Fulcrum Therapeutics to Evaluate Losmapimod as Potential Treatment for COVID-19

June 10, 2020 at 7:00 AM EDT

Investigational New Drug (IND) application submitted; Company preparing to initiate Phase 3 trial

ReDUX4 interim analysis in facioscapulohumeral dystrophy (FSHD) on track for Q3 2020 readout; FTX-6058 Phase 1 trial on track for Q4 2020 initiation

Conference call scheduled for 8:30 a.m. ET today

CAMBRIDGE, Mass., June 10, 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 plans to evaluate losmapimod as a potential treatment for patients with COVID-19. Fulcrum has submitted an investigational new drug (IND) application to support initiation of a randomized, placebo-controlled, Phase 3 clinical trial in hospitalized patients in the United States following Pre-IND consultation via the Coronavirus Treatment Acceleration Program (CTAP).

"The decision to advance this development program is a reflection of the compelling science that supports losmapimod's potential in COVID-19," said Robert J. Gould, Ph.D., Fulcrum's president and chief executive officer. "Prior clinical trials have shown its ability in other disease states to reduce acutely the inflammatory cytokines, such as C-reactive protein and IL-6, that are associated with poor prognosis. This new planned Phase 3 program adds to our robust development portfolio including potential treatments for facioscapulohumeral dystrophy (FSHD) and sickle cell disease. We are excited to apply our insights and understanding of losmapimod in COVID-19 as a potential differentiated treatment option in the global fight against this virus. I am proud of the work by our team and collaborators to rapidly advance this planned clinical program and look forward to collaborating with regulators and our outstanding team of clinical investigators to move this important effort forward as quickly as possible."

"An extensive body of data in the literature suggests that inhibiting p38 MAP kinase may be beneficial for patients with COVID-19," said Owen B. Wallace, Ph.D., Fulcrum's chief scientific officer. "Poor prognosis for COVID-19 patients has been attributed to an exaggerated inflammatory response following SARS-CoV-2 infection. Losmapimod has been shown in preclinical and clinical studies to reduce proteins associated with acute inflammatory stress. Additionally, p38 inhibition has been reported to reduce pathophysiology associated with an activated renin-angiotensin system and positively impact the innate-adaptive immune system imbalance, both of which have been linked to increased morbidity and mortality in COVID-19. The p38 MAPK pathway has been implicated in other viral infections, and there may be the opportunity to explore losmapimod in additional serious infections."

The Potential Role of p38 Inhibition in the Treatment of COVID-19

Several lines of preclinical and clinical evidence indicate that activation of the p38 mitogen-activated protein kinase (MAPK) significantly contributes to the pathogenesis of coronavirus infections including COVID-19. p38 MAPK is well known as an important mediator of acute response to stress, including acute inflammation.

In two clinical studies reported in the literature, an oral dose of 15 mg twice per day of losmapimod in older individuals restored the normal immune response to a viral antigen challenge and demonstrated resolution of acute inflammation, a relevant observation because the majority of severe and fatal cases of COVID-19 occur in older individuals. 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). In previous trials in more than 3,600 subjects, losmapimod exhibited favorable safety and tolerability not significantly different from placebo. These trials have also indicated that losmapimod had good exposure after oral dosing and robust target engagement.

The Company believes that losmapimod has the potential to treat COVID-19 by reducing the acute exaggerated pro-inflammatory responses to SARS-CoV-1 infection and restoring the antigen-specific immune responses needed for clearance of SARS-CoV-2, potentially leading to improved clinical outcomes. Additionally, p38 inhibition has been demonstrated to reduce angiotensin II (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.

Losmapimod for FSHD

Fulcrum's clinical program in COVID-19 is not expected to impact the timing or prioritization of other key Company milestones, including the interim analysis of ReDUX4, a randomized, double-blind, placebo-controlled multicenter international Phase 2b clinical trial in 80 subjects with FSHD. The Company remains on track to report data from this interim analysis late in the third quarter of 2020. Additionally, Fulcrum believes that it has sufficient supply of losmapimod for ongoing clinical trials in patients with FSHD, as well as for the planned Phase 3 trial in patients with COVID-19. Fulcrum owns all worldwide development and commercialization rights to losmapimod.

FTX-6058 in Sickle Cell Disease

FTX-6058 is an oral small molecule therapeutic discovered by Fulcrum and designed to induce expression of fetal hemoglobin (HbF) in red blood cells to compensate for the mutated adult hemoglobin in sickle cell disease. Fulcrum has completed IND-enabling studies including toxicology work with FTX-6058 and remains on track to initiate a Phase 1 trial by the end of 2020.

Financial Expectations

The Company expects that its cash, cash equivalents, and marketable securities of $81.2 million as of March 31, 2020, together with the $68.5 million in gross proceeds from its private placement announced today, will be sufficient to fund its operating expenses and capital expenditure requirements into the first quarter of 2022.

Conference Call and Webcast

Fulcrum Therapeutics, Inc. will host a conference call and webcast today at 8:30 a.m. ET to discuss today's developments. The webcast will be accessible through the Investor Relations section of Fulcrum's website at www.fulcrumtx.com. Following the live webcast, an archived replay will also

be available.

Dial-in Number
U.S./Canada Dial-in Number: 800-527-6973
International Dial-in Number: 470-495-9162
Conference ID: 3895852

Replay Dial-in Number: 855-859-2056
Replay International Dial-in Number: 404-537-3406
Conference ID: 3895852

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 Sickle Cell Disease

Sickle cell disease (SCD) is a genetic disorder of the red blood cells caused by a mutation in the HBB gene. This gene encodes a protein that is a key component of hemoglobin, a protein complex whose function is to transport oxygen in the body. The result of the mutation is less efficient oxygen transport and the formation of red blood cells that have a sickle shape. These sickle shaped cells are much less flexible than healthy cells and can block blood vessels or rupture cells. SCD patients typically suffer from serious clinical consequences, which may include anemia, pain, infections, stroke, heart disease, pulmonary hypertension, kidney failure, liver disease and reduced life expectancy.

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 plans to advance losmapimod to Phase 3 for the treatment of COVID-19. Fulcrum also anticipates filing an IND 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 planned evaluation of losmapimod as a potential treatment for COVID-19 and the potential benefits of such treatment, the development status of the Company’s product candidates, including the 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; 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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