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): June 24, 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 June 24, 2021, Fulcrum Therapeutics, Inc. (the "Company") announced results from ReDUX4, a randomized, double-blind, placebo-controlled multicenter international Phase 2b clinical trial in 80 participants with facioscapulohumeral muscular dystrophy ("FSHD") designed to investigate the efficacy and safety of oral administration of 15 mg of losmapimod twice per day. Losmapimod is a small molecule that the Company is developing for the treatment of FSHD, a rare, progressive and disabling muscle wasting disorder that leads to significant physical impairments and disability. The Company plans to meet with health authorities, including the U.S. Food and Drug Administration, in the second half of 2021 to determine the regulatory path for losmapimod in FSHD.

As a result of the COVID-19 pandemic, the Company announced in May 2020 that the trial had been extended from 24 to 48 weeks to ensure the safety of participants during the pandemic. This extension also enabled the collection of safety and efficacy data, including structural, functional and patient reported data, over a longer time period.

The primary endpoint was the change in DUX4-driven gene expression in affected skeletal muscle over 16 or 36 weeks, which was included as an experimental biomarker. The trial was also designed to capture a wide range of data relating to FSHD progression in addition to safety, target engagement and pharmacokinetic data. The secondary endpoints were evaluation of safety and tolerability in FSHD patients, pharmacokinetics in blood, losmapimod concentration in skeletal muscle biopsies, target engagement in blood and in muscle biopsies, and efficacy based on the whole-body skeletal muscle MRI biomarker. The whole-body MRI scans evaluated changes in muscle fat infiltration, muscle fat fraction and lean muscle volume. The muscles evaluated in the trial were classified as normal appearing (not affected by disease), intermediate (clearly affected by disease but not so severely fat replaced to have lost all function) or end stage (severely fat replaced and have lost most if not all function). The exploratory endpoints included reachable workspace, timed up and go (TUG) test, an optimized timed up and go test for FSHD (FSHD TUG), muscle function measures and patient reported outcomes.

The trial did not meet the primary endpoint. The data from certain of the secondary and exploratory endpoints showed clinically relevant and nominally statistically significant benefits in the losmapimod treated group versus placebo on multiple measures of structural and functional FSHD progression and patient reported outcomes at 48 weeks. In order to provide context for the results observed with respect to the secondary and exploratory endpoints, the Company is presenting p-values for these endpoints to show nominal statistical significance regardless of the specific testing procedure in the statistical analysis plan. These p-values do not take into account any statistical adjustments to account for the fact that the primary endpoint was not met.

Losmapimod was generally well-tolerated in the trial, with no drug-related serious adverse events reported. Over the course of the trial there were three discontinuations, none of which were assessed to be related to losmapimod, and 99% of eligible participants elected to continue in the open label extension trial. The Company will continue to analyze data from each endpoint to determine their viability for future trials.

DUX4-Driven Gene Expression

The primary endpoint, change from baseline in DUX4-driven gene expression in affected skeletal muscle at week 16 or week 36, was not met. Reduction in DUX4-driven gene expression was included as an experimental biomarker endpoint because the Company believed it would correlate with downstream clinical improvements in patients with FSHD.

Losmapimod reduced DUX4-driven gene expression in preclinical *in vivo* and *in vitro* experiments. ReDUX4 was the first interventional clinical trial to test whether changes in intramuscular DUX4-driven gene expression could be assessed in patients with FSHD. FSHD is a highly heterogenous disease, and DUX4 expression in each patient's muscle is heterogeneous and stochastic. In the losmapimod treatment arm, repeat muscle needle biopsies at week 16 or week 36 did not demonstrate a difference in DUX4 activity, including from the prespecified subgroup analyses by DUX4-expressing quartiles. The ability to detect changes in DUX4-driven gene expression was confounded by significant variability across biopsies at baseline and upon repeat biopsy in both the placebo and losmapimod groups. The Company believes the sources of the variability include the stochastic nature of DUX4 expression in which biopsy samples showed a dynamic state of expression (over 1,000-fold variation), the scarcity of DUX4 positive myonuclei (~1/1000), as well as the relative imprecision in the needle biopsy procedure across multiple clinical trial sites. While a reduction in the molecular biomarker of DUX4-driven gene expression was not observed, the Company believes that the benefits observed in the losmapimod treated group on muscle health and function and patient reported improvement were consistent with a reduction of DUX4-driven gene expression.

MRI biomarkers: Muscle Fat Infiltration, Muscle Fat Fraction and Lean Muscle Volume

Losmapimod-treated participants showed decreased progression of muscle fat infiltration (MFI) versus placebo as measured in intermediate muscles, which are the muscles most likely to change ($p=0.01$). Normal-appearing muscles appeared to be preserved in the losmapimod group versus placebo based on a post-hoc analysis.

Muscle fat infiltration is a measure of diffuse fatty infiltration in lean muscle tissue that is correlated with disease severity in FSHD. Participants in the ReDUX4 trial were assessed with a quantitative whole body musculoskeletal magnetic resonance imaging (WB-MSK-MRI) which provides a holistic evaluation of skeletal musculature with the ability to volumetrically measure fat replacement of skeletal muscle in FSHD. Prior clinical trials, not involving losmapimod, have demonstrated that the amount of muscle fat replacement correlates with muscle function in many neuromuscular diseases, including FSHD. Furthermore, changes in fat content are correlated with changes in function. Taken together, ReDUX4 demonstrated that this MRI technology has sufficient sensitivity to detect FSHD progression.

There was no meaningful difference in change in muscle fat fraction or lean muscle volume between the losmapimod and placebo groups in intermediate muscles at 48 weeks. The Company believes that it may observe meaningful differences in these measures with more time.

Reachable Workspace

Losmapimod-treated participants showed a slower rate of decline and improved accessible surface area in reachable workspace (RWS) measures when patients were challenged with 500g weights ($p<0.05$).

RWS provides an objective measure of upper extremity range of motion and function by measuring arm and shoulder mobility with and without weights. Prior studies have shown that RWS correlates with changes in the ability of patients to independently perform activities of daily living. FSHD tends to progress from the upper body down, and loss of shoulder movement leads to loss of mobility. Participants in the losmapimod group showed improvements of up to 1.5% from baseline in the accessible surface area when using a 500g weight on their wrist compared to placebo. Participants in the placebo group were able to access 2 to 4% less total surface area from baseline (with and without 500g weights) measured by RWS after 48 weeks.

Dynamometry

In a post-hoc analysis, dynamometry, which measures muscle strength, demonstrated that participants in the losmapimod group showed non-statistically significant trends of slower progression (less than 4% decline), as well as meaningful improvements (12 to 27%) in the strength of non-dominant shoulder abductors and right ankle dorsiflexors compared to the placebo group, two muscle groups particularly affected in FSHD, compared to placebo. The participants in the placebo group lost about 15% of shoulder and ankle dorsiflexor strength after 48 weeks. The dynamometry data is reported as percent change from baseline rather than the pre-specified plan to report as mean change from baseline in kilograms. The mean change from baseline in kilograms did not show changes.

Timed Up and Go

Losmapimod-treated participants showed a trend in decreased slowing in the TUG test completion time versus placebo ($p=0.30$). Participants in the placebo group showed an increase of approximately three fourths of a second versus an increase of less than one fourth of a second in the losmapimod group. This difference of approximately one half second has been shown to be clinically meaningful in other muscular dystrophy studies not involving losmapimod. The TUG test measures the time that it takes to rise from a chair, walk three meters, turn round, walk back to the chair and sit down.

Patient Global Impression of Change

Participants reported feeling better when treated with losmapimod compared to placebo through the Patient Global Impression of Change (PGIC) assessment (p=0.02).

PGIC, a measure of self-reported change in how a patient feels and functions, showed that participants were able to recognize improvements after 48 weeks of treatment. Four times more losmapimod participants reported improvement at 48 weeks as compared to participants treated with placebo. Importantly, fewer losmapimod participants reported worsening as compared to placebo, and no losmapimod participants reported being “much worse” as compared to more than 13% of placebo participants who reported that their disease had become “much worse” after 48 weeks.

FSHD TUG. Motor Function Measure and FSHD Health Index

Two other exploratory endpoints (FSHD TUG, and FSHD Health Index) did not demonstrate changes from baseline in either group or differences between losmapimod and placebo groups, suggesting that these tests are not sensitive to change over the 48-week time period. Motor function measure also showed no changes in either group or differences between the groups over 48 weeks.

Pharmacokinetics and Target Engagement

Blood concentrations and target engagement in muscle were consistent with previous studies and were within the expected range for clinical efficacy.

Safety and Tolerability

Safety and tolerability data were consistent with previously reported results with no drug-related serious adverse events reported. Losmapimod was generally well-tolerated and the majority of treatment emergent adverse events were deemed unlikely related or not related to study drug by the investigator. There were three serious adverse events (post-op wound infection, alcohol poisoning and a suicide attempt) reported in two participants in the losmapimod group, each was assessed as unrelated to losmapimod. There were no deaths or discontinuations due to adverse events. Losmapimod has now been evaluated in more than 3,600 subjects in clinical trials across multiple indications, including FSHD.

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 planned meetings with regulatory agencies and availability of clinical trial data. 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 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 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 10-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: June 24, 2021

By: /s/ Bryan Stuart

Name: Bryan Stuart
Title: President and Chief Executive Officer