Background

Introduction

- Duchenne Muscular Dystrophy (DMD) - A progressive, fatal, and ultimately fatal inherited neuromuscular disorder affecting approximately 1:3,500 to 1:8,000 live male births worldwide in a prevalence of approximately 50,000 in the United States.
- Cause: mutations in the gene encoding dystrophin, a critical part of the protein complex that connects the cytoskeleton of a muscle fiber to the extracellular matrix.

Edasalonexent

- An oral inhibitor of M6b in development for all patients DMD with any mutation type.
- A close analog of sphingosine1-phosphate (S1P), a ligand of the S1P receptors. 
- Following oral cell uptake, edasalonexent is metabolized into its active metabolite, enabling the indirect delivery of S1P to key intracellular signaling pathways.

Clinical trials in adult subjects

- Three studies in adult subjects assessed the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of oral edasalonexent in patients over 12 days in healthy volunteers up to 100 mg.
- MoveDMD trial of edasalonexent in pediatric patients
  - Phase 1: 12-week study evaluating its safety, efficacy, and PK of edasalonexent in pediatric patients, conducted at 61 to 66 days of age with a genetically confirmed diagnosis of DMD.

Results

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

Musk Cell Differentiation in Primary Human Myoblasts with and without Treatment of Edasalonexent

Muscle macrophage cells

Synergistic Efficacy of Edasalonexent: In Vitro and In Clinic

Treatment with placebo, edasalonexent (2000 mg), or salubrinal (100 mg) + DHA (1400 mg) in humans (n=20)

Oral Absorption of Edasalonexent in: Nonclinical Species and Human

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

Edasalonexent Produces Synergistic Efficacy

Pharmacology in mdx Mouse Model and Tissue Distribution of Edasalonexent

DHA and/or EPA (n-3 polyunsaturated fatty acid) (Vegepro® and LOVaza)

SMART Linker Technology: Metabolic Pathway Comparison with Saliycylates

Metabolite Profiling and Identification of Edasalonexent in Human Plasma

In addition, the following metabolites were detected:

- M1: oxo metabolite, similar to that seen in plants and diet
- M2: oxo metabolite, similar to that seen in plants and diet
- M3: oxo metabolite, similar to that seen in plants and diet
- M4: oxo metabolite, similar to that seen in plants and diet

SMART Linker Technology: Metabolic Pathway Comparison with Saliycylates

Similar metabolic pathways on the DHA moiety

In addition, sequential glucuronidation as seen in 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 entered in Phase 2
  - Cross-over: 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

- Results from preclinical and clinical studies of edasalonexent demonstrated two core principles of the SMART Linker technology platform: synergistic biological effects of the metabolite, and metabolic pathway similarity to that of Westerfield- and well-characterized biologics.
- Edasalonexent 100 mg/kg/day treatment group in the MoveDMD trial consistently showed numerical improvements 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 M6b, edasalonexent may potentially reduce inflammation and muscle degeneration with potential effects on muscle regeneration in DMD patients regardless of mutation type.

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

Pharmacokinetics of Edasalonexent in DMD Patients

M1: oxo metabolite, similar to that seen in plants and diet

- Individual scores for placebo-controlled analysis of 31 study sites, 70 meter walk test, time to stand, KSS and PEDI were pooled for this analysis. No change.
- Post-hoc analysis: average composite scores in individual improved vs. placebo.

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