Fulcrum Therapeutics® Announces REACH, a Phase 3 Clinical Trial of Losmapimod in Facioscapulohumeral Muscular Dystrophy (FSHD)

March 3, 2022

- *Reachable Workspace (RWS) primary endpoint based on discussions with FDA and EU regulatory agencies*
- *Trial expected to begin in 2Q 2022*
- *Potential first-to-market therapy for FSHD*
- *Fulcrum to host virtual Key Opinion Leader webcast on FSHD on March 24 at 10:00am ET*

CAMBRIDGE, Mass., March 03, 2022 (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 its plans to initiate REACH, a Phase 3 clinical trial of losmapimod in people with facioscapulohumeral muscular dystrophy (FSHD), in the second quarter of 2022. FSHD is a serious, rare, progressive and debilitating disease for which there are no approved treatments. It is characterized by fat infiltration of skeletal muscle leading to muscular atrophy involving the face, scapula and shoulders, upper arms, and abdomen. Impact on patients includes profound decreases in the ability to perform activities of daily living, loss of upper limb function, loss of mobility and independence, and chronic pain.

“We are excited to advance losmapimod into the REACH Phase 3 trial for FSHD,” said Bryan Stuart, Fulcrum’s president and chief executive officer. “Results from the Phase 2b clinical trial demonstrated that losmapimod slowed disease progression and improved function in people with FSHD. Based on these data as well as insights gained from the trial on optimal measures of disease progression, we aligned with regulators, including the FDA, on key aspects of the design of the REACH trial. With positive data, we expect REACH to be the basis for approval. This marks a significant milestone for FSHD patients and caregivers, and Fulcrum remains committed to serving the FSHD community.”

“There are no approved therapies for FSHD, and there is a clear and urgent need for a treatment to slow or stop disease progression,” said Nicholas Johnson, MD, M.Sci., FAAN, associate professor, division chief of neuromuscular, and vice chair of research in the department of neurology at Virginia Commonwealth University. “For people with FSHD, every day without a treatment is another day that they may lose strength, the ability to lift their arms, or walk unassisted. Losmapimod is the first and only investigational medicine in clinical development. The data to date are very promising, showing meaningful clinical benefit and a well-established safety and tolerability profile. I look forward to further investigating losmapimod in the REACH trial.”

Based on results from a Phase 2b study of losmapimod showing clinical benefit, Fulcrum engaged with U.S. and EU regulatory agencies, including the Food and Drug Administration (FDA), and gained alignment on key aspects of the design for a Phase 3 trial. REACH will be a randomized, double-blind, placebo-controlled, multi-national trial to evaluate the efficacy and safety of losmapimod for the treatment of FSHD. The trial is expected to enroll approximately 230 adults with FSHD. Patients will be randomized 1:1 to receive either losmapimod, administered orally as a 15 mg tablet twice a day, or placebo, and evaluated over a 48-week treatment period. The primary endpoint of the study is the absolute change from baseline in Reachable Workspace (RWS). Secondary endpoints include muscle fat infiltration (MFI), Patient Global Impression of Change (PGIC), and Quality of Life in Neurological Disorders of the upper extremity (Neuro QoL UE). REACH will also include patient-centered assessments of healthcare utilization.

Judith A. Dunn, Ph.D., Fulcrum’s president of research and development, said, “We learned from our Phase 2b trial that RWS, MFI and patient-reported outcomes are reliable measures of disease progression and that we can observe meaningful differences in these endpoints compared to placebo after just 48 weeks of treatment with losmapimod. REACH is optimized to demonstrate similar statistically and clinically significant benefits and represents an important step in delivering a life-changing therapy to people with FSHD.”

Results from ReDUX4, a randomized, double-blind, placebo-controlled Phase 2b trial, which enrolled approximately 80 patients treated for 48 weeks, demonstrated clinically relevant benefits on multiple measures of muscle health and function as well as patient-reported outcomes. Notably, losmapimod improved accessible surface area in RWS, a quantitative measure of upper extremity range of motion and function that has shown to correlate with the ability to independently perform activities of daily living. Losmapimod also decreased progression of fat infiltration in muscles already affected by disease and preserved the health of normal-appearing muscles. Additionally, losmapimod-treated patients reported feeling better compared to those on placebo using the assessment. Consistent with losmapimod’s extensive safety and tolerability profile from clinical trials outside of FSHD, there were no serious treatment-related adverse events observed in the Phase 2b trial.

KOL Event to Discuss Unmet Need in FSHD, REACH Trial and Key Measures of Disease Progression

Fulcrum will host a KOL meeting on Thursday, March 24, 2022 from 10:00am – 12:00pm ET with Nicholas E. Johnson, MD, M.Sci., FAAN, associate professor, division chief of neuromuscular, and vice chair of research in the department of neurology at Virginia Commonwealth University and Jay J. Han, MD, professor and vice chair residency program director, University of California, Irvine. The live webcast will be accessible through the Investor Relations section of the company’s website fulcrumtx.com. Following the live webcast, an archived replay will also be available on the website for up to 90 days.

About FSHD
FSHD is a serious, rare, progressive and debilitating disease for which there are no approved treatments. It is characterized by fat infiltration of skeletal muscle leading to muscular atrophy involving primarily the face, scapula and shoulders, upper arms, and abdomen. Impact on patients includes profound decreases in the ability to perform activities of daily living, loss of upper limb function, loss of mobility and independence and chronic pain. FSHD is one of the most common forms of muscular dystrophy and has an estimated patient population of 16,000 to 38,000 in the United States alone.

About Reachable Workspace (RWS)
RWS is a quantitative measure of upper extremity range of motion and function. Specifically, it evaluates total shoulder and proximal arm mobility by utilizing 3D motion sensor technology. Preserving function, as assessed by RWS, is critical for maintaining abilities for self-care and other activities of daily living that directly influence quality of life. Based on published results, reachable workspace is an important measure of independence.

About Losmapimod

Losmapimod is an investigational, selective p38α/β mitogen activated protein kinase (MAPK) inhibitor. Fulcrum exclusively in-licensed losmapimod from GSK following Fulcrum's discovery of the role of p38α/β inhibitors in the reduction of DUX4 expression and an extensive review of known compounds. Results reported from the ReDUX4 trial demonstrated slowed disease progression and improved function, including positive impacts on upper extremity strength, supporting losmapimod's potential to be a transformative therapy for the treatment of FSHD. Although losmapimod had never previously been explored in muscular dystrophies, it had been evaluated in more than 3,500 subjects in clinical trials across multiple other indications, with no safety signals attributed to losmapimod. Losmapimod has been granted U.S. Food and Drug Administration (FDA) Fast Track designation and Orphan Drug Designation for the treatment of FSHD.

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 two lead programs in clinical development are losmapimod, a small molecule for the treatment of facioscapulohumeral muscular dystrophy (FSHD) and FTX-6058, a small molecule designed to increase expression of fetal hemoglobin for the treatment of sickle cell disease and other hemoglobinopathies, including beta-thalassemia. The company's proprietary product engine, FulcrumSeek™, identifies drug targets that 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. All statements, other than statements of historical facts, contained in this press release are forward-looking statements, including statements regarding the planned REACH trial including its expected start date and enrollment target, losmapimod's potential as a therapy for FSHD, the ability of the selected endpoints to support regulatory approval and the sufficiency of Fulcrum's cash resources. 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 continue to advance its product candidates in clinical trials; initiate and enroll clinical trials on the timeline expected or at all; obtain and maintain necessary approvals from the FDA and other regulatory authorities; replicate in clinical trials positive results found in preclinical studies and/or earlier-stage clinical trials of losmapimod, FTX-6058 and its other product candidates; 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 Fulcrum'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 Fulcrum's most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent Fulcrum's views as of the date hereof and should not be relied upon as representing Fulcrum's views as of any date subsequent to the date hereof. Fulcrum anticipates that subsequent events and developments will cause Fulcrum's views to change. However, while Fulcrum may elect to update these forward-looking statements at some point in the future, Fulcrum specifically disclaims any obligation to do so.

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