Fulcrum Therapeutics® Announces Additional HBG mRNA Induction from Higher Dose Cohorts in Phase 1 Healthy Adult Volunteer Trial of FTX-6058 for Sickle Cell Disease and New Preclinical Mechanism Data

December 6, 2021 at 7:00 AM EST

Achieved mean 5.6-fold HBG mRNA induction at 20mg and mean 6.2-fold at 30mg after 14 days of once-daily dosing, further supporting potential of FTX-6058 to provide a functional cure

Continues to be well-tolerated at higher doses with no serious adverse events observed to date

New mechanism data demonstrate potent downregulation of BCL11A and MYB, key repressors of fetal hemoglobin

On track to initiate enrollment in Phase 1b clinical trial in people with sickle cell disease and to submit an IND for treatment of other hemoglobinopathies by year-end 2021

Company to review results on conference call, including guest KOL Dr. Gerd Blobel, at 8:00 am ET today

CAMBRIDGE, Mass., Dec. 06, 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 results from the 20mg and 30mg dose cohorts in healthy adult volunteers in its Phase 1 clinical trial of FTX-6058. The company also shared new preclinical mechanism data showing that FTX-6058 downregulated known repressors of fetal hemoglobin (HbF). FTX-6058 is an investigational oral HbF inducer that is being developed for the treatment of sickle cell disease and other hemoglobinopathies, such as beta-thalassemia.

Data from the 20mg and 30mg dose cohorts demonstrated a mean 5.6-fold induction and a mean 6.2-fold induction in HBG mRNA, respectively, at day 14. These increases were higher than those observed in the previously reported 2, 6 and 10mg dose cohorts. In preclinical studies of FTX-6058, increases in HBG mRNA have consistently translated to the same fold increases in HbF protein. Notably, human genetics show that 2-3-fold increases in HbF are associated with significantly improved outcomes, and even functional cures, in people with sickle cell disease. FTX-6058 has now demonstrated greater than a mean 2-fold induction starting with the 6mg dose.

“Despite progress in the treatment of sickle cell disease, existing therapies either offer limited benefit or, in the case of gene therapy, are not amenable to the great majority of patients and carry certain risks,” said Gerd Blobel, MD, PhD, Frank E. Weise III Endowed Chair in Pediatric Hematology at Children’s Hospital of Philadelphia. “The strategy of increasing the levels of fetal hemoglobin is based on solid genetic and clinical data. It can substantially reduce mortality and morbidity, and in cases where HbF reaches greater than 25-35% of total hemoglobin, lead to asymptomatic disease. The emerging clinical data on FTX-6058, combined with the new preclinical data showing that it downregulates *BCL11A* and *MYB*, two validated HbF repressors, is encouraging.”

“The data for FTX-6058 continue to exceed our expectations,” said Bryan Stuart, Fulcrum’s president and chief executive officer. “We believe the fold increases in HBG mRNA that we have now seen at multiple doses, starting at 6mg once-daily, have the potential to translate to levels of HbF protein that could provide a functional cure for people with sickle cell disease. Additionally, with the new insights into the mechanism of action, there's now a clear relationship between FTX-6058 and HbF induction that further affirms our conviction. We remain on track to begin enrolling people with sickle cell disease in our Phase 1b trial by year-end, with an eye toward reporting initial data, including HbF protein levels, in the second quarter of next year.”

FTX-6058 Continues to be Well-Tolerated and Achieved Maximal HBG mRNA Induction at Higher Doses

The Phase 1 randomized, double-blind, placebo-controlled trial was designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of ascending doses of FTX-6058 (NCT04586985). In the single-ascending dose (SAD) cohorts, healthy volunteers received one dose of either placebo or 2, 4, 10, 20, 30, 40 or 60mg of FTX-6058. In the multiple-ascending dose (MAD) cohorts, healthy volunteers received a once-daily dose of placebo or 2, 6, 10, 20 or 30mg of FTX-6058 for 14 consecutive days. Each MAD cohort had six subjects on drug and two on placebo. Food effect was also studied in a separate 20mg dose cohort. Exploratory measures were included in the MAD cohorts to assess target engagement, as well as changes in HBG mRNA and HbF-containing reticulocytes (F-reticulocytes). A 6mg dose cohort in people with sickle cell disease was recently added to this trial to further inform PK and pharmacodynamic modeling for future dose selection. All other cohorts in the trial have been completed, and data from the 2-40mg SAD cohorts and 2-10mg MAD cohorts were reported in August 2021.

Consistent with the earlier reported data, FTX-6058 has been generally well-tolerated with no serious adverse events reported to date and there were no discontinuations due to treatment-emergent adverse events (TEAEs) across all SAD and MAD cohorts. Across all cohorts, all TEAEs deemed possibly related to FTX-6058 were mild (Grade 1 or 2) and resolved. There was one Grade 4 TEAE in the 10mg MAD cohort and one Grade 3 TEAE in the food effect cohort, both of which were determined to be unrelated to FTX-6058. Data continued to show dose-proportional PK, with a mean half-life of approximately 6-7 hours in the MAD cohorts, supporting once-daily dosing, and no food effect was observed with FTX-6058. Data from the MAD cohorts continued to show robust target engagement, as evidenced by an approximately 75-95% reduction from baseline in H3K27me3 after 14 days of treatment.

The data also showed higher-fold induction of HBG mRNA at the higher doses, with FTX-6058 achieving maximal rate of HBG mRNA induction in the 20mg and 30mg cohorts. Maximal HBG induction has not yet been achieved with the higher doses of FTX-6058. Persistent HBG mRNA induction was observed for 7-10 days after treatment. F-reticulocytes also increased by a mean of 1.8-fold in the 20mg cohort and a mean of 2.4-fold in the 30mg cohort as of the safety follow up visit, which was seven to 10 days after conclusion of dosing. Increases in F-reticulocytes of any magnitude are a first indicator that HBG mRNA is translating to HbF protein production, which Fulcrum anticipates observing in the Phase 1b trial that will dose people with sickle cell disease for up to three months.

HBG mRNA Mean Fold Induction for FTX-6058 versus Placebo

2mg*	6mg*	10mg*	20mg	30mg

	Mean Fold Induction	P-value	Mean Fold Induction	P-value	Mean Fold Induction	P-value	Mean Fold Induction	P-value	Mean Fold Induction	P-value
Day 7	1.28	0.3494	1.94	0.0135	2.08	0.0063	2.06	0.0072	2.29	0.0025
Day 14	1.20	0.5122	2.45	0.0025	3.54	<0.0001	5.63	<0.0001	6.15	<0.0001
Safety Follow-up (Day 21-24)	1.21	0.3736	2.75	<0.0001	3.22	<0.0001	6.45	<0.0001	6.13	<0.0001

F-Reticulocyte Mean Fold Increase for FTX-6058 versus Placebo

	2mg*		6mg*		10mg*		20mg		30mg	
	Mean Fold Increase	P-value	Mean Fold Increase	P-value	Mean Fold Increase	P-value	Mean Fold Increase	P-value	Mean Fold Increase	P-value
Day 7	0.53	0.1070	1.02	0.9524	0.83	0.6214	0.71	0.3831	1.50	0.2928
Day 14	0.88	0.6881	1.25	0.4895	2.23	0.0180	1.00	0.9880	1.71	0.1049
Safety Follow-up (Day 21-24)	0.63	0.2167	1.65	0.0943	3.93	<0.0001	1.79	0.0591	2.38	0.0059

* Fold changes from these cohorts were updated to reflect the fold-increase over pooled placebo data across all cohorts from 2-30mg versus previously reported fold changes over pooled placebo data across 2-10mg cohorts.

FTX-6058 Downregulated Expression of HbF Master Regulators BCL11A and MYB

Fulcrum also announced new preclinical data demonstrating that FTX-6058 potently downregulated expression of *BCL11A* and *MYB* in multiple *in vitro* and *in vivo* models, suggesting that FTX-6058 may induce HbF protein production by silencing two validated master regulators of HbF induction. FTX-6058 achieved dose-dependent decreases in *BCL11A* and *MYB* expression. Further, FTX-6058's downregulation of *BCL11A* was correlated with both HBG mRNA induction and HbF induction, with a 2-3-fold increase in HbF when *BCL11A* expression was reduced >50%.

Clinical Development Plans for FTX-6058

Fulcrum is on track to initiate enrollment in the Phase 1b clinical trial of FTX-6058 by the end of 2021, with the aim of establishing early proof of concept in people with sickle cell disease. The open label trial is designed to assess safety, tolerability, PK and PD 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 10 patients who will be treated for up to three months. Fulcrum expects to report initial data from the trial in the second quarter of 2022 and plans to initiate a potentially pivotal Phase 2/3 trial in 2023. Additionally, Fulcrum plans to submit an Investigational New Drug (IND) application with the U.S. Food and Drug Administration by the end of 2021 to support the initiation of a clinical trial of FTX-6058 in additional hemoglobinopathies, including beta-thalassemia. As with sickle cell disease, genetic and clinical data suggest that elevated HbF levels may lead to better outcomes for people with other hemoglobinopathies.

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: 6673629

Replay Dial-in Number: 855-859-2056
Replay International Dial-in Number: 404-537-3406
Conference ID: 6673629

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. The validation of EED as a target for sickle cell disease and the discovery of FTX-6058 as a novel oral HbF-inducing small molecule were conducted using FulcrumSeek™. Fulcrum is developing FTX-6058 for sickle cell disease and other hemoglobinopathies, including beta-thalassemia.

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 and design 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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