

Fulcrum Therapeutics Announced Results of Phase 1 Clinical Trial of Losmapimod in FSHD

October 4, 2019

Data presented in an oral presentation at World Muscle Society meeting highlighted safety, tolerability, pharmacokinetics and target engagement of losmapimod in patients with facioscapulohumeral dystrophy.

CAMBRIDGE, Mass., Oct. 04, 2019 (GLOBE NEWSWIRE) -- [Fulcrum Therapeutics, Inc.](#) (Nasdaq: FULC), a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined rare diseases, today announced preliminary results of a Phase 1 clinical trial of losmapimod to treat the root cause of facioscapulohumeral dystrophy (FSHD). Losmapimod is a selective p38 α / β mitogen activated protein kinase (MAPK) inhibitor. Fulcrum exclusively in-licensed losmapimod following Fulcrum's discovery that the inhibition of p38 α / β reduced expression of the DUX4 gene in muscle cells derived from patients with FSHD, a disease which is caused by the mis-expression of DUX4 in skeletal muscle. Results were presented today by Michelle Mellion, MD, medical director at Fulcrum Therapeutics, in an oral presentation during the 24th International Annual Congress of the World Muscle Society in Copenhagen, Denmark.

"Losmapimod has previously been shown to have adequate safety and tolerability in over 3,500 patients and healthy volunteers across multiple indications, with no safety signals attributed to the drug in those trials. Until now, losmapimod had not been tested in patients with FSHD, nor was it known if it was muscle-penetrant in humans," said Dr. Mellion. "The preliminary results from our Phase 1 clinical trial of losmapimod in patients with FSHD indicate that losmapimod was generally well tolerated and achieved dose-dependent concentrations in plasma and muscle believed to be adequate for efficacy based on preclinical pharmacology studies."

The primary objective of the trial was to investigate the safety and tolerability of losmapimod in healthy volunteers and in FSHD patients. The secondary objective was to evaluate repeated dose pharmacokinetics (PK) and target engagement (TE) in FSHD patients. In the first cohort, 10 healthy volunteers were randomized to a single oral dose of losmapimod (n=8) 7.5 mg followed by a single oral dose of 15 mg after a wash out period or to single oral dose placebo (n=2) in both dosing periods. In the second cohort, 15 FSHD patients were randomized and treated with placebo (n=3) or losmapimod 7.5 mg (n=6) or 15 mg (n=6) taken orally twice daily for 14 days.

Losmapimod was well tolerated with no serious adverse events (SAEs) reported. Similar tolerability, safety and PK were observed in healthy volunteers and patients with FSHD. Treatment with losmapimod demonstrated dose-dependent PK and TE in blood. This was consistent with previously reported data from more than 3,500 patients treated with losmapimod across multiple other indications. FSHD patients treated with losmapimod also achieved dose-dependent concentrations in skeletal muscle, with a muscle to plasma exposure ratio of approximately 1:1. The losmapimod 15 mg dose taken orally twice daily demonstrated sustained drug concentrations that in preclinical models with human FSHD myotubes resulted in a robust reduction of DUX4-driven gene expression. Analysis of target engagement in muscle is ongoing. These data support the selection of the 15 mg dose of losmapimod taken orally twice daily in the Company's ongoing Phase 2b placebo-controlled 24-week clinical trial, referred to as ReDUX4, as well as its ongoing Phase 2 open label-study of losmapimod for the treatment of patients with FSHD.

"There are currently no approved treatment options available for patients with FSHD. They face a lifetime of accumulating disability that can severely impact their day-to-day function and quality of life," said Diego Cadavid, MD, senior vice president of clinical development at Fulcrum Therapeutics. "We are very encouraged by these results and are working rapidly to advance our development program for losmapimod."

About FSHD

FSHD is characterized by progressive skeletal muscle loss that initially causes weakness in muscles in the face, shoulders, arms and trunk, and progresses to weakness throughout the lower body. Skeletal muscle weakness results in significant physical limitations, including an inability to smile and difficulty using arms for activities, with many patients ultimately becoming dependent upon the use of a wheelchair for daily mobility.

FSHD is caused by mis-expression of DUX4 in skeletal muscle, resulting in the presence of DUX4 proteins that are toxic to muscle tissue. Normally, DUX4-driven gene expression is limited to early embryonic development, after which time the DUX4 gene is silenced. In people with FSHD, the DUX4 gene is turned "on" as a result of a genetic mutation. The result is death of muscle and its replacement by fat, leading to skeletal muscle weakness and progressive disability. There are no approved therapies for FSHD, one of the most common forms of muscular dystrophy, with an estimated patient population of 16,000 to 38,000 in the United States alone.

About Losmapimod

Losmapimod is a selective p38 α / β mitogen activated protein kinase (MAPK) inhibitor that was exclusively in-licensed by Fulcrum Therapeutics following Fulcrum's discovery of the role of p38 α / β inhibitors in the reduction of DUX4 expression and an extensive review of known compounds. Utilizing its internal product engine, Fulcrum discovered that inhibition of p38 α / β reduced expression of the DUX4 gene in muscle cells derived from patients with FSHD. Although losmapimod has never previously been explored in muscular dystrophies, it has been evaluated in more than 3,500 subjects in clinical trials across multiple other indications, including in several Phase 2 trials and a Phase 3 trial. No safety signals were attributed to losmapimod in any of these trials. Fulcrum is currently conducting Phase 2 trials investigating the safety, tolerability, and efficacy of losmapimod to treat the root cause of FSHD.

About Fulcrum Therapeutics

Fulcrum Therapeutics is a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need, with an initial focus on rare diseases. Fulcrum's proprietary product engine identifies drug targets which can modulate gene expression to treat the known root cause of gene mis-expression. Please visit www.fulcrumtx.com.

Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the development status of the Company's product candidates and the timing of availability of clinical trial data. All statements, other than statements of historical facts, contained in this press release, including statements regarding the Company's strategy, future operations, future financial position, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "target," "will," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of

risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, risks associated with Fulcrum's ability to obtain and maintain necessary approvals from the FDA and other regulatory authorities; continue to advance its product candidates in clinical trials; replicate in later clinical trials positive results found in preclinical studies and early-stage clinical trials of losmapimod and its other product candidates; advance the development of its product candidates under the timelines it anticipates in current and future clinical trials; obtain, maintain or protect intellectual property rights related to its product candidates; manage expenses; and raise the substantial additional capital needed to achieve its business objectives. For a discussion of other risks and uncertainties, and other important factors, any of which could cause the Company's actual results to differ from those contained in the forward-looking statements, see the "Risk Factors" section, as well as discussions of potential risks, uncertainties and other important factors, in the Company's most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent the Company's views as of the date hereof and should not be relied upon as representing the Company's views as of any date subsequent to the date hereof. The Company anticipates that subsequent events and developments will cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so.

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