Fulcrum Therapeutics Announces Results from ReDUX4 Trial with Losmapimod in Facioscapulohumeral Muscular Dystrophy (FSHD) Demonstrating Slowed Disease Progression and Improved Function

- *Primary endpoint, change in DUX4-driven gene expression which was included as an experimental biomarker, was not met*
- *Losmapimod showed statistically significant* ($p \leq 0.05$) and clinically relevant benefit across multiple structural, functional and patient reported endpoints*
  - *Decreased Muscle Fat Infiltration*
  - *Improved Reachable Workspace*
  - *Improved Patient Global Impression of Change*
- *Losmapimod was well tolerated with no treatment related discontinuations or treatment related serious adverse events*
- *Positive benefit/risk supports losmapimod's potential to be a transformative therapy for the treatment of FSHD*
- *Fulcrum expects to engage with health authorities, including the FDA, in H2 2021*
- *Fulcrum to host conference call today at 8:00am ET; Full data to be presented at FSHD International Research Congress today at 1:33pm ET*

CAMBRIDGE, Mass., June 24, 2021 – **Fulcrum Therapeutics, Inc.** (Nasdaq: FULC), a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined rare diseases, today announced results from the company's Phase 2b trial, ReDUX4, in people with facioscapulohumeral muscular dystrophy (FSHD). Results being presented with losmapimod at the FSHD International Research Congress today showed clinically relevant and statistically significant* benefits versus placebo on multiple measures of structural and functional FSHD disease progression and patient reported outcomes at 48 weeks. Losmapimod was generally well-tolerated, with no drug-related serious adverse events reported. Consistent with the previously reported interim analyses the primary endpoint was not met. Changes in DUX4-driven gene expression, which were included in the trial as an experimental biomarker endpoint, could not be demonstrated, the Company believes due to several technical and biologic variables with the endpoint. Based on today's results, the Company plans to meet with health authorities, including the U.S. Food and Drug Administration (FDA), in the second half of 2021 to determine the regulatory path for losmapimod in FSHD.

"These results provide strong support that treatment with losmapimod has a meaningful clinical benefit in relevant measures of FSHD disease progression, despite the challenges of measuring DUX4," said Rabi Tawil, MD, ReDUX4 principal investigator and professor of neurology at University of Rochester Medical Center. "I am enthusiastic about the potential for losmapimod to offer meaningful improvements in preserving muscle function and patient quality of life."

"People living with FSHD experience a progressive loss of function," said Fran Sverdrup, Ph.D., FSHD parent and FSHD researcher and associate professor of biochemistry and molecular biology at Saint Louis University. "The ReDUX4 trial with losmapimod is the first trial to demonstrate a positive benefit in several measures of FSHD, including slower disease progression and patient reported improvement over time. I am excited about today's findings and hopeful for the many patients who suffer from this devastating disease."

***Nominally statistically significant means the p-value of a test is ≤ 0.05, calculated without regard to the test procedures in the trial's statistical analysis plan.**

FSHD is a serious, rare, progressive and disabling disease for which there are no approved treatments. FSHD is characterized by muscle degeneration and fat infiltration, initially affecting movement of the face and eventually the arms, trunk and legs. Disease progression results in accumulation of disability, with many patients ultimately becoming dependent upon the use of a wheelchair for daily mobility. Impact on patients includes decreased ability to perform activities of daily living, maintain independence, and lost ability to function or work.

"We are thrilled with the data reported from ReDUX4," said Bryan Stuart, Fulcrum's president and chief executive officer. "These results showing consistent reduction in fat infiltration and correlating benefit on multiple measures with losmapimod represent a major advance for the potential treatment of this devastating disease. Our broader molecular insights confirm the variability in DUX4 expression in skeletal muscle and can play an important role in guiding future research, while our structural and functional results show statistically significant* differences in several novel and established measures of disease progression between losmapimod and placebo at 48 weeks. I would like to thank the patients, caregivers and clinicians who participated in ReDUX4 for their important contributions and dedication."

"These structural, functional, and patient-reported results observed in ReDUX4 are unprecedented in FSHD," continued Mr. Stuart. "In particular, we are pleased by the fact that we observed these results within a 48-week time period. We plan to meet with health authorities, including the FDA, in the second half of the year to determine the regulatory path for losmapimod in FSHD."

About ReDUX4

ReDUX4 was an equally randomized, double-blind, placebo-controlled multicenter international Phase 2b clinical trial in 80 participants with FSHD designed to investigate the efficacy and safety of oral administration of losmapimod 15 mg twice per day. As a result of the COVID-19 pandemic, Fulcrum announced in May 2020 that the trial had been extended from 24 to 48 weeks to ensure the safety of participation during the pandemic. This extension also enabled the collection of safety and efficacy data over a longer time period. Over the course of the trial, there were three discontinuations, none of which were assessed to be related to study drug. Following the completion of the trial, 99% of eligible participants elected to continue in the Open Label Extension trial.

The following data describe key results from the primary, secondary and exploratory endpoints showing clinically relevant and nominally statistically significant benefits versus placebo on multiple measures of structural and functional FSHD disease progression and patient reported outcomes at 48 weeks.

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 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 benefits on muscle health, function and patient benefit observed in the clinical trial were associated with a reduction of DUX4-driven gene expression.

Muscle Fat Infiltration (MFI)

- Losmapimod-treated participants showed decreased progression in the treatment efficacy composite measure of muscle fat infiltration as measured in intermediate muscles, those 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 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 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 relevant disease progression.

Reachable Workspace (RWS)

- Treatment with losmapimod was shown to slow the rate of decline and improve accessible surface area in Reachable Workspace (RWS) measures *($p \leq 0.05$*)*.

RWS is a measure of upper extremity range of motion and function. Prior studies have shown that RWS correlates with changes in the ability of patients to independently perform activities of daily living. Based on published results, reachable workspace is an important measure of disability. The disease 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 (with and without 500g weights) measured by RWS after 48 weeks.

Patient Global Impression of Change (PGIC)

- Participants reported feeling better when treated with losmapimod compared to placebo through the Patient Global Impression of Change 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. More participants in the losmapimod group reported improvement at 48 weeks compared to placebo. Four times more losmapimod participants reported improvement over time 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.”

Additional Secondary and Exploratory Endpoints, Pharmacokinetics and Target Engagement

Additional secondary and exploratory endpoints measuring disease progression and function demonstrated differences between losmapimod and placebo at week 48. 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, as well as meaningful improvements (12-27%) in the strength of bilateral shoulder abductors and ankle dorsiflexors, two muscle groups particularly affected in FSHD, compared to placebo. Functional scales including RWS and TUG showed improvements in limb function consistent with dynamometry results. Two recently designed scales, (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.

There was no difference in muscle fat fraction or lean muscle volume between losmapimod and placebo groups at 48 weeks in intermediate muscles. The Company believes it may observe statistically significant differences in these measures with more time. Additional MRI data will be presented during the IRC meeting. Fulcrum will continue to analyze data from each endpoint to determine their viability for future trials. Blood concentrations and target engagement in muscle were consistent with previous studies and were within the expected range for clinical efficacy.

Overall 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 assessed as unrelated to losmapimod. There were no deaths or discontinuations due to adverse events. Losmapimod has now been evaluated in over 3,600 subjects in clinical trials across multiple indications, including FSHD.

Fulcrum will present detailed results from the ReDUX4 trial during the FSHD International Research Congress today at 1:33pm ET.

Conference Call Information

Fulcrum will host a conference call and webcast today at 8:00 am ET to discuss the ReDUX4 data. 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: 3005948

Replay Dial-in Number: 855-859-2056
Replay International Dial-in Number: 404-537-3406
Conference ID: 3005948

About FSHD
FSHD is a serious, rare, progressive and disabling disease for which there are no approved treatments. FSHD is characterized by muscle degeneration and fat infiltration, initially affecting movement of the face and eventually the arms, trunk and legs. Disease progression results in accumulation of disability, with many patients ultimately becoming dependent upon the use of a wheelchair for daily mobility. Impact on patients includes decreased ability to perform activities of daily living, maintain independence, and lost ability to function or work.

FSHD is caused by mis-expression of DUX4 in skeletal muscle, resulting in the presence of DUX4 proteins that are toxic to muscle tissue. Normally, DUX4-driven gene expression is limited to early embryonic development, after which time the DUX4 gene is silenced. In people with FSHD, the DUX4 gene is turned "on" as a result of a genetic mutation. The result is death of muscle and its replacement by fat, leading to skeletal muscle weakness and progressive disability. There are no approved therapies for FSHD, one of the most common forms of muscular dystrophy, with an estimated patient population of 16,000 to 38,000 in the United States alone.

About Losmapimod
Losmapimod is a selective p38α/β mitogen activated protein kinase (MAPK) inhibitor that was exclusively in-licensed from GSK by Fulcrum Therapeutics following Fulcrum's discovery of the role of p38α/β inhibitors in the reduction of DUX4 expression and an extensive review of known compounds. Utilizing its proprietary product engine, FulcrumSeek, Fulcrum discovered that inhibition of p38α/β reduced expression of the DUX4 gene in muscle cells derived from patients

with FSHD. Although losmapimod has never previously been explored in muscular dystrophies, it has been evaluated in more than 3,600 subjects in clinical trials across multiple other indications, including in several Phase 2 trials and a Phase 3 trial. No safety signals were attributed to losmapimod in any of these trials. Losmapimod has been granted U.S. Food and Drug Administration (FDA) Fast Track designation and Orphan Drug Designation for the treatment of FSHD.

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 planned meetings with regulatory agencies and availability of clinical trial data. 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; 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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