Fulcrum Therapeutics Enrolls First Patient in Pivotal Global Phase 3 Clinical Trial of Losmapimod for Facioscapulohumeral Muscular Dystrophy (FSHD)

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– REACH is the first Phase 3 trial for this rare, progressive, and debilitating muscular disease –
– Losmapimod is an oral small molecule that has the potential to be the first therapy to treat FSHD, the second most common form of muscular dystrophy –
– U.S. Food and Drug Administration (FDA) granted Fast Track Designation in 2021 –

CAMBRIDGE, Mass., July 05, 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 that the first patient has been dosed in REACH, a Phase 3 clinical trial designed to evaluate the safety and efficacy of losmapimod for the treatment of FSHD. The randomized, double-blind, placebo-controlled, multi-national Phase 3 trial will enroll approximately 230 adults at over 30 sites in North America and Europe. The pivotal trial is designed to support the U.S. FDA and European Medicines Agency (EMA) regulatory applications of lospmapimod for the treatment of FSHD. If approved, losmapimod would be the first and only therapy for the disease.

FSHD is a rare, serious, progressive, and debilitating disease that is caused by the aberrant expression of the DUX4 gene, which leads to skeletal muscle cell death and fat infiltration. Patients with FSHD experience progressive muscle weakness leading to significant impairment in function, including the inability to use their upper limbs, communicate via facial expression, and walk unassisted.

“The progression of FSHD can make it increasingly difficult to pursue work, hobbies, social and family life,” said Mark Stone, CEO of the FSHD Society. “The REACH trial with losmapimod represents the first real hope for those living with the disease, their families and their caregivers, who have waited so long for a potential treatment to be found.”

The primary efficacy endpoint in the REACH study will be the absolute change from baseline in reachable workspace (RWS). RWS is a quantitative and reliable functional measurement of disease progression in people with FSHD which correlates closely with how people living with the disease feel and function in a real-world setting. Secondary endpoints include muscle fat infiltration (MFI), an indicator of muscle health, Patient Global Impression of Change (PGIC), and Quality of Life in Neurological Disorders of the upper extremity (Neuro QoL UE), a measure of patient self-reported health-related quality of life.

Results from Fulcrum’s Phase 2 clinical trial, ReDUX4, demonstrated that losmapimod was superior to placebo across a number of clinically relevant endpoints. Losmapimod slowed disease progression and helped maintain function in adults with FSHD, as assessed by RWS at 48 weeks of treatment. Losmapimod also preserved muscle health over the course of 48 weeks, as assessed by MFI. The correlations between muscle health (MFI) and muscle function (RWS) was validated in a study recently published in the Journal of the American Academy of Neurology. Losmapimod has been studied in over 3600 people across multiple indications and has been found to be generally safe and well tolerated.

“The results from the Phase 2 study confirm the potential of losmapimod to be the first disease-modifying therapy for FSHD,” said Judy Dunn, Fulcrum’s president of research and development. “Based on input from patients, regulatory agencies, and the clinical community, we selected RWS as the primary efficacy measure in order to most effectively quantify the impact of losmapimod on slowing disease progression. The initiation of the REACH trial is a testament to our deep commitment to addressing the unmet medical needs of those living with genetically defined rare diseases and exemplifies our leadership in FSHD.”

More information on the REACH trial can be found at:
www.REACH*fshd*study.com
www.clinicaltrials.gov/ NCT05397470

About the REACH Phase 3 Trial
REACH is a randomized, double- blind, placebo-controlled, multi-national trial to evaluate the efficacy and safety of losmapimod for the treatment of 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.

About Reachable Workspace (RWS)
RWS is an objective 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 3,600 subjects in clinical trials across multiple other indications, with no safety signals attributed to losmapimod. Losmapimod has been granted FDA Fast Track designation and Orphan Drug Designation for the treatment of FSHD.

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 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 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. Follow Fulcrum on LinkedIn at https://www.linkedin.com/company/fulcrum-therapeutics/, Twitter at https://twitter.com/FulcrumTx, Facebook https://www.facebook.com/FulcrumTx and Instagram at https://www.instagram.com/fulcrumtx/.

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, presentation of data from first dose cohort in Phase 1b trial of FTX-6058 and the second dose cohort, the clinical development plan for FTX-6058 as well as timing for expansion into other hemoglobinopathies and initiation of registrational trial for sickle cell disease, nomination of additional development candidates and timing of fourth IND, the sufficiency of Fulcrum's cash resources, losmapimod's potential as a therapy for FSHD and the ability of the selected endpoints of the REACH trial to support regulatory approval . 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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