Preclinical development and clinical translation of edasalonexent (CAT-1004), a small molecule using SMART Linker[SM] technology as a potential disease modifying therapy for the treatment of Duchenne muscular dystrophy

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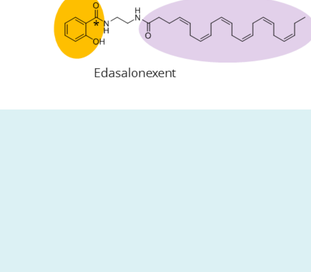
Background

Introduction

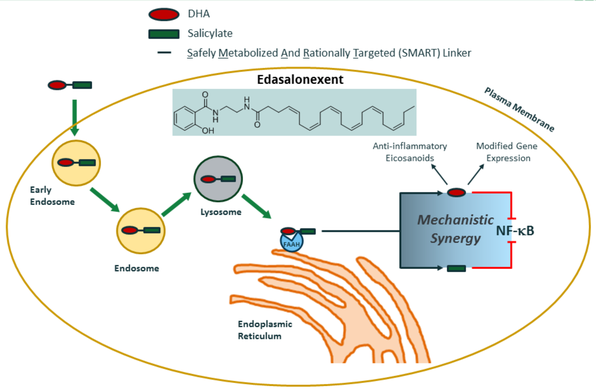
- **Duchenne Muscular Dystrophy (DMD)**
  - A progressively debilitating and ultimately fatal inherited neuromuscular disorder affecting approximately 1 in 3,500 to 5,000 live male births worldwide with a prevalence of approximately 5/100,000 in the United States
  - Caused by mutations in the gene encoding dystrophin, a critical part of the protein complex that connects the cytoskeletal actin of a muscle fiber to the extracellular matrix
- **Edasalonexent**
  - An oral inhibitor of NF-κB in development for all patients with DMD with any mutation type
  - A bioconjugate of salicylate (SA) and omega-3 fatty acid (DHA) using the SMART (Safely Metabolized And Rationally Targeted) Linker drug discovery platform
  - Following its cellular uptake, edasalonexent (CAT-1004) was hydrolyzed into its constituents by endogenous fatty acid amide hydrolase (FAAH), simultaneously delivering SA and DHA to key intracellular targets where they inhibit NF-κB, which is activated in DMD and drives inflammation and fibrosis, muscle degeneration and suppresses muscle regeneration.
- **Clinical trials of edasalonexent in adult human subjects**
  - Three studies in adult human subjects assessed the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of single or multiple edasalonexent oral doses up to 6000 mg
- **MoveDMD trial of edasalonexent in pediatric patients**
  - 3-part, Phase 1/2, multi-site study to evaluate the safety, efficacy, PK and PD of edasalonexent in pediatric patients (enrolled at ≥ 4 to < 8 years of age) with a genetically confirmed diagnosis of DMD

The Intersection of Pathway Biology and the SMART Linker Platform

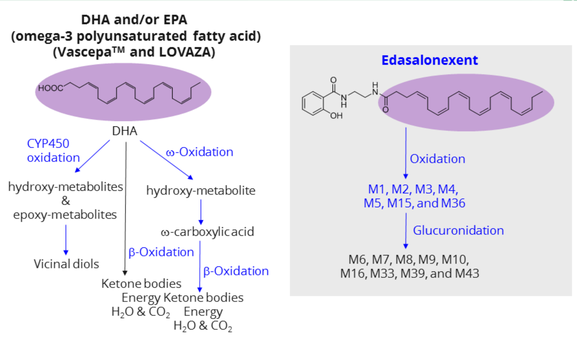
- **Conjugates engineered from proprietary, enzyme-cleavable small chemical linkers ("SMART linkers")**
- **Cellular uptake by endocytosis**
- **Intracellular hydrolysis of linker**
- **Bioactives "reactivated" upon cleavage**
  - Released to interact with intended targets
- **Product candidates with composition of matter and method of use patents**



Edasalonexent Produces Synergistic Efficacy



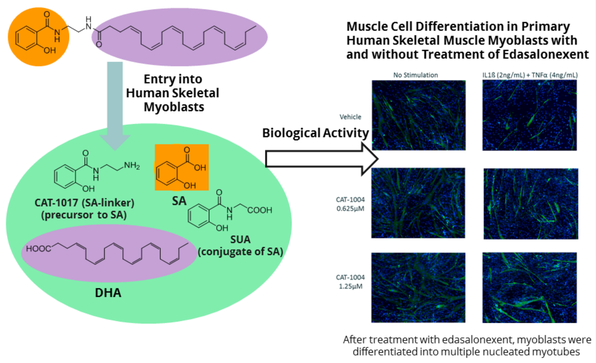
SMART Linker Technology: Metabolic Pathway Comparison with Drugs Containing DHA/EPA



- ❑ **Similar metabolic pathways on the DHA moiety**
- ❑ **In addition, sequential glucuronidation as seen in the SA moiety**

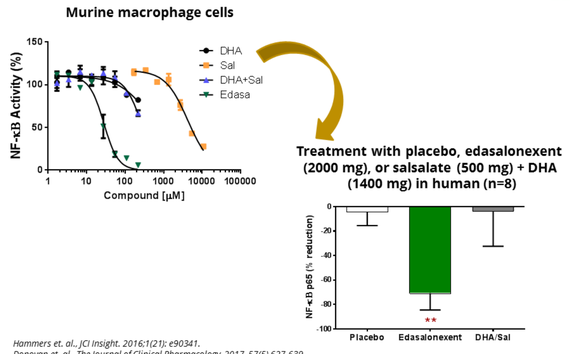
Results

SMART Linker Technology in Target Human Cells and Intersection with Biological Activity



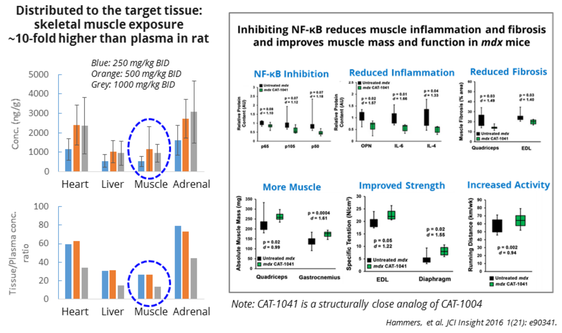
After treatment with edasalonexent, myoblasts were differentiated into multiple nucleated myotubes

Synergistic Efficacy of Edasalonexent: *In Vitro* and *In Clinic*



Hammers et. al., JCI Insight. 2016;1(21): e90341.
Donovan et. al., The Journal of Clinical Pharmacology, 2017, 57(5) 627-639

Pharmacology in *mdx* Mouse Model and Tissue Distribution of Edasalonexent

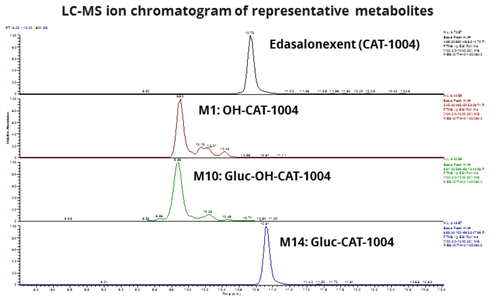


Note: CAT-1041 is a structurally close analog of CAT-1004

Hammers. et al. JCI Insight 2016 1(21): e90341.

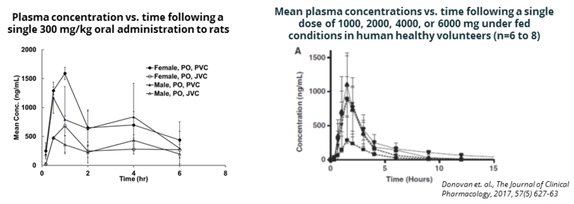
Target exposure ⇒ **Target engagement**

Metabolite Profiling and Identification of Edasalonexent in Human Plasma



In addition, the following metabolites were detected:
- ✓ M2, M3, M4, M5, M15, and M36 from oxidation of DHA moiety
- ✓ M6, M7, M8, M9, M16, M33, M39, and M43 from oxidation of DHA moiety followed by conjugation
- ✓ SA, SUA, and CAT-1017 from hydrolysis

Oral Absorption of Edasalonexent in: *Nonclinical Species and Human*

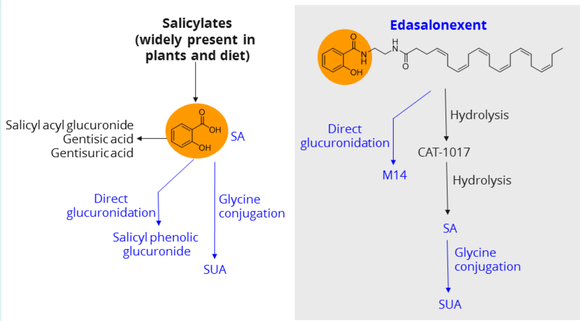


Donovan et. al., The Journal of Clinical Pharmacology, 2017, 57(5) 627-63

Species	Dose	Mean t_{max} (h)	Mean C_{max} (ng/mL)	Mean AUC_{last} (ng.h/mL)
Mouse (M/F)	363/393 mg/kg	0.5	185/733	455/915
Rat (M/F)	300 mg/kg	3.5/1.0	527/685	1871/1919
Dog (fasted, M/F)	1200 mg/kg, BID	3.6/3.2	313/321	1620/2030
Dog (fed, M/F)	1000 mg/kg, BID	0.5	681/893	5550/6560
Human (fasted)	300, 1000, 2000, 4000, 6000 mg	0.8 to 1.5	87, 69, 162, 206, 193	130, 155, 359, 596, 546
Human (fed)	1000, 2000, 4000, 6000 mg	1.5 to 1.8	383, 996, 1108, 946	801, 2331, 2852, 3573

Fast, saturable, and food effect observed in nonclinical species and human oral absorption

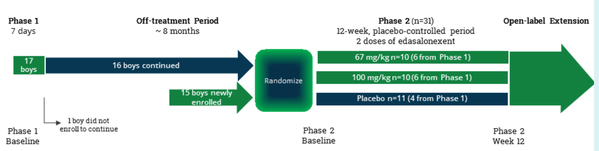
SMART Linker Technology: Metabolic Pathway Comparison with Salicylates



- ❑ **Similar metabolic pathways on the SA moiety**

MoveDMD Phase 2 Study Design

- **Study Design: enrolled 31 boys ages 4 to 7 not on corticosteroids**



- **Study designed to allow two pre-specified analyses in Phase 2:**
  - **Placebo-controlled:** Comparison of changes between edasalonexent and placebo for the 31 boys enrolled in Phase 2
  - **Crossover:** Comparison of changes during off-treatment period to edasalonexent treatment period for 12 boys who were in both parts of the study

MoveDMD Phase 2 Demonstrated Delayed Loss of Function in Critical Function and Mobility Parameters

Two Pre-specified Analyses

	Placebo-Controlled			Crossover
	Edasa 67 mg/kg/day (n=10)	Edasa 100 mg/kg/day (n=10)	Edasa Pooled (n=20)	Edasa Pooled (n=12)
10-meter walk/run	+	+	+	+
4-stair Climb	+	+	+	+
Time to stand	-	+	-	+
North Star Ambulatory Assessment (NSAA)	+	+	+	+
Pediatric Outcomes Data Collection Instrument (PODCI)	+	+	+	+*

* $p < 0.05$

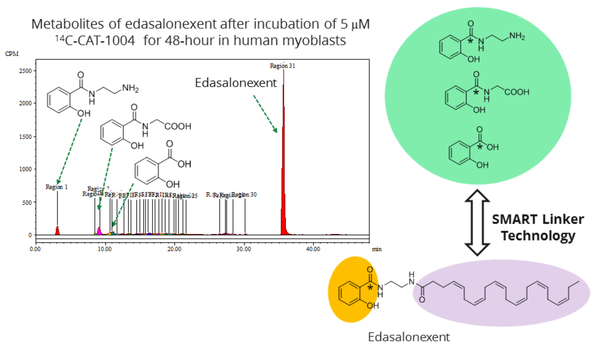
Placebo-Controlled: Comparison of changes between edasalonexent and placebo for the 31 boys enrolled in Phase 2

Crossover: Comparison of changes during off-treatment period to edasalonexent treatment period for 12 boys who were in both parts of the study

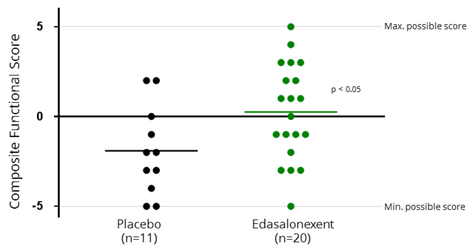
+ indicates numerical improvement with edasalonexent compared to placebo or off-treatment period

Results

Edasalonexent Metabolized to its Bioactive Components in Human Muscle Cells

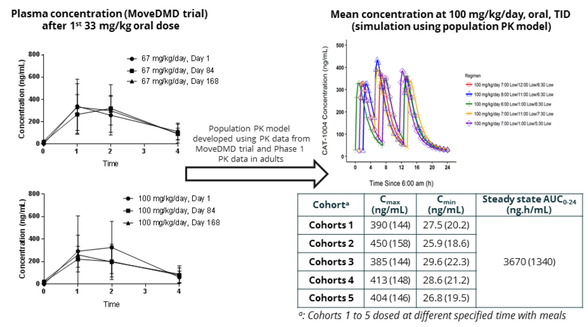


Composite Score for Phase 2 Functional Assessments Edasalonexent Preserves Function by Slowing Rate of Decline



- **Individual scores for placebo-controlled analysis of 4-stair climb, 10-meter walk/run, time to stand, NSAA and PODCI were pooled**
  - +1 for improvement, -1 for decline, 0 for no change
- **Post-hoc analysis: average composite scores by individual improved vs. placebo**

Pharmacokinetics of Edasalonexent in DMD Patients



Cohort[a]	C_{max} (ng/mL)	C_{min} (ng/mL)	Steady state $AUC_{0\text{-}24}$ (ng.h/mL)
Cohorts 1	390 (144)	27.5 (20.2)	3670 (1340)
Cohorts 2	450 (158)	25.9 (18.6)	
Cohorts 3	385 (144)	29.6 (22.3)	
Cohorts 4	413 (148)	28.6 (21.2)	
Cohorts 5	404 (146)	26.8 (19.5)	

[a]: Cohorts 1 to 5 dosed at different specified time with meals

Total daily exposure at 100 mg/kg/day in DMD patients ~ 7-fold greater than the exposure in *mdx* mouse at pharmacologically active dose

Conclusions

- **Results from preclinical and clinical studies of edasalonexent demonstrated two core principles of the SMART Linker technology platform: synergistic biological effects of the molecule, and metabolic pathway similarity to that of two well-characterized bioactives.**
- **Edasalonexent 100 mg/kg/day treatment group in the MoveDMD trial consistently showed numerical improvement vs. placebo across multiple measures although the changes were not statistically significant.**
- **Importantly, no safety signals were seen in the 12-week placebo-controlled MoveDMD trial and oral edasalonexent was well tolerated with an adverse event profile consistent with prior findings. There were no dose reductions or discontinuations.**
- **The open-label extension portion of the MoveDMD trial is ongoing to assess effects in patients on edasalonexent over a longer time.**
- **Based on edasalonexent's inhibition of NF-κB, edasalonexent may potentially reduce inflammation and muscle degeneration with positive effects on muscle regeneration in DMD patients regardless of mutation type.**

Acknowledgments:
–Patients and Families
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–ImagingDMD Staff
–Catabasis team

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE
MDA
Jerry Lewis Foundation
Cure Duchenne

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