Fulcrum Therapeutics Announces Proof-of-Concept for FTX-6058 in Sickle Cell Disease Based on Initial Data from the Ongoing Phase 1b Trial

June 10, 2022

- Achieved up to 6.3% hemoglobin F (HbF) induction in initial subjects in first cohort; HbF was increasing at last measured timepoint

- Supports proof-of-concept that FTX-6058 is a novel oral HbF inducer

- FTX-6058 was generally well tolerated; no serious treatment emergent adverse events (TEAEs) reported

- Data to be presented as a poster at European Hematology Association (EHA) Hybrid Congress; highlights to be presented at the Foundation for Sickle Cell Disease Research Symposium (FSCDR) on June 11, 2022

- Fulcrum to review results during an investor conference call, including guest KOL Dr. Julie Kanter, at 8:00 a.m. ET today

CAMBRIDGE, Mass., June 10, 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 clinical proof-of-concept data from the ongoing Phase 1b trial of FTX-6058 for the treatment of sickle cell disease (SCD). Initial data from the first subjects to receive a 6 mg dose of FTX-6058, an oral HbF inducer, showed a rapid and robust induction of HbF, and subjects achieved increases of up to 6.3% over baseline. HbF levels were increasing at the last measured time point, and maximal levels of HbF may have not yet been achieved.

Increases in HbF have been shown to reduce the frequency or severity of a broad range of SCD symptoms, including vaso-occlusive crises (VOC), anemia, pain, infection, stroke, and others. Based on a large body of genetic, clinical, and observational evidence showing the effects of higher levels of HbF in patients with SCD, the induction of HbF by 5-10% over baseline is associated with reduced disease burden and improved clinical outcomes. These initial data showing that FTX-6058 increases HbF levels by up to 6.3% support its potential to become a transformative therapy for people living with SCD.

“People with sickle cell disease have a tremendous need for therapeutic options that can reduce morbidity and mortality and improve their quality of life,” said Julie Kanter, M.D., associate professor of Hematology and Oncology and director of the Adult Sickle Cell Program at the University of Alabama at Birmingham. “These initial data from FTX-6058 showing measurable increases in HbF induction are very encouraging. Achieving significant absolute increases over baseline in an oral, once-daily treatment option could have a major impact on the SCD treatment paradigm.”

The first cohort of the Phase 1b study has enrolled six of up to ten subjects. These six subjects (none on background hydroxyurea) received at least one 6 mg dose of FTX-6058 and all were included in the safety analyses. As of the data cut-off on May 25, 2022, three subjects were evaluable at day 28 and beyond for increases in HbF. Three subjects were not evaluated due to non-adherence or protocol deviation, as specified in the statistical analysis plan.

All subjects evaluable for HbF change over baseline achieved increases in HbF by day 28. Changes in additional parameters, such as total bilirubin, reticulocyte count, and total hemoglobin were also observed, consistent with reduced hemolysis. A table showing the percent increase in HbF at pre-specified time-points is provided below.

Absolute HbF (%)									
	Baseline	Day 14	Day 28	Day 42	Day 56	Day 70	Day 84 (EOS)	Post Tx + 7D	Increase from baseline
Subject 1	9.2%	9.8%	10.9%	13.5%	14.0%	13.7%	13.7%	14.4%	5.2%
Subject 2	3.7%	5.0%	7.8%	9.6%	10.0%				6.3%
Subject 3	6.2%	6.5%	7.3%	8.3%					2.1%

FTX-6058 was generally well-tolerated in the initial cohort. No serious TEAEs were reported, and there were no discontinuations due to TEAEs. All non-serious TEAEs were transient and deemed unrelated to study drug.

“This is a compelling first look at HbF protein induction in people with sickle cell disease who have been treated with FTX-6058. The levels of HbF protein induction that we have seen thus far reinforce our belief that FTX-6058 could provide a transformational benefit to people living with sickle cell disease,” said Bryan Stuart, president and chief executive officer at Fulcrum. “By the end of this year, we plan to complete enrollment in our current dose cohort, as well as our second and third cohorts in this dose-ranging study, with the goal of initiating a registrational trial in 2023.”

Conference Call Information
Fulcrum will host a conference call and webcast today at 8:00 am ET to discuss these results. 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: 4477738

Replay Dial-in Number: (855) 859-2056
Replay International Dial-in Number: (404) 537-3406
Conference ID: 4477738

About FTX-6058
FTX-6058 is an investigational oral small-molecule inhibitor of Embryonic Ectoderm Development (EED) that was discovered using FulcrumSeek™,

Fulcrum's proprietary discovery engine. It is being developed for the treatment of sickle cell disease (SCD) and other hemoglobinopathies. Results from a Phase 1 healthy volunteer study demonstrated robust induction of HBG mRNA after 14 days of dosing. FTX-6058 has also shown robust induction of fetal hemoglobin (HbF) protein in study participants with SCD. To date, FTX-6058 has been generally well-tolerated with no serious treatment-related adverse events reported.

About the Phase 1b Study
The Phase 1b study of FTX-6058 is an ongoing open label, multi-center dose-ranging study designed to establish proof of concept that an oral Embryonic Ectoderm Development (EED) inhibitor can induce fetal hemoglobin (HbF) in people with sickle cell disease (SCD). The trial will assess the safety, tolerability, pharmacokinetics and pharmacodynamic effects, including HbF protein induction, of up to three doses, starting with a 6 mg once daily dose, to inform dose selection for future development. Each dose cohort will have up to ten subjects (on or off hydroxyurea) who will be treated for up to three months.

About Sickle Cell Disease
Sickle cell disease 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 the formation of abnormal, sickle-shaped red blood cells that can rupture or block blood vessels. People with sickle cell disease typically suffer from serious clinical consequences, which may include 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 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. Fulcrum's proprietary product engine, FulcrumSeek™, identifies drug targets that can modulate gene expression to treat the known root cause of gene mis-expression.

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 of the potential benefits of FTX-6058 and achieving a 5-10% increase in HbF and effects on SCD, the clinical development plan for FTX-6058 and initiation of registrational trial for sickle cell disease, as well as timing for expansion into other hemoglobinopathies, among others. 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.

Contact:
Investors:
Stephanie Ascher
Stern Investor Relations, Inc.
stephanie.ascher@sternir.com
212-362-1200

Media:
Dee Smith
Executive Director, Corporate Communications
dsmith@fulcrumtx.com
202-746-1324