Fulcrum Therapeutics Announces Preclinical Proof-of-Concept Data for FTX-6058 at the Virtual 14th Annual Sickle Cell Disease Research & Educational Symposium and 43rd National Sickle Cell Disease Scientific Meeting

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- Fetal Hemoglobin expression in human cellular models increased up to ~30% by FTX-6058 for the potential treatment of sickle-cell disease

- Company plans to initiate Phase 1 trial in healthy volunteers by year-end

- Non-provisional composition of matter patent application covering FTX-6058 published

CAMBRIDGE, Mass., Sept. 25, 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 preclinical proof-of-concept data supporting the development of FTX-6058 to treat sickle cell disease and beta-thalassemia. FTX-6058, a small molecule designed to increase expression of fetal hemoglobin, demonstrated target engagement and good tolerability in multiple preclinical rodent models with once-a-day oral dosing. The Company presented these data today at the 14th Annual Sickle Cell Disease Research & Educational Symposium and 43rd National Sickle Cell Disease Scientific Meeting being held virtually. Slides from the presentation will be available on Fulcrum's website at ir.fulcrumtx.com/events-and-presentations.

"Despite newly approved therapies for sickle cell disease, a significant unmet need remains," said Martin H. Steinberg, MD, Professor of Medicine at Boston University School of Medicine. "An orally available small molecule therapeutic acting through a novel mechanism to induce increased pancellular HbF should be an important disease-modifying agent."

Fetal Hemoglobin (HbF) is a key modulator of sickle cell disease. Increasing HbF levels has the potential to prevent or reduce disease-related pathophysiology, resulting in reduction of recurring events such as vaso-occlusive crises (VOCs) and hemolysis. In some cases, sickle cell patients with high HbF levels have asymptomatic disease, underscoring the protective effect of HbF. Fulcrum has identified FTX-6058, a highly potent small molecule inhibitor of Embryonic Ectoderm Development (EED) capable of inducing robust HbF protein expression in cell and murine models. Additionally, Fulcrum believes that pharmacokinetics and human dose simulations support FTX-6058 may be given as a once daily oral compound.

The validation of EED as a target for sickle cell disease and the discovery of FTX-6058 as a novel HbF-inducing small molecule were conducted using Fulcrum's Product Engine. Through inhibition of EED, Fulcrum has demonstrated the ability to modulate the activity of the Polycomb Repressive Complex 2 (PRC2), a key regulator of HbF expression, in preclinical studies. Fulcrum validated the role between EED binding/PRC2 modulation and HbF induction utilizing its proprietary CRISPR and chemical probe screening platform. Treatment of human CD34^{+}-derived erythroid cells from healthy and sickle cell disease donors with FTX-6058 resulted in clinically desirable fetal hemoglobin levels (up to ~30% of total hemoglobin), demonstrating a superior globin profile relative to hydroxyurea and other small molecule compounds or mechanisms currently under development. In these preclinical studies, FTX-6058 also induced pancellular distribution of HbF similar to hereditary persistence of fetal hemoglobin.

In vivo preclinical studies showed elevation of HbF at the mRNA and protein levels at plasma concentrations predicted by Fulcrum to be achievable in patients. FTX-6058 treatment led to, elevation of the human HBG1 mRNA and HbF protein in the Townes SCD mouse model. In a head-to-head *in-vivo* preclinical study, FTX-6058 demonstrated superior HbF induction over hydroxyurea in the Townes SCD mouse model.

"We continue to demonstrate important progress with our Product Engine, developing a robust pipeline focused on treatments for rare diseases and areas of significant unmet need," said Owen Wallace, Fulcrum's chief scientific officer. "We are very encouraged by these *in vitro* and *in vivo* findings, as the preclinical data support our novel approach to treating hemoglobinopathies, such as sickle cell disease and beta-thalassemia. In addition to achieving robust fetal hemoglobin levels in cell and murine models, an extensive nonclinical safety package and off-target profile has been established for FTX-6058. We believe FTX-6058 has the potential to offer a durable and transformative therapy for people living with sickle cell disease."

Fulcrum completed a comprehensive IND-enabling package, including preclinical safety studies and up to 28-day Good Laboratory Practices (GLP) toxicology studies, as well as Good Manufacturing Practices (GMP) material scale-up for its planned Phase 1 clinical trial. The Company remains on track to initiate a Phase 1 clinical trial by year-end. In addition, Fulcrum's non-provisional composition of matter patent application covering FTX-6058 and related structures has published.

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 has advanced losmapimod to Phase 3 for the treatment of COVID-19. Fulcrum also anticipates filing an IND in the third quarter with initiation of a clinical trial in the fourth quarter 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 development status of the Company's product candidates, including the timing of initiation of a Phase 1 clinical trial for FTX-6058, and the potential advantages and therapeutic potential of our product candidates. 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.

Contact:

Investors:
Christi Waarich
Director, Investor Relations and
Corporate Communications
cwaarich@fulcrumtx.com
617-651-8664

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

Media:
Kaitlin Gallagher
Berry & Company Public Relations
kgallagher@berrypr.com
212-253-8881