EDG-5506 is a selective inhibitor of fast skeletal muscle myosin being developed as a novel oral treatment for Becker and Duchenne muscular dystrophy. In a Phase 1 study, five adults with Becker muscular dystrophy were administered 20 mg EDG-5506 daily for two weeks for assessment of safety, tolerability and pharmacokinetics. Specific analysis of circulating muscle injury biomarkers in response to treatment with EDG-5506 was conducted.

To understand how EDG-5506 treatment changes other circulating proteins and what those changes may tell us about the broader effects of this investigational therapeutics, the high-throughput and unbiased SOMAscan proteomics platform was utilized.

Here, we report on the effects of EDG-5506 treatment on those biomarkers that distinguish pre-treatment BMD from healthy volunteers. Then, using biomarker signatures annotated from a prior non-interventional study, we examine how EDG-5506 affects biomarkers that specifically describe skeletal muscle injury.

Clinical Trial Design and Outcomes

Figure 1. Clinical Trial Participants and Biomarker Changes

The multiple ascending dose arm of the phase I clinical trial recruited 7 BMD participants, with an average age of 33.8 years. When compared to age-matched healthy volunteers, these participants demonstrated diminished physical capabilities as measured in both 10 meter walk/ run and rise-from-the-floor tests, as well as lower creatinine and elevated creatinine kinase levels, consistent with decreased muscle mass and ongoing injury.

After 14 days of intervention, BMD individuals treated with EDG-5506 exhibited a greater reduction in circulating creatine kinase and myoglobin, both associated with skeletal muscle damage, than did participants receiving the placebo.

Figure 2. Biomarker changes at Baseline and after EDG-5506

Selection criteria of p < 0.05 and fold-change of at least 1.5-fold (log2 change of +/- 0.581) identified 125 elevated circulating proteins that distinguished BMD from healthy volunteers (left). Structural and metabolic proteins associated with muscle were heavily represented in this group. Upon treatment with 20 mg of EDG-5506 for 14 days, this panel of 125 biomarkers exhibited significant reduction relative to administration of placebo or treatment of healthy volunteers with EDG-5506 at similar exposure.

Figure 3. Design of the Non-Interventional Exercise trial

Volunteers diagnosed with one of several inherited myopathies were recruited for an exercise regimen consisting of aerobic and strength components and compared against healthy individuals. Following exercise, blood was drawn at timepoints up to 24 h and analyzed by SOMAscan.

Figure 4. Biomarker Annotation and Tissue Expression Profile

The universal baseline set (proteins changed in all myopathies at baseline) and the BMD-specific muscle injury set (BMD-elevated proteins that change after exercise) were strongly associated with skeletal muscle. By contrast, the BMD-specific exercise nonresponsive set exhibited little expression in muscle, instead being more heavily expressed in liver and kidney, and are likely representative of disease processes and responses not directly associated with elevated muscle damage.

Figure 5. EDG-5506 Reduces Universal Baseline Proteins

Figure 6. EDG-5506 Reduces Muscle Injury Biomarkers

Figure 7. EDG-5506 Reduces Exercise Nonresponsive Proteins

EDG-5506 is a novel fast skeletal myosin inhibitor that is in development for the treatment of BMD and DMD. The therapeutic hypothesis is that inhibition of myosin will alleviate the skeletal muscle damage that occurs in myopathies. The results presented here provide proteomic evidence that supports this hypothesis and that EDG-5506 is active both in general, myopathic-elevated biomarker panels as well as a specific biomarker fingerprint for exercise-induced skeletal muscle injury. Additionally, there are indications that even short-term administration of EDG-5506 is able to reduce circulating other process and tissue-associated biomarkers not directly elevated by acute muscle injury. Whether such reduction provides evidence of the body's homeostatic or adaptive responses to high levels of muscle injury remains to be explored.

Phase 2 studies in Becker and Duchenne individuals are planned.

Conclusions

References

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