UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of report (Date of earliest event reported): December 6, 2021

Fulcrum Therapeutics, Inc.
(Exact Name of Registrant as Specified in Charter)

Delaware	**001-38978**	**47-4839948**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

26 Landsdowne Street **Cambridge, Massachusetts**	**02139**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's telephone number, including area code: (617) 651-8851

Not applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common stock, par value $0.001 per share	**FULC**	**Nasdaq Global Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On December 6, 2021, Fulcrum Therapeutics, Inc. (the "Company") announced additional results from the 20mg and 30mg dose cohorts of the Company's Phase 1 randomized, double-blind, placebo-controlled trial designed to evaluate the safety, tolerability, and pharmacokinetics ("PK") of multiple ascending doses of FTX-6058 in healthy adult volunteers. On December 6, 2021, the Company also disclosed new preclinical mechanism data showing that FTX-6058 downregulated known repressors of fetal hemoglobin ("HbF").

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.

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 30 mg 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 ("PD") modeling for future dose selection. All other cohorts in the trial have been completed.

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 the Company 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

The Company 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 by greater than 50%.

Clinical Development Plans for FTX-6058

The Company 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 6mg 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. The Company expects to report initial data, including HbF protein levels, from the trial in the second quarter of 2022 and plans to initiate a potentially pivotal Phase 2/3 trial in 2023. Additionally, the Company 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.

Forward-Looking Statements

This Current Report on Form 8-K 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 design of planned clinical trials, 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 Current Report on Form 8-K, 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 Current Report on Form 8-K 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.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

FULCRUM THERAPEUTICS, INC.

Date: December 6, 2021

By: /s/ Bryan Stuart
Name: Bryan Stuart
Title: President and Chief Executive Officer