Fulcrum Therapeutics Announces Initiation of Multi-Center Phase 3 (LOSVID) Trial with Losmapimod for Hospitalized COVID-19 Patients

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Fulcrum receives early notification from U.S. Food and Drug Administration (FDA) that study may proceed

CAMBRIDGE, Mass., June 24, 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 that it received early notification from the U.S. Food and Drug Administration (FDA) that the company may proceed with initiating a Phase 3, randomized, double-blind, placebo-controlled trial of losmapimod in higher risk hospitalized adults with COVID-19. Losmapimod is an orally available selective p38α/β mitogen activated protein kinase (MAPK) inhibitor.

The LOSVID trial is a Phase 3, international, multicenter trial designed to assess the safety and efficacy of a 15 mg twice per day oral dose of losmapimod compared to placebo for 14 days on top of standard of care in approximately 400 patients hospitalized with COVID-19 and at risk of progression to critical illness based on older age and elevated systemic inflammation. The primary endpoint is the proportion of patients who progress to death or respiratory failure by day 28. Additional secondary endpoints include clinical status on days seven and 14 as measured on the nine point WHO ordinal scale of COVID-19 severity, total number of study days free of oxygen supplementation, all-cause mortality, length of hospitalization and ICU stay, adverse events and viral clearance.

An interim analysis will be conducted in the fourth quarter of 2020 for futility and sample size re-estimation by an independent data monitoring committee when approximately 50 percent of subjects complete the 28-day visit. Topline data is expected to be reported in the first quarter of 2021.

“We believe that losmapimod has the potential to be a differentiated treatment option in the global fight against COVID-19,” said Robert J. Gould, Ph.D., president and chief executive officer. “The speed with which we have advanced this program reflects our deep understanding of the mechanism of action of losmapimod, the pressing need for treatment options and the commitment of our team to develop therapies that result in meaningful outcomes for patients. We are encouraged by the feedback we have received from investigators, and we expect to have all sites participating in the trial to be activated in the coming weeks.”

“We look forward to conducting this important trial in parallel with our ongoing clinical program for losmapimod as a potential treatment of facioscapulohumeral muscular dystrophy (FSHD),” continued Dr. Gould. “We have several anticipated upcoming data readouts in the next six to 12 months from both the COVID-19 and FSHD trials and we look forward to the outcomes of these trials which will tell us more about losmapimod’s impact in both these patient populations. Additionally, we continue our progress with FTX-6058 towards the clinic for the potential treatment of sickle cell disease.”

Based on its mechanism of action and preclinical and clinical studies, Fulcrum believes that inhibiting the p38 MAPK pathway with 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.

“Studies in elderly people indicating that p38 inhibition can decrease inflammatory responses but enhance T-cell responses to a viral antigen suggest that losmapimod could ameliorate the pathology of COVID-19 in multiple ways,” said Robert Finberg, MD, Professor of Medicine, University of Massachusetts Medical School. “Losmapimod is a promising treatment candidate that could address multiple key contributors to the pathogenesis of COVID-19 and already has an extensive amount of safety and tolerability data across multiple age groups, including the elderly. The rapid initiation of this pivotal trial reflects the data supporting this research and the pressing need for effective therapies that reduce the morbidity associated with COVID-19.”

The Potential Role of p38 Inhibition in the Treatment of COVID-19
p38 MAPK is well known as an important mediator of acute response to stress, including acute inflammation. Multiple preclinical and clinical studies have shown that activation of the p38 MAPK significantly contributes to the pathogenesis of coronavirus infections including COVID-19. In two clinical studies reported in the literature, an oral dose of 15 mg twice per day of losmapimod in older individuals decreased inflammatory responses and enhanced normal immune responses. Additionally, in prior human clinical trials predominantly in chronic inflammatory conditions, losmapimod had an immediate effect on a number of inflammatory biomarkers that have been associated with poor prognosis in COVID-19, including C-reactive protein (CRP) and interleukin-6 (IL-6). p38 inhibition has also been demonstrated to reduce Ang II-induced endothelial and organ damage in several experimental models and may address the renin-angiotensin system imbalance that is believed to contribute to key morbidities in COVID-19 patients.

About Losmapimod
Losmapimod is a selective p38α/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 p38α/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 p38α/β reduced expression of the DUX4 gene in muscle cells derived from patients with FSHD. Researchers at Fulcrum 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 prior clinical research across multiple other 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. 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 a

regulatory filing in the second half 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 Company's initiation of a clinical trial and evaluation, and the potential benefits, of losmapimod as a potential treatment for COVID-19, the development status of the Company's product candidates, including the planned timing of submission of the Company's IND for FTX-6058, 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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