

Fulcrum Therapeutics Announces Interim Analysis Data from its ReDUX4 Trial in Facioscapulohumeral Muscular Dystrophy (FSHD)

August 11, 2020

Reduction in DUX4-driven gene expression observed in biopsies with highest baseline levels of DUX4-driven gene expression

Topline data on-track for Q1 2021 with full data in Q2 2021

Company to review clinical data on second quarter earnings call today at 8:00am ET

CAMBRIDGE, Mass., Aug. 11, 2020 (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 results from a pre-specified interim analysis of the primary endpoint of the Phase 2 ReDUX4 trial in subjects with facioscapulohumeral muscular dystrophy (FSHD). The primary endpoint is the reduction from baseline of DUX4-driven gene expression in affected skeletal muscle after subjects have been treated with losmapimod or placebo. Secondary and exploratory endpoints were not assessed as part of this analysis. Results from the interim analysis in the first 29 randomized subjects indicate that DUX4-driven gene expression did not show a separation from placebo at 16 weeks. However, in a pre-specified sensitivity analysis, those with the highest pre-treatment DUX4-driven gene expression in their muscle biopsy sample showed a 38-fold reduction in DUX4-driven gene expression following treatment with losmapimod compared to a 5.4 fold reduction with placebo.

FSHD is a rare, progressive and disabling disease for which there are no approved treatments. FSHD is caused by aberrant expression of DUX4 in skeletal muscle, resulting in the inappropriate presence of the DUX4 protein, which causes the death of muscle and its replacement by fat. In preparatory studies, the range of DUX4 expression levels within affected muscles throughout a patient's body have been shown to be relatively stable over time at the site of a muscle biopsy.

"Preliminary evidence from our interim analysis suggests that muscles with higher DUX4-driven gene expression in pre-treatment biopsies show greater reduction of DUX4-driven gene expression following treatment with losmapimod compared to placebo. These results, which provide evidence of the ability of losmapimod to reduce DUX4-driven gene expression, are very encouraging," said Robert J. Gould, Ph.D., president and chief executive officer. "This initial data represents the first time a treatment is being evaluated to impact the root cause of FSHD in a placebo-controlled trial and are helping to inform our longer-term clinical strategy for losmapimod. We look forward to further leveraging the open label study to evaluate the long-term effects of losmapimod in additional FSHD subjects. We remain on track to share topline results on the primary endpoint in the first quarter of 2021 and full data, including all secondary and exploratory endpoints, in the second quarter of 2021."

Interim Analysis Summary

The interim results included an analysis of the first 29 subjects who completed their 16-week biopsy out of the 80 subjects enrolled. Pharmacokinetics, demographics and the primary endpoint were assessed. Subjects were randomized to receive an oral dose of losmapimod 15mg (n=15) or placebo (n=14) twice per day. While results showed a significant reduction in DUX4-driven gene expression in the muscle biopsies of subjects whose baseline biopsy showed the highest levels of DUX4 gene expression (38-fold decrease with losmapimod, n=3, and 5.4 fold-decrease with placebo, n=5), the population level data analysis of the reduction in DUX4-driven gene expression from all 29 subjects did not show a separation of losmapimod from placebo (3.7 fold increase with losmapimod, n=15, and 2.8 fold increase with placebo, n=14). Results indicate that muscle biopsies within the higher levels of DUX4-driven gene expression may be needed to observe a reduction from baseline.

Interim Analysis Results (All Subjects)			Interim Analysis Results (Highest Expressing Muscle Biopsies)*	
	Sample Size	Fold change (Δ CT)	Sample Size	Fold change (Δ CT)
Losmapimod	n=15	+3.7	n=3	-38
Placebo	n=14	+2.8	n=5	-5.4

* Highest expressing muscle biopsies represent the top quartile of biopsies assessed based on baseline DUX4-driven gene expression.

Losmapimod was generally well tolerated with no serious drug-related adverse events (SAEs) reported. The interim analysis was not powered for statistical significance and did not include individual patient level data. ReDUX4 remains blinded.

"One of the critical factors in patients with FSHD is that there can be significant variability in the magnitude of DUX4-driven gene expression at the site of each pre-treatment needle biopsy," said Diego Cadavid, MD, Fulcrum's senior vice president, clinical development. "The initial observation of greater reduction by losmapimod over placebo in DUX4-driven gene expression in the biopsied muscles with the highest baseline expression may represent the potential losmapimod has to treat the root cause of the disease. We're excited about the study progress and look forward to the final analysis."

About ReDUX4

ReDUX4 is a randomized, double-blind, placebo-controlled multicenter international Phase 2b clinical trial in 80 subjects with FSHD to investigate the efficacy and safety of oral administration of losmapimod 15 mg twice per day. The primary endpoint is to evaluate the reduction of DUX4-driven gene expression in affected skeletal muscle biopsies. The original design of ReDUX4 included a muscle biopsy at week 16 during the 24-week treatment period followed by an open label extension.

As a result of the COVID-19 pandemic, Fulcrum announced in May 2020 that the trial had been extended from 24 to 48 weeks through a protocol amendment to ensure the safety of the subjects and to allow for the opportunity for a biopsy at week 16 as originally intended or at week 36.

The extension from 24 to 48 weeks also allows for a longer assessment in a placebo-controlled design of the skeletal muscle MRI secondary endpoint and the various exploratory clinical endpoints, such as reachable workspace, FSHD-Timed Up and GO, muscle function measures and patient reported outcomes. Topline data from approximately 80 patients is expected in the first quarter of 2021. Approximately 68 subjects remain active in the

randomized portion of the trial and 12 remain active in the open label extension.

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 from GSK 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. Researchers at Fulcrum also believe that losmapimod has the potential to treat COVID-19 by reducing the acute exaggerated pro-inflammatory responses to SARS-CoV-2 infection and restoring the antigen-specific immune responses needed for viral clearance, potentially leading to improved clinical outcomes. Losmapimod has been evaluated in more than 3,600 subjects in clinical research across multiple indications, including in several Phase 2 trials and a large Phase 3 trial in acute myocardial infarction. No safety signals were attributed to losmapimod in any of these trials. In 2020, the Company received U.S. and European Orphan Drug Designation for losmapimod for the treatment of FSHD. Fulcrum is currently conducting Phase 2 trials investigating the safety, tolerability, and efficacy of losmapimod to treat the root cause of FSHD and initiating a Phase 3 trial investigating the safety, tolerability, and efficacy of losmapimod to treat hospitalized patients with COVID-19.

About Fulcrum Therapeutics

Fulcrum Therapeutics is a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined rare diseases in areas of high unmet medical need. Fulcrum's proprietary product engine identifies drug targets which can modulate gene expression to treat the known root cause of gene mis-expression. The company has advanced losmapimod to Phase 2 clinical development for the treatment of facioscapulohumeral muscular dystrophy (FSHD) and is advancing losmapimod to Phase 3 for the treatment of COVID-19. Fulcrum also anticipates filing an IND in the third quarter with initiation of a clinical trial in the fourth quarter of 2020 with FTX-6058 for the treatment of sickle cell disease.

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, such as the planned timing of submission of the Company's IND and initiation of the Company's clinical trial for FTX-6058, the potential advantages and therapeutic potential 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; initiate and enroll clinical trials on the timeline expected or at all; correctly estimate the potential patient population and/or market for the Company's product candidates; replicate in clinical trials positive results found in preclinical studies and/or earlier-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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