May 28, 2019

Robert J. Gould
President and Chief Executive Officer
Fulcrum Therapeutics, Inc.
26 Landsdowne Street
Cambridge, MA 02139

Re: Fulcrum Therapeutics, Inc.
Draft Registration Statement on Form S-1
Submitted May 1, 2019
CIK No. 0001680581

Dear Dr. Gould:

We have reviewed your draft registration statement and have the following comments. In some of our comments, we may ask you to provide us with information so we may better understand your disclosure.

Please respond to this letter by providing the requested information and either submitting an amended draft registration statement or publicly filing your registration statement on EDGAR. If you do not believe our comments apply to your facts and circumstances or do not believe an amendment is appropriate, please tell us why in your response.

After reviewing the information you provide in response to these comments and your amended draft registration statement or filed registration statement, we may have additional comments.

Draft Registration Statement on Form S-1 filed May 1, 2019

Prospectus Summary
Overview, page 1

1. We refer to your statement in the first paragraph that your proprietary product engine identifies and validates cellular drug targets that can modulate gene expression to treat the known root cause of genetically defined diseases. Please revise this disclosure to avoid the implication that your proprietary product engine has generated successful treatments for genetically defined diseases. Also revise the first sentence to clarify that you are a clinical stage biopharmaceutical company.

2. With reference to your disclosure on page 109, please revise the first paragraph of the Overview to explain that you recently commenced a Phase 1 clinical trial to establish the initial safety and tolerability of losmapimod in patients with FSHD. Also, revise your product pipeline table on page 3 to depict clearly that your Phase 1 trial work is ongoing and to identify the next Phase 1 milestone in the last column.

3. You state in the first full paragraph on page 2 that you believe you may be able to apply for accelerated approval of losmapimod for the treatment of FSHD because of prior safety data from GSK. Please balance your statement by noting that the FDA may not agree with your proposed endpoints for accelerated approval, as you more fully explain on pages 18-19 and 46, and that the FDA may raise questions regarding your planned transition from GSK-manufactured tablets to tablets manufactured by you or another party, and you may be required to conduct comparability assessments,

as you discuss on
page 17.
Our Pipeline, page 3

4. Please revise to remove the "Discovery Screening Indications" graphic from your
Summary presentation. Given that you have neither identified a drug nor a drug target, it
is premature to highlight this "screening" work prominently in your Summary. For
guidance, please refer to the Instruction to Item 503(a) of Regulation S-K.
Risks Associated with Our Business, page 3

5. Please expand the penultimate bullet to explain that the composition of matter patent for
losmapimod that is licensed to you expires in February 2023.
6. Please revise the third bullet point on page 4 to identify the "conditions and events." Also
clarify that your auditors have issued a going concern opinion.
Implications of Being an Emerging Growth Company, page 5

7. Please supplementally provide us with copies of all written communications, as defined
in Rule 405 under the Securities Act, that you, or anyone authorized to do so on your
behalf, present to potential investors in reliance on Section 5(d) of the Securities Act,
whether or not they retain copies of the communications.
Risk Factors
Our ability to use our NOLs and research and development tax credit carryforwards. . ., page 14

8. Please quantify the NOLs and other tax attributes that are subject to limitation and clarify
the factors that will determine the extent of the limitation.

Our internal computer systems, or those of our collaborators. . ., page 58

9. You state that you make extensive use of cloud-based storage systems and that you
experienced a breach of one such system in October 2018. Although you explain that the
breach did not result in permanent loss of data, please expand your disclosure, here or
elsewhere as appropriate, to discuss the magnitude of the incident and its consequences, as
well as remediation steps you have taken.
Our certificate of incorporation that will become effective. . ., page 64

10. We note that your forum selection provision identifies a state court located within the
State of Delaware (or, if the Court of Chancery of the State of Delaware does not have
jurisdiction, the federal district court for the District of Delaware) as the exclusive forum
for certain litigation, including any "derivative action." Please disclose whether this
provision applies to actions arising under the Securities Act or Exchange Act. If so,
please also state that there is uncertainty as to whether a court would enforce such
provision. If the provision applies to Securities Act claims, please also state that
stockholders will not be deemed to have waived the company's compliance with the
federal securities laws and the rules and regulations thereunder. In that regard, we note
that Section 22 of the Securities Act creates concurrent jurisdiction for federal and state
courts over all suits brought to enforce any duty or liability created by the Securities Act
or the rules and regulations thereunder. To the extent the provision does not apply to

claims arising under the Securities Act and the Exchange Act, please ensure the exclusive forum provision in your governing documents states this clearly.

Management's Discussion and Analysis
Critical Accounting Policies and Estimates
Stock-Based Compensation, page 86

11. Once you have an estimated offering price or range, please explain to us how you determined the fair value of the common stock underlying your equity issuances and the reasons for any differences between the recent valuations of your common stock leading up to the IPO and the estimated offering price. This information will help facilitate our review of your accounting for equity issuances including stock compensation and beneficial conversion features.

Business
Our Opportunity, page 94

12. We refer to your statement that you have demonstrated the ability to accurately model human disorders of gene mis-expression in vitro. Please revise to discuss the work that supports this performance claim or tell us where you present this work in the prospectus.

CRISPR Screening, page 97

13. We refer to your statement that you use a "pooled, custom-designed" CRISPR library. Please expand your disclosure to explain what you mean by "pooled."

Prior Clinical Development of Losmapimod by GSK, page 106

14. You disclose that GSK conducted multiple trials, and your tables disclose the number of serious adverse events that occurred in two different trials of losmapimod conducted by GSK. Please revise your disclosure to explain all serious adverse events that occurred.

Preclinical Studies, page 114

15. You state that the graphic on the left on page 116 shows drug target engagement in mouse blood cells after treatment, shown as a percentage of the average vehicle-treated value. Please further explain the graphic, as it appears that the level of target engagement is lower in the drug-treated cells.

Right of Reference and License Agreement with GlaxoSmithKline, page 119

16. Please revise to disclose your royalty range within a ten-percent range (e.g., 5% to 15% or single digit to mid-teens). In addition, please clarify the duration of the royalty term and the term of the agreement by disclosing the expiration dates underlying the patents to the extent not otherwise disclosed.

Intellectual Property, page 120

17. You disclose the projected expiration date for any patents that may issue from pending applications. Please also disclose the expiration date for any owned patent(s). In addition, please expand your disclosure to identify the foreign jurisdictions where you have filed patent applications.

Transactions with Related Persons
Consulting Services Provided by Third Rock Ventures, LLC, page 173

18. Please disclose whether Third Rock will continue to provide you with consulting and management services following the offering.

General

19. Please provide us proofs of all graphics, visual, or photographic information you will provide in the printed prospectus prior to its use, for example in a preliminary prospectus.

Please note that we may have comments regarding this material.

You may contact Mary Mast at 202-551-3613 or Mark Brunhofer at 202-551-3638 if you have questions regarding comments on the financial statements and related matters. Please contact Dorrie Yale at 202-551-8776 or Joe McCann at 202-551-6262 with any other questions.

Sincerely,

Division of Corporation Finance

Office of Healthcare & Insurance