

Fulcrum Therapeutics Announces Positive Interim Results from Phase 1 Healthy Adult Volunteer Trial of FTX-6058 for Sickle Cell Disease

August 10, 2021 at 7:00 AM EDT

- *Achieved dose proportional pharmacodynamic changes in HBG mRNA and F-reticulocytes in whole blood*
 - *Mean 4.5-fold induction in HBG mRNA at 10mg after 14 days of once-daily dosing*
 - *Mean 4.2-fold increase in F-reticulocytes at 10mg after 14 days of once-daily dosing*
- *Achieved maximal target engagement by day seven in 6mg and 10mg cohorts*
- *FTX-6058 was generally well tolerated with no serious adverse events observed to date*
- *Company plans to initiate enrollment in a Phase 1b clinical trial in sickle cell patients in 4Q 2021*
- *Company plans to submit Investigational New Drug (IND) application in non-sickle cell hemoglobinopathies (e.g., beta-thalassemia) by year-end 2021*
- *Company to review clinical results on second quarter earnings call today at 8:00am ET*

CAMBRIDGE, Mass., Aug. 10, 2021 (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 positive interim results from the ongoing single- and multiple-ascending dose (SAD and MAD) Phase 1 trial with FTX-6058 in healthy adult volunteers. FTX-6058 is an investigational, potent, and selective small molecule inhibitor of EED designed to increase the expression of fetal hemoglobin (HbF) with the potential to treat hemoglobinopathies, such as sickle cell disease and beta-thalassemia. Results from the MAD portion of the trial demonstrated proof of biology as evidenced by a dose proportional induction in HBG mRNA and accompanying increases in HbF-containing reticulocytes (F-reticulocytes). At 10mg, the highest dose studied to date, the mean changes were 4.5-fold and 4.2-fold, respectively. The increases in F-reticulocytes indicate that the HBG mRNA increases observed with FTX-6058 treatment are translating to HbF protein production.

Additionally, all FTX-6058 doses in the MAD portion of the trial achieved maximal target engagement as evidenced by decreases in trimethylation at lysine 27 of histone H3 (H3K27me3), a downstream target of the polycomb repressive complex 2 (PRC2). These proof of mechanism results were achieved with once-daily, oral administration of FTX-6058 for 14 consecutive days, which was also generally well-tolerated in all SAD and MAD cohorts completed to date.

"These results with FTX-6058 are very encouraging," said Julie Kanter, MD, co-director, Lifespan Comprehensive Sickle Cell Center at the University of Alabama at Birmingham. "Tremendous unmet need exists for many people with sickle cell disease and the availability of an effective, tolerable, oral, once-daily treatment option could represent a significant advancement."

"We are very pleased with the interim results from this clinical trial of FTX-6058, which demonstrated compelling results across all primary, secondary, and exploratory endpoints included in this study," said Bryan Stuart, Fulcrum's president and chief executive officer. "We are excited to have been able to demonstrate proof of mechanism and proof of biology, as evidenced by maximal target engagement and increases in fetal hemoglobin parameters, including HBG mRNA and F-reticulocytes. These PD effects were further supported by predictable pharmacokinetics and being generally well tolerated."

"Preclinically, we demonstrated consistent 2-3-fold induction of HBG mRNA and HbF protein both in vitro and in vivo," continued Mr. Stuart. "These clinical results reported today not only underscore the consistency observed preclinically, but also demonstrate the first evidence that FTX-6058 can achieve or exceed these preclinical thresholds predicted to provide meaningful clinical benefits to individuals with SCD. We look forward to moving this program forward into a trial in people living with sickle cell disease in the fourth quarter of 2021."

FTX-6058 Phase 1 Healthy Volunteer Trial to Assess Safety, Tolerability, and Pharmacokinetics

The Phase 1 randomized, double-blind, placebo-controlled trial is designed to evaluate the safety, tolerability, and pharmacokinetics of FTX-6058 ([NCT04586985](#)). In the SAD portion of the trial, healthy volunteers have received to date a single oral dose of either placebo or 2, 4, 10, 20, 30 or 40mg of FTX-6058. In the MAD portion of the trial, healthy volunteers have received to date a single oral dose of placebo or 2, 6, or 10 mg of FTX-6058 daily for 14 consecutive days. Safety assessments are performed regularly throughout the trial. The trial is also collecting secondary pharmacokinetic measurements, including bioavailability and half-life assessments. Exploratory measures were included to assess target engagement, HBG mRNA changes and F-reticulocyte changes. Target engagement of FTX-6058 was assessed as a change from baseline in H3K27me3/Total Histone H3 ratio in circulating monocytes. Pharmacodynamic parameters assessed include changes in HBG mRNA and F-reticulocytes. Subjects were seen seven to 10 days after the conclusion of study drug or placebo for a safety follow-up.

Results from the MAD cohorts showed maximal target engagement as evidenced by 70% – 80% reduction in baseline H3K27me3 levels. The 10mg dose showed a mean 4.5-fold induction in HBG mRNA at day 14 and mean 4.2-fold increases in F-reticulocytes at the safety follow-up, indicating increased HbF protein expression. The kinetics observed across the target engagement and pharmacodynamic endpoints are consistent with the process of erythropoiesis in healthy individuals. These results demonstrated a time- and dose-dependent relationship between target engagement, mRNA induction and F-reticulocyte increases.

HBG mRNA Mean Fold Induction for FTX-6058 versus Placebo

	2mg		6mg		10mg	
	Mean Fold Induction	P-value	Mean Fold Induction	P-value	Mean Fold Induction	P-value
Day 7	1.56	0.1873	2.29	0.0179	2.34	0.0157
Day 14	1.67	0.1120	3.28	0.0008	4.50	<0.0001
Safety Follow-up (Day 21-24)	1.44	0.1214	3.25	<0.0001	3.74	<0.0001

F Reticulocyte Mean Fold Increase for FTX-6058 versus Placebo

	2mg		6mg		10mg	
	Mean Fold Increase	P-value	Mean Fold Increase	P-value	Mean Fold Increase	P-value
Day 7	0.78	0.4836	1.56	0.2168	1.27	0.5032
Day 14	0.74	0.4793	1.11	0.8086	1.98	0.1076
Safety Follow-up (Day 21-24)	0.63	0.1253	1.75	0.0320	4.23	<0.0001

There were no serious adverse events reported and no discontinuations. All treatment-emergent adverse events (TEAEs) deemed at least possibly related were mild (Grade 1 or 2) in both the SAD and MAD cohorts. There was one Grade 4 TEAE in the 10mg MAD cohort, which was determined to be unrelated to FTX-6058. No clinically significant changes in safety-related laboratory tests were reported during treatment periods for any of the FTX-6058 dose cohorts included in the analysis.

Fulcrum anticipates presenting additional results from all Phase 1 dose cohorts at an upcoming medical meeting in the fourth quarter of 2021, pending abstract acceptance.

Based on the results reported today, Fulcrum anticipates initiating enrollment in a clinical trial in sickle cell patients in the fourth quarter of 2021. The Phase 1b trial will be an open-label multi-dose trial starting at 6mg once-daily dosing and will include a treatment period of up to three months. This trial could provide the opportunity to demonstrate HbF protein induction in people living with sickle cell disease and will be used to help inform a potential Phase 2/3 trial. These results also support the initiation of a clinical trial in non-SCD hemoglobinopathies (e.g., beta-thalassemia) and Fulcrum plans to submit an IND by year-end 2021.

Conference Call Information

Fulcrum will host a conference call and webcast today at 8:00 am ET to discuss these results and the company's second quarter financial 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: 3291056

Replay Dial-in Number: 855-859-2056
Replay International Dial-in Number: 404-537-3406
Conference ID: 3291056

About FTX-6058

FTX-6058 is a highly potent small molecule inhibitor of Embryonic Ectoderm Development (EED) capable of inducing robust HbF protein expression in cell and murine models. Fulcrum believes the pharmacokinetics and human dose simulations support that 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 proprietary product engine. Preclinical data with FTX-6058 showed an increase in HbF levels up to approximately 30% of total hemoglobin. Fulcrum is conducting a Phase 1 trial with FTX-6058 in healthy adult volunteers.

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, FulcrumSeek, 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). Fulcrum has also advanced FTX-6058, a small molecule designed to increase expression of fetal hemoglobin for the treatment of sickle cell disease and beta-thalassemia into Phase 1 clinical development.

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, the potential advantages and therapeutic potential of the Company's product candidates, initiation and enrollment of clinical trials and availability of clinical trial

data, the timing of planned clinical trials and the Company's ability to submit an IND by year end. 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, FTX-6058 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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