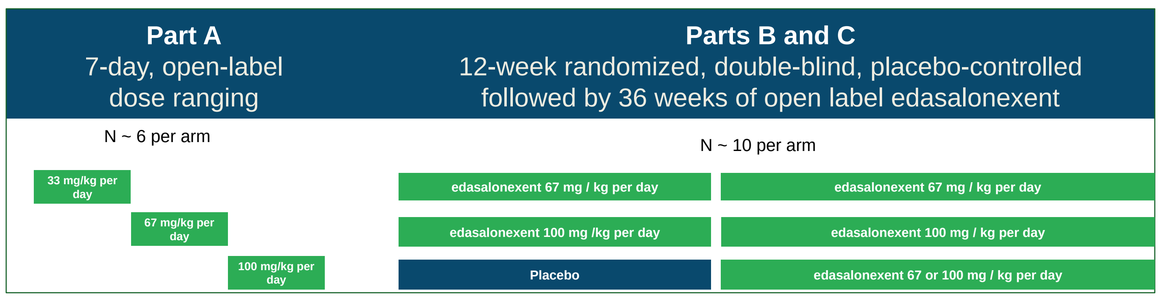
Introduction

- In DMD, muscle NF-κB is activated from infancy, driving inflammation, muscle degeneration and inhibiting muscle regeneration.[1]
- Edasalonexent is an oral small molecule that inhibits NF-κB and improves muscle degeneration, regeneration, function and exercise endurance in preclinical models.[2]
- In Phase 1 trials in adults, edasalonexent was generally well tolerated without safety signals and evidence of NF-κB inhibition was seen after single and multiple doses.
- Since MRI (T2) in DMD demonstrates progressive leg muscle inflammation that is reduced with steroid therapy,[3] a proof-of-concept study of CAT-1004 with MRI endpoints was designed.

Methods and Trial Design

- The MoveDMD is a three-part trial that is evaluating edasalonexent in boys aged 4-7 with confirmed DMD who are not on glucocorticoid therapy for >6 months.
- Part A evaluated safety, tolerability and pharmacokinetics (PK) for 7 days at three different doses (n=17), with exploratory measures of NF-κB.
- Ongoing Part B of the trial is a 12-week, double-blind, placebo-controlled efficacy trial in approximately 30 boys aged 4–7 with confirmed DMD, followed by a 36-week open-label extension.



Results I: Safety and Tolerability

- Edasalonexent was generally well-tolerated
  - No serious adverse events, no discontinuations
  - All patients able to take CAT-1004 capsules
  - Adverse events (AE) predominantly mild, most common AE was diarrhea
- Assessments:
  - Laboratory: no trends or safety issues in liver, renal, hematology
  - Physical exam, EKG, vitals: no safety issues

Table 1: Adverse Events

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

- Baseline Functional Assessments:
  - For boys with assessments at both Baseline Parts A / B

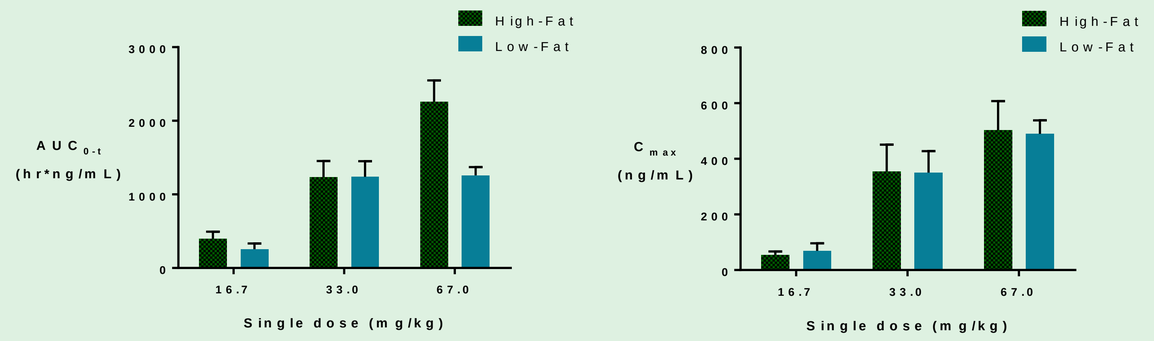
Table 2: Baseline Timed Functional Tests

	Part A (n=15*)	Part B (n=15*)
10 Meter Walk/Run	6.2 ± 1.3	6.8 ± 1.7
4-Step Climb	4.7 ± 2.3	6.0 ± 3.5
Time-to-stand	6.1 ± 2.7	8.5 ± 5.9

*For 15 boys with available data at data cut of the 16 boys who went on to Part B

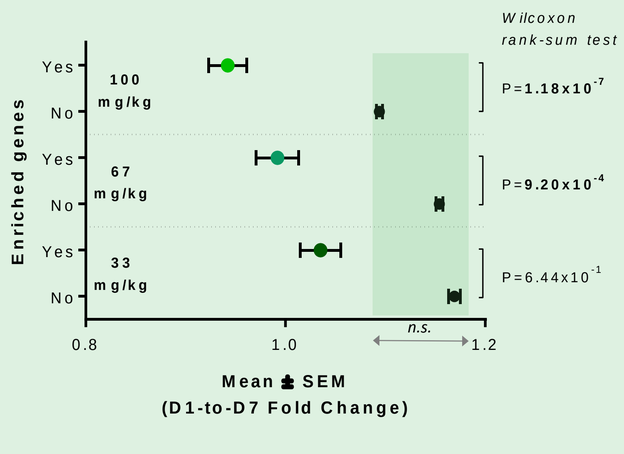
Results II: Pharmacokinetics

- AUC and C_{max} were approximately dose-proportional, and plasma levels were consistent with those previously measured in adults at which inhibition of NF-κB was seen.

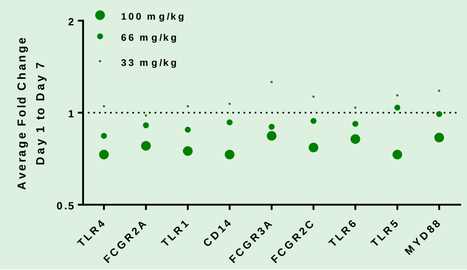


Results III: Exploratory NF-κB measures

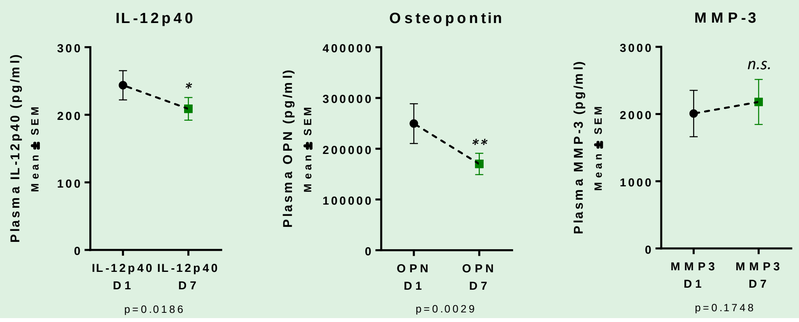
- Genes enriched for NF-κB targets were assessed in whole blood mRNA after one week on edasalonexent. Compared with baseline, NF-κB gene-set was significantly inhibited with the two higher doses.



- Broad Institute curated *HALLMARK* NF-κB gene-set (comprises 200 NF-κB regulated genes) was significantly decreased when compared to all other genes
- Dose-proportional decrease seen in the two higher dose groups with this gene-set
- TLR and Fc-receptor genes showed a dose-dependent reduction in whole blood



- NF-κB regulated serum proteins such as IL-12 and Osteopontin were also reduced with the two higher doses. However, MMP-3 levels were unchanged.



- Serum proteins from 67 mg/kg and 100 mg/kg were analyzed together
- P-values represent Wilcoxon matched-pairs signed rank test (two-tailed)

Conclusions

- In MoveDMD Part A, edasalonexent was found to be generally well-tolerated. AUC and C_{max} were approximately dose-proportional.
- After one-week of dosing, NF-κB gene-set was significantly inhibited in whole blood mRNA with the two higher doses. IL-12 and Osteopontin protein levels in serum were also reduced.
- These results support the ongoing Part B of the trial, a 12-week, double-blind, placebo-controlled efficacy trial with MRI and functional endpoints.
- By reducing inflammation and muscle degeneration with potentially positive longer-term effects on muscle regeneration and function, edasalonexent may have the potential to be disease-modifying in DMD patients regardless of mutation type.

Acknowledgments

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References

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