Selective PPARδ modulator MA-0211 improves disease phenotype in DMD muscle cells and mdx mice

Matt Goddeeris, Eric Bell, Peter Dwyer, Jennifer Truong, Andrew Basinski, George Mulligan, Bharat Lagu, Mike Patane, Effie Tozzo.

Mitochondrial deficits are an early and critical facet of DMD.

Summary

Mitochondrial dysfunction is detected in Duchenne Muscular Dystrophy (DMD) patient tissues and cultured cells as well as animal models, and may represent a critical early deficit contributing to muscle fiber pathology. MA-0211 (MTP-1, A0367) is a novel, potent and selective modulator that increases muscle fatty acid oxidation (FAO) and mitochondrial biogenesis. The findings summarized here support the hypothesis that mitochondrial dysfunction may be a key component of the dystrophin deficient phenotype and suggest that MA-0211 improves cellular, histological and functional measures of skeletal and cardiac muscle health.

Background

DMD Muscle fuel utilization is unbalanced

- Fat
- Protein
- Carbohydrate

MA-0211 improves mitochondrial function in DMD Myotubes

Figure 2: Fatty acid oxidation was increased after 24 hours of treatment in DMD myotubes from 17 month old donor; measured using Seahorse XF analyzer. Mitochondrial DNA synthesis measured by BrDU incorporation, a marker related to mitochondrial biogenesis, increases with 72 hour treatment. Similar results obtained from second donor.

Introduction

- Mitochondrial deficits are an early and critical facet of DMD.
- Mitochondrial dysfunction in DMD leads to poor utilization of fatty acids by cells, a crucial fuel source for skeletal and cardiac muscle.
- MA-0211 is a transcription factor that can increase cellular capacity for fatty acid oxidation.
- MA-0211 is a potent, highly-selective orally-available small molecule modulator of PPARδ.

Figure 3: mdx mice were treated orally, once daily for 5 weeks starting at about 5 weeks of age. Treated mice demonstrated a decrease in muscle necrosis and inflammation (scored in a double-blind fashion) and reduced necrosis (fewer necrotic fibers and smaller injury foci), measured by detecting IgM-positive muscle fibers. Data represents two independent studies.

Figure 4: Reduced diaphragm fibrosis, measured by hyaluronan content, was observed after 5 weeks of once daily treatment.

Figure 5: Treated mdx mice were trained and tested for endurance capacity using a treadmill. The average run distance across three runs per mouse was compared.

MA-0211 increases PPARδ Target Gene expression in DMD Myotubes

Donor 1: 17 months old

Donor 2: 20 years old

Figure 1: qPCR gene expression of DMC myotubes treated for 24 hours demonstrates potent engagement of PPARδ target genes in DMD myotubes with MA-0211.

Conclusions and Future Directions

- MA-0211 is an oral agent that has reproducibly demonstrated efficacy across multiple symptoms of DMD via improvement in mitochondrial function and metabolism.
- Mitochondrial/metabolic benefits are independent of dystrophin mutation and offer potential for combination with other treatments.
- IND has been submitted. Developing clinical plan in partnership with Actelis Pharma.