# CLINICAL STUDY PROTOCOL

IND: 138739

EUDRACT: 2019-001181-15

## A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Subjects with Facioscapulohumeral Muscular Dystrophy (FSHD) with Open-Label Extension (OLE)

## PROTOCOL FIS-002-2019

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**Version of Protocol:** Version 5.0

**Date of Protocol:** 17 August 2022

**CONFIDENTIAL**



The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

# SUMMARY OF CHANGES TO THE PROTOCOL

| **Protocol History** | |
|---|---|
| **Version and Date of Protocol** | **Comments** |
| Version 1.0, 27 March 2019 | Original version |
| Version 2.0, 30 July 2019 | • Clarified benefit/risk ratio.<br>• Clarified exclusion criterion #18.<br>• Clarified unblinding procedure in the event of an emergency.<br>• Added instructions for missed doses and study drug compliance details.<br>• Added adverse events of special interest and stopping criteria for abnormal liver tests.<br>• Updated the process for calculating the number of D4Z4 repeats.<br>• Updated language for the analysis of the primary endpoint and secondary endpoints to match the statistical analysis plan.<br>• Clarified collection time points in the schedule of events.<br>• Updated language referencing regulatory authorities.<br>• Clarified that the sponsor has no plans to provide study drug to subjects after study closure or termination. |
| Version 3.0, 27 November 2019 | • Added an open-label extension (OLE) to the protocol. Added language to differentiate the placebo-controlled treatment period part of the study versus the OLE part of the study. Clarified that baseline is prior to the first dose in the placebo-controlled treatment period. |

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| | • Change from baseline in lean muscle tissue volume and fat fraction in facioscapulohumeral muscular dystrophy 1 (FSHD1) subjects, as measured by musculoskeletal (MSK) magnetic resonance imaging (MRI), changed from exploratory objective/endpoint to a secondary objective/endpoint and revised to include muscle fat infiltration (MFI).<br>• Increased the number of randomized subjects from approximately 66 to approximately 76.<br>• Clarified that for scheduled study visits that are split over 2 days, the visits may not be more than 5 business days apart.<br>• Clarified that subjects can travel for MRI or muscle biopsy if needed, but the use of a study-approved MRI scanner should be consistent during the trial.<br>• Clarified in inclusion criterion #3 that "appropriate documentation" is documentation from an accredited laboratory.<br>• Clarified in inclusion criterion #4 that a RICCI score between 2 and 4 does not include subjects that use wheelchairs or walkers for any reason.<br>• Clarified in exclusion criterion #12 that that subjects should not be vaccinated with a live attenuated vaccine throughout the study.<br>• Added clarifications on the identity of investigational product, study drug packaging, study drug accountability, and compliance.<br>• Clarified pregnancy reporting. |

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| | • Removed collection of blood sample for coagulation at the early termination visit and 7-day safety follow up visit.<br>• Clarified that a full physical examination will be performed at the screening visit and the 7-day safety follow up visit and a symptom directed physical examination will be performed at all other visits.<br>• Added additional details for the safety and tolerability endpoint. Revised the secondary and exploratory endpoints to include specific time points.<br>• Clarified that functional workspace is a part of the reachable workspace (RWS) assessment. |
| Version 4.0, 10 April 2020 (COVID-19 Pandemic Emergency Amendment)<br>• This amendment includes permanent changes to the ReDUX4 protocol.<br>• Refer to the ReDUX4 Emergency Guidance document implemented 31 March 2020 for details related to temporary procedures enacted during the COVID-19 pandemic. | • Extended randomized placebo-controlled portion of the study from 24 to 48 weeks due to the COVID-19 pandemic and disruptions to the protocol-defined clinical trial conduct.<br>• Noted that enrollment has been completed.<br>• All Week 24 efficacy assessments moved to Week 48.<br>• Muscle biopsies will be performed at Week 16 or at Week 36 for those subjects.<br>• unable to have the biopsy at Week 16 due to the COVID-19 pandemic.<br>• Removed the one-time biopsy from the open-label extension (OLE) portion of the study.<br>• Added an interim analysis to be performed after a minimum of 22 paired muscle biopsies have been collected.<br>• Removed OLE secondary endpoints evaluating long-term efficacy in subjects originally randomized to losmapimod and in subjects originally randomized to placebo during the placebo-controlled treatment period, to evaluate the efficacy of losmapimod in inhibiting or reducing expression of DUX4, the root cause of FSHD, as measured by a subset of DUX4- |

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| | regulated gene transcripts in skeletal muscle biopsies.<br>• Elevated placebo-controlled treatment period secondary objective and endpoint for evaluation of safety and tolerability of losmapimod in FSHD1 subjects.<br>• Removed measurement of the metabolite, GSK198602. |
| Version 5.0, 16 August 2022 | • Removed study assessments for extension: MSK MRI, exploratory biomarkers, RWS, Timed Up and Go (TUG), dynamometry, Motor Function Measure (MFM), FSHD Health Index (FSHD-HI), and Patients' Global Impression of Change (PGIC).<br>• Removed language specifying that the 15-mg dose of study drug is administered as two 7.5-mg tablets.<br>• Extended study duration for extension.<br>• Changed name of metabolite from GSK198602 to FTX-5508. |

Key changes to the current version of the protocol are summarized below:

| Change and Rationale | Affected Sections |
|---|---|
| • Removed study assessments for extension to reduce participant and site burden given study duration: MSK MRI, exploratory biomarkers, RWS, TUG, dynamometry, MFM, FSHD-HI, and PGIC | Section 6.4, Schedule of Events: Open-Label Extension (Table 3) |
| • Removed study objectives and endpoints for the extension to reflect the removed study assessments | PROTOCOL SYNOPSIS, Section 2.2 |
| • Clarified that extension will continue until 90 days after commercial drug is available post regulatory approval | PROTOCOL SYNOPSIS, Section 3.1.2, Schedule of Events: Open-Label Extension (Table 3) |
| • Changed name of metabolite from GSK198602 to FTX-5508 | Section 1.2, Section 1.3, Section 1.5 |
| • Extended study duration | Schedule of Events: Open-Label Extension (Table 3) |
| • Removed language specifying that the 15-mg dose of study drug is administered as two 7.5-mg tablets to account for a manufacturing change. | PROTOCOL SYNOPSIS, Section 5.2, Section 5.3, Schedule of Events: Open-Label Extension (Table 3) |
| • Added language for justification for dosing change from two 7.5-mg tablets to one 15-mg tablet. | Section 3.2.1 |
| • Typographical and administrative changes were also made to improve the clarity of the document. | Throughout |

# PROTOCOL APPROVAL – SPONSOR SIGNATORY

**Study Title** A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Subjects with Facioscapulohumeral Muscular Dystrophy (FSHD) with Open-Label Extension (OLE)

**Protocol Number** FIS-002-2019, Version 5.0

**Protocol Date** 16 August 2022

Protocol accepted and approved by:

| Name and Title | Signature | Date |
|---|---|---|
| [redacted], PhD<br>Vice President, Biometrics<br>Fulcrum Therapeutics, Inc. | DocuSigned by:<br>[redacted]<br>3A430D4441A640C... | 2022-Aug-16 |
| [redacted], PharmD<br>Senior Clinical Scientist<br>Fulcrum Therapeutics, Inc. | DocuSigned by:<br>[redacted]<br>CF8EC056E512400... | 2022-Aug-16 |
| [redacted], PhD<br>President, Research and Development<br>Fulcrum Therapeutics, Inc. | DocuSigned by:<br>[redacted]<br>E76FC22527DA4E7... | 2022-Aug-17 |

# PROTOCOL APPROVAL – PRINCIPAL INVESTIGATOR

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|---|---|
| **Study Title** | A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Subjects with Facioscapulohumeral Muscular Dystrophy (FSHD) with Open-Label Extension (OLE) |
| **Protocol Number** | FIS-002-2019, Version 5.0 |
| **Protocol Date** | 16 August 2022 |

Protocol accepted and approved by:

**Principal Investigator**

[redacted], MD
[redacted]

DocuSigned by:
[redacted]
C417E0C86414418...

2022-Aug-16

Signature Date

# DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Subjects with Facioscapulohumeral Muscular Dystrophy (FSHD) with Open-Label Extension (OLE)" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 5.0, dated 16 August 2022, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Fulcrum Therapeutics or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Fulcrum Therapeutics.

_____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

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# PROTOCOL SYNOPSIS

| | |
|---|---|
| **Protocol Number:** | FIS-002-2019 |
| **Title:** | A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Subjects with Facioscapulohumeral Muscular Dystrophy (FSHD) with Open-Label Extension (OLE) |
| **Sponsor:** | Fulcrum Therapeutics<br>26 Landsdowne Street<br>Cambridge, MA 02139 USA |
| **Study Phase:** | 2 |
| **Study Sites:** | Up to 25 sites |
| **Indication:** | FSHD |
| **Rationale:** | Treatment of FSHD with losmapimod is predicted to reduce double homeobox 4 (DUX4) in affected skeletal muscle. It is anticipated that the proposed human dose of losmapimod for FSHD at 15 mg orally (PO) twice daily (BID) will provide drug concentrations in skeletal muscles sufficient to significantly inhibit p38α/β, resulting in the reduction of aberrant expression of DUX4.<br>This study will be conducted in 2 parts: a randomized, double-blind placebo-controlled treatment period for 48 weeks, followed by an open-label treatment period with losmapimod. The placebo-controlled treatment period will evaluate the efficacy and safety of losmapimod in treating subjects with FSHD1 over 48 weeks. The open-label extension (OLE) will evaluate the safety and tolerability of long-term dosing with losmapimod in treating subjects with FSHD1.<br>Prior to the COVID-19 pandemic, subjects who reached the Week 24 visit had the option to roll over into the OLE. Subjects that have already rolled over to the OLE prior to the COVID-19 pandemic will remain on open-label treatment. Their next clinic visit will follow the assessments for the Week 36 and Week 48 visit in the placebo-controlled portion of the study in the COVID-19 Pandemic Emergency protocol version 4.0. These subjects will not undergo the Week 36 biopsy. Subjects who did not roll over prior to the COVID-19 pandemic will roll over into the OLE at the Week 48 visit as described in the COVID-19 Pandemic Emergency protocol version 4.0. |

**Objectives:**

**Placebo-Controlled Treatment Period**

**Primary Objective:**

- To evaluate the efficacy of losmapimod in inhibiting or reducing expression of DUX4, the root cause of FSHD, as measured by a subset of DUX4-regulated gene transcripts in skeletal muscle biopsies from FSHD1 subjects

**Secondary Objectives:**

- To evaluate the safety and tolerability of losmapimod in FSHD1 subjects
- To evaluate the change from baseline in muscle fat fraction (MFF), lean muscle volume (LMV), and muscle fat infiltration (MFI) in FSHD1 subjects, as measured by musculoskeletal (MSK) magnetic resonance imaging (MRI)
- To evaluate the plasma concentrations of losmapimod in FSHD1 subjects
- To evaluate the levels of losmapimod in skeletal muscle in FSHD1 subjects
- To evaluate losmapimod target engagement in blood and in skeletal muscle in FSHD1 subjects

**Exploratory Objectives:**

- To evaluate the change from baseline in the following clinical outcome assessments (COAs):
  - Reachable Workspace (RWS) with and without weights
  - Classic and FSHD Timed Up and Go (TUG)
  - Muscle strength by hand-held quantitative dynamometry
  - Motor Function Measure (MFM) Domain 1
  - FSHD Health Index (FSHD-HI)
  - Patients' Global Impression of Change (PGIC)
- To evaluate the change from baseline in inflammatory, immune, apoptotic, and other muscle disease transcripts in muscle biopsy and circulating proteins in plasma and serum

**Open-Label Extension**

**Primary Objective:**

- To evaluate the safety and tolerability of long-term dosing of losmapimod in FSHD1 subjects

**Secondary Objective:**

- To evaluate the plasma concentrations of losmapimod in FSHD1 subjects

**Study Population:** Males and females between 18 and 65 years of age, inclusive, who have a confirmed diagnosis of FSHD1 with 1 to 9 repeats via assessment of the size of the D4Z4 array on chromosome 4; a clinical severity score of 2 to 4 (RICCI score; range 0-5), inclusive, at screening; and an MRI-eligible muscle for biopsy, as determined by a central reader. Enrollment has completed for this study. A total of 80 subjects have been enrolled.

**Study Design:** This study will be conducted in 2 parts: a randomized, double-blind placebo-controlled treatment period for 48 weeks, followed by an open-label treatment period with losmapimod. The placebo-controlled treatment period will evaluate the efficacy and safety of losmapimod in treating subjects with FSHD1 over 48 weeks. The OLE will evaluate the safety and tolerability of long-term dosing with losmapimod in treating subjects with FSHD1.

During the placebo-controlled treatment period, a total of approximately 76 subjects with FSHD1 will be randomized 1:1 to receive 15 mg PO of losmapimod (n=38) or placebo (n=38) tablets BID for 48 weeks. Blood samples for pharmacokinetic (losmapimod concentrations) endpoints will be collected at Day 1, Week 4, Week 16, and Week 36 at the following time points: immediately predose and 4 hours (±30 minutes) after administration of the study dose. Pharmacokinetic samples will also be taken, when feasible, after dosing during the Week 12, Week 24, and Week 48 visits, preferably ≥1 hour after dosing. Blood samples for target engagement will be collected at Day 1 and Week 16 or Week 36, at the following time points: immediately predose and 4 hours (±30 minutes) after administration of the study dose. Serum and plasma samples taken at baseline (Day 1; predose) and at Weeks 4, 12, 16, 24, 36, and 48 (predose or postdose) will be used to aid in the discovery of potential biomarkers of FSHD disease activity and treatment effects.

Musculoskeletal MRIs will be performed at screening, Week 12, and Week 48. Muscle biopsies will be taken at Day 1 and Week 16 or Week 36 if the muscle biopsy could not be performed at Week 16 due to the COVID-19 pandemic. In skeletal muscle, change from baseline in aberrant DUX4 activity, losmapimod concentrations, and target engagement will be evaluated at Day 1 and Week 16 or Week 36. A portion of the muscle biopsies may be used to aid in the discovery of potential biomarkers of FSHD disease activity and treatment effects.

Once subjects reach Week 48, they will have the option to roll over into the OLE, with all subjects receiving 15 mg PO of losmapimod tablets BID. Subjects who wish to roll over into the OLE must complete all procedures from the Week 48 end of placebo-controlled treatment period/start of OLE visit. Prior to the COVID-19 pandemic, subjects who reached the Week 24 visit had the option to roll over into the OLE. Subjects that have already rolled over to the OLE prior to the COVID-19 pandemic will remain on open-label treatment. Their next clinic visits will follow the assessments for the Week 36 and Week 48 visit in the placebo-controlled portion of the study in the COVID-19 Pandemic Emergency protocol version 4.0. These subjects will not undergo the Week 36 biopsy. Subjects who did not roll over prior to the COVID-19 pandemic will roll over into the OLE at the Week 48 visit as described in the COVID-19 Pandemic Emergency protocol version 4.0.

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| | During the OLE, subjects will attend clinic visits approximately every 12 weeks until 90 days after commercial drug is available post regulatory approval or until the study is discontinued by the sponsor.<br>Blood samples for pharmacokinetics (losmapimod concentration) will be collected after dosing at the Week 144 clinic visit, preferably ≥1 hour after dosing.<br>Safety and tolerability will be evaluated throughout the study based on the assessment of adverse events (AEs), AEs of special interest (AESIs), serious adverse events (SAEs), laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations. |
| **Estimated Study Duration:** | Subjects will complete a 4-week screening period followed by a 48-week placebo-controlled treatment period. Subjects who rolled over to the OLE portion of the study prior to the COVID-19 pandemic (under protocol version 3.0) will remain on open-label treatment. These subjects completed a 4-week screening period followed by a 24-week placebo-controlled treatment period. At their next clinic visits, these subjects will follow the assessments for the Week 36 visit followed by the Week 48 visit in the placebo-controlled portion of the study under the COVID-19 Pandemic Emergency protocol version 4.0. During the OLE, subjects will attend clinic visits approximately every 12 weeks until 90 days after commercial drug is available post regulatory approval or until the study is discontinued by the sponsor. All subjects will complete a safety follow-up visit 7 (±3) days after their last dose of study drug. |
| **Efficacy Assessments:** | • Change from baseline in DUX4 activity in affected skeletal muscle, as measured by quantitative reverse transcription polymerase chain reaction in a panel of DUX4-regulated gene transcripts<br>• Change from baseline in MFF, LMV, and MFI, as measured by MSK MRI |
| **Pharmacokinetic and Pharmacodynamic Assessments:** | • Plasma concentrations of losmapimod<br>• Concentrations of losmapimod in skeletal muscle biopsy at steady state<br>• Target engagement parameters in blood and skeletal muscle biopsy |
| **Safety Assessments:** | Adverse events, AESIs, SAEs, laboratory tests, ECGs, vital signs, and physical examinations |

**Other Assessments:**

- Change from baseline in COAs
  - RWS with and without weights
  - Classic and FSHD TUG
  - Muscle strength by hand-held quantitative dynamometry
  - MFM Domain 1
  - FSHD-HI
  - PGIC
- Change from baseline in inflammatory, immune, apoptotic, and other muscle disease transcripts in muscle biopsy and circulating proteins in plasma and serum

**Study Drug, Dosage, and Route of Administration:**

**Placebo-Controlled Treatment Period:**

Losmapimod tablets 15 mg PO BID or matching placebo tablets PO BID for 48 weeks (or 24 weeks if rolled over to the OLE under protocol version 3.0, prior to the COVID-19 pandemic).

**Open-Label Extension:**

Losmapimod tablets 15 mg PO BID until 90 days after commercial drug is available post regulatory approval or until the study is discontinued by the sponsor.

Study drug should be administered with food.

**Sample Size:**

Assuming an effect size of 0.70, a sample size of 68 subjects (34 subjects per group) will be needed to provide 80% power with a 2-sided test at a 0.05 significance level to detect a difference between losmapimod and placebo in change from baseline in DUX4 activity in affected skeletal muscle after 16 or 36 weeks (depending upon when the muscle biopsy was performed) during the placebo-controlled treatment period.

Assuming that approximately 10% of subjects will be non-evaluable, approximately 76 subjects will be randomly assigned at a 1:1 ratio to losmapimod and placebo (38 subjects per group).

**Statistical Methods:**

Continuous variables will be summarized using the mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. All statistical tests will be 2-sided and performed using a 0.05 significance level.

The primary endpoint for the placebo-controlled treatment period will be evaluated using an analysis of covariance (ANCOVA) model to analyze the change from baseline in DUX4 activity in affected skeletal muscle after 16 weeks or 36 weeks of treatment, with repeat number category and treatment group as fixed effects and baseline DUX4 activity in affected skeletal muscle as a covariate. Least-square (LS) mean, standard error, and 95% confidence interval (CI) of the LS mean will be provided for each treatment group. The difference in LS means between treatment groups and 95% CI of the difference will also be calculated. The final p-value will be compared against the significance level of approximately 0.05. All available data will be used.

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| | The full analysis set will be used for the primary analysis in the placebo-controlled treatment period.<br><br>Secondary endpoints will be summarized using descriptive statistics. Continuous endpoints with multiple post-baseline assessments will be analyzed using mixed-effect model for repeated measures methods including repeat number category, treatment group, visit, and treatment-by-visit interaction as fixed effects and baseline value as a covariate; continuous endpoints with a single post-baseline assessment will be analyzed using ANCOVA methods, with repeat number category and treatment group as fixed effects and baseline value as a covariate.<br><br>Secondary endpoints in the OLE will be summarized according to the treatment assigned at randomization. For all subjects, changes in measurements will be calculated relative to measurements obtained at baseline (ie, prior to first dose in the placebo-controlled treatment period).<br><br>Hypothesis testing on key study endpoints will be conducted using the FAS. A sequential testing procedure will be used to control for Type I Error to test the following key study endpoints: DUX4 change from baseline at Week 16 or Week 36; LMV change from baseline at Week 48, and FSHD TUG change from baseline at Week 48.<br><br>Safety data in the placebo-controlled treatment period will be analyzed using the safety analysis set and summarized by treatment group and visit (if applicable) using descriptive statistics. Safety data in the OLE will be analyzed using the open-label analysis set. Treatment-emergent AEs will be summarized by Medical Dictionary for Regulatory Activities system organ class and preferred term; separate summaries will be produced for treatment-related AEs, AESIs, SAEs, and discontinuations due to AEs. Laboratory tests, vital signs, findings from physical examinations, and ECGs will be summarized for changes over time during treatment using descriptive statistics.<br><br>**Interim Analysis**<br><br>One interim analysis (IA) will be performed after a minimum of 22 paired muscle biopsies have been collected. A group sequential method (O'Brien Fleming Spending Function) will be used to ensure an overall significance level of 0.05 (double- sided) due to multiple looks at the DUX4 primary endpoint. |
| **Version and Date of Protocol:** | Version 5.0, 16 August 2022 |

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 3D | 3-dimensional |
| β-hCG | β-human chorionic gonadotropin |
| AE | adverse event |
| AESI | adverse event of special interest |
| ANCOVA | analysis of covariance |
| AUC | area under the plasma concentration-time curve |
| $AUC_{0\text{-}inf}$ | area under the plasma concentration-time curve extrapolated to infinity |
| BCRP | breast cancer resistance protein |
| BID | twice daily |
| BMI | body mass index |
| CI | confidence interval |
| $C_{max}$ | maximum plasma concentration |
| $C_{min}$ | minimum plasma concentration |
| COA | clinical outcome assessment |
| COPD | chronic obstructive pulmonary disease |
| COVID-19 | coronavirus disease 2019 |
| DILI | drug-induced liver injury |
| DUX4 | double homeobox 4 |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| ET | early termination |
| FAS | full analysis set |
| FDA | US Food and Drug Administration |
| FSHD | facioscapulohumeral muscular dystrophy |
| FSHD1 | facioscapulohumeral muscular dystrophy type 1 |
| FSHD2 | facioscapulohumeral muscular dystrophy type 2 |
| FSHD-HI | Facioscapulohumeral Muscular Dystrophy Health Index |
| GCP | Good Clinical Practice |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |

| Abbreviation | Definition |
|---|---|
| HSP27 | heat shock protein 27 |
| IB | investigator's brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | independent ethics committee |
| IRB | institutional review board |
| IRT | Interactive Response Technology |
| LMV | lean muscle volume |
| LS | least-square |
| MAPK | mitogen-activated protein kinase |
| MATE | multidrug and toxin extrusion |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFF | muscle fat fraction |
| MFI | muscle fat infiltration |
| MFM | Motor Function Measure |
| MMRM | mixed-effect model for repeated measures |
| MRI | magnetic resonance imaging |
| MSK | musculoskeletal |
| OAT | organic anion transporter |
| OATP | organic anion transporting polypeptides |
| OCT | organic cation transporter |
| OLE | open-label extension |
| PD | pharmacodynamic(s) |
| PGIC | Patients' Global Impression of Change |
| pHSP27 | phosphorylated heat shock protein 27 |
| PK | pharmacokinetic(s) |
| PO | orally |
| PPS | per-protocol set |
| QRT-PCR | quantitative reverse transcription polymerase chain reaction |
| QTcF | QT interval corrected for heart rate by Fridericia's formula |
| RWS | Reachable Workspace |
| SAE | serious adverse event |
| SAP | statistical analysis plan |

| Abbreviation | Definition |
|---|---|
| SRC | safety review committee |
| STIR | short tau inversion recovery |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| $T_{max}$ | time to maximum plasma concentration |
| TUG | Timed Up and Go |
| ULN | upper limit of normal |

# 1. INTRODUCTION

## 1.1. BACKGROUND

Facioscapulohumeral muscular dystrophy (FSHD) is a rare disabling disease with an estimated worldwide population prevalence of between 1:15,000 and 1:20,000 (Statland and Tawil, 2014), or approximately 16,000 to 21,000 affected individuals in the United States. A higher prevalence rate of 12/100,000 was reported in a population-based study in the Netherlands (Deenen et al, 2014). About two-thirds of cases are familial-inherited in an autosomal dominant fashion, and one-third are sporadic. FSHD is characterized by descending progressive skeletal muscle weakness affecting the face, shoulders, arms, and trunk, followed by weakness of the distal lower extremities and pelvic girdle. Symptoms typically first appear later in the second decade of life but can begin at any age (Tawil et al, 2015). Most cases present with shoulder girdle weakness, which is eventually found in nearly all patients (Padberg, 1982). Muscle biopsies show myopathic or dystrophic changes, including variability in fiber size, rounded fibers, central nuclei, necrotic or regenerating fibers, increased connective tissue, and fatty deposition. Up to one-third of muscle biopsies show a lymphocyte-predominant perivascular inflammatory infiltrate (Statland et al, 2015b). Muscle strength, as measured by quantitative muscle testing, decreases at an average rate of 1% to 4% per year (Statland and Tawil, 2014). The most frequent newly developed functional motor limitations include difficulty getting up from lying down in bed and difficulty using arms for activities of daily living (Statland and Tawil, 2014). The 6-year risk of wheelchair use is 24% (Statland et al, 2015a). All quality of life domains on the 36-Item Short Form Health Survey are significantly impaired, and over half of patients with FSHD report at least mild to moderate pain (Morís et al, 2018; Padua et al, 2009). Asymmetry of muscle involvement is common. Cardiac muscle is spared, and respiratory muscles are involved in a minority of patients.

FSHD is caused by aberrant overexpression of the double homeobox 4 (DUX4) gene, a homeobox transcription factor. DUX4 is located within D4Z4 macrosatellite repeats on chromosome 4q35 and is not normally expressed in adult skeletal muscle when the number of repeats is >10. Approximately 95% of patients with FSHD have type 1 (FSHD1), in which the D4Z4 repeat array is contracted to 1 to 10 units on one allele (Lemmers et al, 2010; Statland and Tawil, 2014). FSHD patients carrying a smaller number of repeats (1 to 3 units) are, on average, more severely affected (Tawil et al, 1996). Loss of these repetitive elements (referred to as contraction) leads to de-repression of the D4Z4 locus and expression of DUX4 (de Greef et al, 2008; Statland and Tawil, 2014). Stable inherited transmission of the repeat is reported within affected families and kindreds, with the most comprehensive analysis conducted on a larger Utah kindred in which the repeat size is the same in multiple, distantly related branches (Flanigan et al, 2001; Lemmers et al, 2004). Patients with FSHD type 2 (FSHD2) have a pathological mutation in a key regulatory protein encoded by the structural maintenance of chromosomes flexible hinge domain 1 (SMCHD1) gene, resulting in reduced methylation of the D4Z4 repeat array and aberrant *DUX4* expression (Lemmers et al, 2012). DUX4 pathological activation in skeletal muscle as a result of the D4Z4 repeat contraction (in FSHD1) or SMCHD1 mutations (in FSHD2) leads to a large, well-characterized transcriptional deregulation cascade (Bosnakovski et

al, 2014; Homma et al, 2015; Jagannathan et al, 2016; Shadle et al, 2017; Yao et al, 2014). DUX4 transcriptional deregulation results in the activation of innumerable pathological cell processes, including inflammatory and immune signaling, oxidative stress, and programmed cell death. The end result of aberrant DUX4 activity is myofiber death with the replacement of skeletal muscle by fat, resulting in a clinical manifestation of progressive loss of strength and accumulation of physical disability.

Compounds that reduce DUX4 and its DUX4-regulated transcripts should provide a robust disease-modifying therapeutic approach for the treatment of FSHD at its root cause.

There are currently no approved disease-modifying treatments for FSHD. Low-intensity aerobic exercise tailored to the patient's distribution of weakness may provide limited beneficial effect (Janssen et al, 2016). Limited range of motion in the shoulder girdle stems from periscapular muscle weakness; in such cases, surgical scapular fixation (scapulodesis) can result in some functional improvement for select patients (Tawil et al, 2015). Very few compounds are currently in clinical development for FSHD, and no therapy has been proven to reduce disease severity or delay the progression of the disease; therefore, there is a high unmet need for an effective therapy for FSHD.

Fulcrum is developing losmapimod, a selective p38α and β kinase small molecule inhibitor that specifically reduces DUX4 in FSHD myotubes, for treatment of FSHD. Extensive exposure and safety data from previous clinical studies with losmapimod provide robust evidence supporting its safety and tolerability, including during chronic dosing, and provide a rationale for the dosing regimen selected. This study will evaluate the efficacy and safety of losmapimod in treating subjects with FSHD1.

## 1.2. NONCLINICAL INFORMATION

In vitro studies, including absorption, distribution, metabolism, and excretion assessments, specifically indicate that losmapimod is a highly selective p38α/β mitogen-activated protein kinase (MAPK) inhibitor with a limited risk of significant interaction with other kinases, transporters, or cytochrome P450 enzymes at pharmacologically relevant concentrations. Further in vitro characterization of the effects of losmapimod in FSHD patient-derived immortalized myotubes showed potent and selective inhibition of the p38α pathway, DUX4 mRNA and protein production, and DUX4-regulated gene expression program as well as profound inhibition of apoptosis and prevention of death of the FSHD myotubes.

In vivo muscle pharmacokinetic (PK)/pharmacodynamic (PD) studies in non-fasted mice and rats demonstrated that a single dose of losmapimod (0.3 mg/kg, orally [PO]) resulted in clinically relevant plasma exposure, significant muscle exposure, and significant p38α/β MAPK pathway inhibition in skeletal muscles. Muscle PK experiments in mice and rats demonstrated that losmapimod rapidly distributes to the target tissue and achieves a muscle:plasma ratio of ≥0.6. The muscle exposures achieved are predicted to result in a >50% reduction in DUX4-dependent targets in FSHD patient skeletal muscle based on the in vitro data obtained using FSHD patient myotubes. The PK/PD analysis additionally indicated that significant p38α/β MAPK pathway

inhibition would be expected in muscle with the proposed clinical dose of 15 mg PO twice daily (BID) (Barbour et al, 2013; Lomas et al, 2012). Losmapimod displayed reasonable oral bioavailability (>30%) in mouse, rat, and cynomolgus monkey and low clearance (<30% hepatic blood flow) in every species tested except dog; these results were supported by in vitro microsomal stability experiments. The half-life following oral administration ranged from 1 to 3.2 hours, depending on the route, dose, and preclinical species.

Metabolism occurs primarily via hydrolysis of the cyclopropylamide group by carboxylesterase-1 to form a pharmacologically inactive primary metabolite, referred to as FTX-5508 (Barbour et al, 2013; Barbour et al, 2015; Ino et al, 2015). The ratio of metabolite to parent is approximately 0.03 to 0.25 in nonclinical species, but it is higher (2-fold) in humans. The major metabolite, FTX-5508, is unlikely to interact with other kinases, transporters, or cytochrome P450 enzymes.

Losmapimod produced no concerning effects either in vitro in human ether-a-go-go related gene assays or in vivo on neurobehavioral function (rats), respiratory function (rats), or cardiovascular function, including electrocardiogram (ECG) and QTc monitoring (monkeys) at multiple exposures and concentrations well above the clinical exposure levels. Data from genotoxicity assessments indicate that losmapimod does not present a genotoxic hazard to humans. The totality of the nonclinical package indicated that there were no findings in chronic toxicology (rodent and non-rodent), safety pharmacology, or genetic toxicity studies that would preclude the oral administration of losmapimod to humans. There were also no concerns in carcinogenicity studies.

## 1.3. CLINICAL PHARMACOLOGY

Elimination of losmapimod is almost exclusively by metabolism, with only 2% of the administered dose recovered as unchanged drug in urine and feces. The principal route of metabolism is via hydrolysis of the cyclopropylamide group to form a pharmacologically inactive metabolite, FTX-5508. The predominant route of elimination of losmapimod, mostly as the FTX-5508 metabolite, is via urine (approximately 65% of the dose), with approximately 29% of the dose eliminated via feces. The absolute oral bioavailability of the tablet formulation is 62%.

Following a single intravenous dose of losmapimod, the steady-state volume of distribution indicated extensive tissue distribution. After single-dose oral administration of 1 to 60 mg losmapimod, the maximum plasma concentration ($C_{max}$) and area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0\text{-}inf}$) of losmapimod increased in an approximately dose-proportional manner for doses up to 20 mg but increased less than proportionally from 20 mg to 60 mg, likely due to saturation of absorption. The terminal half-life was approximately 10 hours for losmapimod and approximately 12 hours for FTX-5508. After single-dose oral administration of losmapimod, exposure (AUC) was approximately 2-fold higher for FTX-5508 than it was for its parent losmapimod. The time to maximum plasma concentration ($T_{max}$) of losmapimod was reached approximately 1 to 4 hours after dose administration, while the $T_{max}$ of FTX-5508 was approximately 3 to 4 hours after dose administration.

Steady-state plasma concentrations of losmapimod were achieved 2 to 3 days after the initiation of repeat dosing. Slight accumulation (up to approximately 30%, on average) for AUC and $C_{max}$ after once or BID dosing was observed. Consistent with single-dose administration, exposure (AUC) was approximately 2-fold higher for the metabolite FTX-5508 than it was for its parent losmapimod. Sex, body weight, and age factors did not result in the need for dose adjustments (Yang et al, 2013). The PK in healthy Japanese subjects are generally similar to those observed in previous studies in healthy non-Japanese subjects with regard to various PK characteristics such as exposure, dose proportionality, and half-life for both losmapimod and the metabolite FTX-5508 (Ino et al, 2015).

A high-fat meal with a dose of 15 mg losmapimod increased the AUC (by approximately 10%) and $C_{max}$ (by approximately 40%) of losmapimod compared to the values observed in the fasted state. $T_{max}$ was delayed, on average, by 1 hour when losmapimod was administered with a high-fat meal. The increase in the exposure measures, ie, AUC and $C_{max}$, and the delay in $T_{max}$ following a high-fat meal compared to the fasted state are not considered clinically significant.

## 1.4. CLINICAL SAFETY

Losmapimod, which is currently in Phase 2 clinical studies for the treatment of FSHD, is a potent p38α/β inhibitor that has been administered to more than 3,600 subjects in GSK and Fulcrum clinical studies, including in a Phase 3 study.

The original developer of losmapimod (GSK) performed extensive testing across at least 10 indications but never in FSHD or other muscle disorders in the clinic. Although development was discontinued due to lack of efficacy in previously tested indications, losmapimod demonstrated a favorable PK, PD, safety, and tolerability profile in more than 3,500 subjects in over 20 studies. Subject data are available from 9 GSK-sponsored completed studies in healthy subjects (4 single dose studies, 3 repeat dose studies and single and repeat dose studies), 1 single dose study in a patient population (rheumatoid arthritis), and 11 completed repeat dose studies in patient populations (including cardiovascular disease, chronic obstructive pulmonary disease [COPD], renal disease, rheumatoid arthritis, major depressive disorder, and neuropathic pain).

From the 9 completed Phase 1 clinical trials in healthy subjects, losmapimod was well tolerated at single doses up to 60 mg and repeat doses up to 10 mg BID for 2 weeks followed by 20 mg daily for 2 weeks. There were no deaths or non-fatal serious adverse events (SAEs) reported during any of these studies. In the 11 completed repeat dose studies in patients, adverse events (AEs) during treatment were typically reported by a similar proportion of patients on losmapimod and placebo (61% [815/1327] and 55% [406/735], respectively). Losmapimod did not consistently result in more AEs leading to permanent discontinuation of study drug or withdrawal from study than placebo.

A thorough QT study (PM1116628) was conducted with losmapimod at 7.5 mg BID or 20 mg daily or with placebo administered for 5 days. At the 20 mg dose of losmapimod, the upper bound of the 90% confidence interval (CI) of the ΔΔQT interval corrected for heart rate by Fridericia's formula (QTcF) (change from baseline in QTcF compared to that for placebo)

exceeded the 10 msec threshold at the 24-hour postdose time point. For the 7.5 mg BID dose, the upper bound of the 90% CI of ΔΔQTcF exceeded the 10 msec threshold at multiple time points. No subjects experienced QTcF values >480 msec or QTcF changes from baseline ≥60 msec at any time in the study. Although the upper bound of the 90% CI exceeded the 10 msec regulatory threshold of concern in the primary PD analysis, GSK stated that there was no clinically relevant effect on the QT interval, as there was no clinically relevant concentration QTc effect using standard placebo/baseline subtracted measured QTc data. Additional information on the QTc interval and its behavior, as demonstrated in the large cohort of patients treated with losmapimod obtained from Study PM1116197, supported the lack of a QT effect. PK/PD modeling using the raw QTcF and plasma concentration data showed that at plasma losmapimod concentrations 4 times the exposure at the therapeutic dose (7.5 mg BID), ie, at exposures approximately 2-fold higher than 15 mg BID, the predicted upper bound of the 90% CI of ΔΔQTcF did not exceed 10 msec and the predicted median ΔΔQTcF was less than 5 msec. Further details are presented in the investigator's brochure (IB).

In summary, review of studies in healthy volunteers and patient populations did not identify differences in the type, frequency, or severity of AEs or SAEs between losmapimod and placebo. No definitive safety signals have been identified.

Further details regarding the nonclinical and clinical data are presented in the IB.

## 1.5. BENEFIT/RISK ASSESSMENT

Losmapimod has been widely tested in various subject populations across at least 10 adult indications, including coronary artery disease, rheumatoid arthritis, and COPD. The majority of these studies lasted 24 weeks, with dosing in one study of up to 52 weeks. The safety data from these studies demonstrate satisfactory safety and tolerability; the severe and/or serious events that have been reported were generally specific to the population under study. Thus, COPD and respiratory events occurred in the studies evaluating subjects with COPD. Similarly, serious cardiac events were observed in those studies that evaluated subjects with coronary artery disease. As these events were generally indication specific, the risk of their occurrence in the FSHD population is considered minimal.

### *Hepatotoxicity*

In clinical trials to date, elevations in transaminases have occurred in few subjects among over 3,500 exposures of losmapimod. These have generally been mild, asymptomatic, and reversible, and the majority were confounded by other medications or clinical conditions. In 11 integrated repeat-dose studies in various patient populations, the frequency of liver events was 0.9% in the losmapimod group (further details are presented in the IB). Preclinical data demonstrate reversible increases in rat liver weight with no clinical chemistry or microscopic correlate. However, hepatotoxicity has been observed after repeat dose administration of some p38 MAPK inhibitors. The mechanism of hepatoxicity for those compounds has not been elucidated and thus applicability to losmapimod is unknown. Exclusion criteria (Section 4.1.2), data collection, and study drug stopping criteria (Section 6.2.1.3) relating to liver tests are well defined.

### *Renal Function*

In clinical studies with losmapimod, a small asymptomatic increase in serum creatinine of 1% to 7% was noted; this increase appeared to attenuate with continued therapy as well as with discontinuation and may be related to inhibition of renal transporters (further details are presented in Section 5.3.2.6.2 of the IB). Individuals with severe renal impairment are excluded from the study (Section 4.1.2). Renal function (Section 6.2.2) and AEs (Section 6.2.1) will be monitored during the trial.

### *Embryo-Fetal Malformations*

Embryo-fetal malformations in rats and rabbits have been observed with losmapimod. Study drug will not be administered to women of childbearing potential unless they are employing adequate contraceptive measures (Section 5.5.1). Pregnancy testing is required before randomization and before dispensation of study drug at all other visits, as specified in the schedule of events (Table 2 and Table 3 ). Study drug will be discontinued if a female participant becomes pregnant during the treatment period. Unexpected pregnancies will be reported with instructions for appropriate follow-up (Section 6.6).

### *Drug-Drug Interactions*

Losmapimod is considered unlikely to have a clinically relevant drug-drug interaction with substrates or inhibitors of cytochrome P450, P-gp, human organic anion transporting polypeptides (OATP) 1B1 and OATP1B3, human organic anion transporter (OAT) 1, or human renal organic cation transporter (OCT) 2. Losmapimod inhibits multidrug and toxin extrusion (MATE) 1 and MATE2-K renal transporters in vitro with a low risk of clinically relevant interaction. Both losmapimod and its major metabolite, FTX-5508, are in vitro inhibitors of human breast cancer resistance protein (BCRP), and FTX-5508 is a relatively potent in vitro inhibitor of OAT3 (further details are presented in the IB). If possible, avoid co-administration of study drug with MATE 1, BCRP, or OAT3 substrates with a narrow therapeutic index. Careful monitoring for adverse effects of these agents is advised if, in the opinion of the investigator, co-administration is warranted (Section 6.2.1). The inhibition of MATE2-K is not considered a clinical drug-drug interaction risk when comparing potency of in vitro transporter inhibition to projected losmapimod $C_{max}$ values at the 15 mg BID dose.

### *Infection/Immunity*

Based on its pharmacology, losmapimod has a modest but broad inhibitory influence on various inflammatory cytokines. Thus, losmapimod may theoretically have an impact on immunity, and be associated with an increased risk of infection. Incidence of infections to date has been similar in losmapimod versus placebo in controlled studies (further details are presented in the IB). Information for all infections identified as SAEs will be collected (Section 6.2.1.2). Subjects who have received attenuated live vaccines within 6 weeks prior to randomization will be excluded (Section 4.1.2).

Given the lack of approved therapy for FSHD and the progressive debilitating nature of the disease, in conjunction with the well characterized current safety profile of losmapimod, the potential benefit of therapy with losmapimod outweighs the potential risks of drug administration.

# 2. STUDY OBJECTIVES

## 2.1. PLACEBO-CONTROLLED TREATMENT PERIOD

### 2.1.1. Primary Objective

The primary objective of the placebo-controlled treatment period is to evaluate the efficacy of losmapimod in inhibiting or reducing expression of DUX4, the root cause of FSHD, as measured by a subset of DUX4-regulated gene transcripts in skeletal muscle biopsies from FSHD1 subjects.

### 2.1.2. Secondary Objectives

The secondary objectives of the placebo-controlled treatment period are as follows:

- To evaluate the safety and tolerability of losmapimod in FSHD1 subjects
- To evaluate the change from baseline in muscle fat fraction (MFF), lean muscle volume (LMV), and muscle fat infiltration (MFI) in FSHD1 subjects, as measured by musculoskeletal (MSK) magnetic resonance imaging (MRI)
- To evaluate the plasma concentrations of losmapimod in FSHD1 subjects
- To evaluate the levels of losmapimod in skeletal muscle in FSHD1 subjects
- To evaluate losmapimod target engagement in blood and in skeletal muscle in FSHD1 subjects

### 2.1.3. Exploratory Objectives

The exploratory objectives of the placebo-controlled treatment period are as follows:

- To evaluate the change from baseline in the following clinical outcome assessments (COAs):
  - Reachable Workspace (RWS) with and without weights
  - Classic and FSHD Timed Up and Go (TUG)
  - Muscle strength by hand-held quantitative dynamometry
  - Motor Function Measure (MFM) Domain 1
  - FSHD Health Index (FSHD-HI)
  - Patients' Global Impression of Change (PGIC)
- To evaluate the change from baseline in inflammatory, immune, apoptotic, and other muscle disease transcripts in muscle biopsy and circulating proteins in plasma and serum

## 2.2. OPEN-LABEL EXTENSION

### 2.2.1. Primary Objective

The primary objective of the open-label extension (OLE) is to evaluate the safety and tolerability of long-term dosing of losmapimod in FSHD1 subjects.

### 2.2.2. Secondary Objective

The secondary objective of the OLE is to evaluate the plasma concentrations of losmapimod in FSHD1 subjects.

# 3. INVESTIGATIONAL PLAN

## 3.1. STUDY DESIGN

This study will be conducted in 2 parts: a randomized, double blind placebo-controlled treatment period for 48 weeks, followed by an open-label treatment period with losmapimod. The placebo-controlled treatment period will evaluate the efficacy and safety of losmapimod in treating subjects with FSHD1 over 48 weeks. The OLE will evaluate the safety and tolerability of long-term dosing with losmapimod in treating subjects with FSHD1.

Prior to the COVID-19 pandemic, subjects who reached the Week 24 visit had the option to roll over into the OLE. Subjects that have already rolled over to the OLE prior to the COVID-19 pandemic will remain on open-label treatment. Their next clinic visits will follow the assessments for the Week 36 and Week 48 visit in the placebo-controlled portion of the study in the COVID-19 Pandemic Emergency protocol version 4.0. These subjects will not undergo the Week 36 biopsy. Subjects who did not roll over prior to the COVID-19 pandemic will roll over into the OLE at the Week 48 visit as described in the COVID-19 Pandemic Emergency protocol version 4.0.

### 3.1.1. Placebo-Controlled Treatment Period

During the placebo-controlled treatment period, a total of approximately 76 subjects with FSHD1 will be randomized 1:1 to receive 15 mg PO of losmapimod (n=38) or placebo (n=38) tablets BID for 48 weeks.

At the time of this protocol amendment (10 April 2020), enrollment was completed. A total of 80 subjects have been enrolled. Twelve subjects had rolled over to the OLE portion of the study at Week 24, prior to the COVID-19 pandemic (under protocol version 3.0). At their next clinic visits, these 12 subjects will follow the assessments for the Week 36 visit followed by the Week 48 visit in the placebo-controlled portion of the study under the COVID-19 Pandemic Emergency protocol version 4.0. These subjects will continue to receive open-label losmapimod during this time.

Subjects will participate in the placebo-controlled treatment period for approximately 53 weeks, including the following:

- a 4-week screening period: Day -28 until Day -1 before the first study drug administration
- a 48-week placebo-controlled treatment period
- for subjects who choose not to roll over into the OLE, a safety follow-up visit 7 days (±3 days) after the last dose of study drug (OLE visits and procedures are described in Section 3.1.2)

The 12 subjects who rolled over to the OLE portion of the study at Week 24, prior to the COVID-19 pandemic (under protocol version 3.0), participated in the placebo-controlled portion of the study for approximately 29 weeks including the following:

- a 4-week screening period: Day -28 until Day -1 before the first study drug administration
- a 24-week placebo-controlled treatment period
- for subjects who chose not to roll over into the OLE, a safety follow-up visit 7 days (±3 days) after the last dose of study drug (OLE visits and procedures are described in Section 3.1.2)

During the placebo-controlled treatment period, subjects will be asked to attend the study clinic at each scheduled visit (Table 2 ). Study drug (losmapimod or placebo) will be administered BID and should be taken with food.

Blood samples for PK (losmapimod concentrations) endpoints will be collected at Day 1, Week 4, Week 16, and Week 36 at the following time points: immediately predose and hours (±30 minutes) after administration of the study dose. Pharmacokinetic samples will also be taken, when feasible, after dosing during the Week 12, Week 24, and Week 48 visits, preferably ≥1 hour after dosing. Blood samples for target engagement will be collected at Day 1, and Week 16 or Week 36, at the following time points: immediately predose and hours (±30 minutes) after administration of the study dose. Serum and plasma samples taken at baseline (Day 1; predose) and at Weeks 4, 12, 16, 24, 36, and 48 (predose or postdose) will be used to aid in the discovery of potential biomarkers of FSHD disease activity and treatment effects.

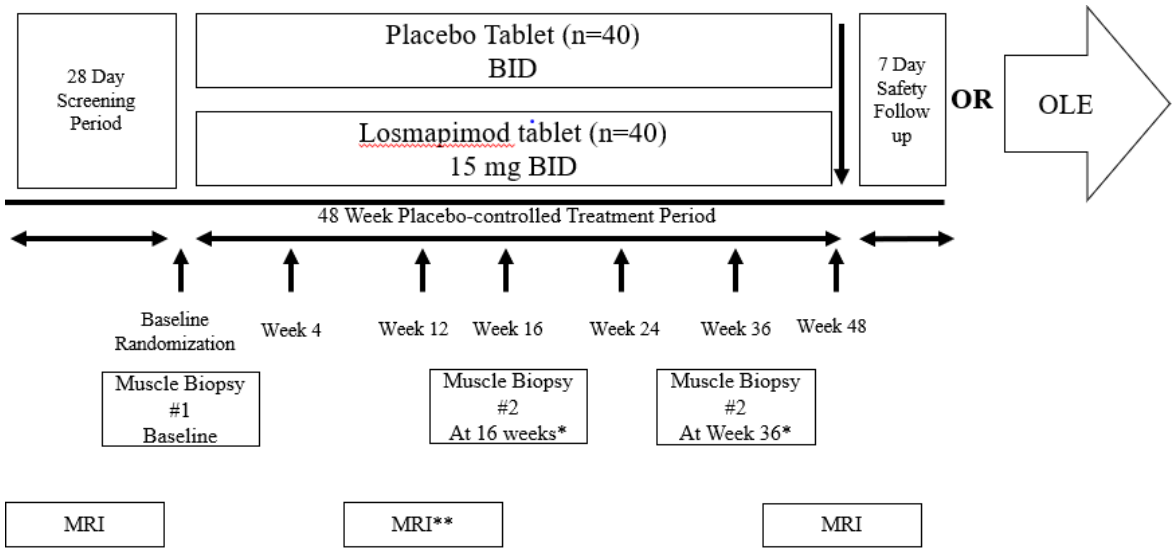
Musculoskeletal MRIs will be performed at screening, Week 12, and Week 48. Muscle biopsies will be taken at Day 1 and Week 16 or Week 36 if the muscle biopsy could not be performed at Week 16 due to the COVID-19 pandemic. In skeletal muscle, change from baseline in aberrant DUX4 activity, losmapimod concentrations, and target engagement will be evaluated at Day 1 and Week 16 or Week 36. A portion of the muscle biopsies may be used to aid in the discovery of potential biomarkers of FSHD disease activity and treatment effects.

Safety and tolerability will be evaluated based on the assessment of AEs, AEs of special interest (AESIs), SAEs, laboratory tests, ECGs, vital signs, and physical examinations.

The full schedule of assessments for the placebo-controlled treatment period is provided in Table 2. Scheduled visits may be split over 2 days if required, with a maximum of business days in between visits. Unscheduled visits may be performed if clinically indicated. Subjects can travel for MRI or muscle biopsy if needed, but the use of a study- approved MRI scanner should be consistent during the trial.

A schematic of the study design is presented in Figure 1.

**Figure 1: Schematic of Study Design for the Placebo-Controlled Treatment Period**




*Muscle biopsy will be performed at Week 16 or at Week 36 if the biopsy could not be performed at Week 16 due to the COVID-19 pandemic
**MRI may not be possible to perform at Week 12 due to the COVID-19 pandemic

Abbreviations: BID, twice daily; MRI, magnetic resonance imaging; OLE, open-label extension.

### 3.1.2. Open-Label Extension

Once subjects reach Week 48, they will have the option to roll over into the OLE, with all subjects receiving 15 mg PO losmapimod tablets BID. Subjects who wish to roll over into the OLE must complete all procedures from the Week 48 end of placebo-controlled treatment period/start of OLE visit (Table 2).

Subjects will remain in the OLE until 90 days after commercial drug is available post regulatory approval or until the study is discontinued by the sponsor. All subjects who complete or discontinue from treatment will complete a safety follow-up visit 7 days (±3 days) after the last dose of study drug.

During the OLE, subjects will attend clinic visits approximately every 12 weeks (Table 3). Study drug (open-label losmapimod) will be administered BID and should be taken with food.

Blood samples for PK (losmapimod concentration) will be collected after dosing at the Week 144 clinic visit, preferably ≥1 hour after dosing.

Safety and tolerability will be evaluated based on the assessment of AEs, AESIs, SAEs, laboratory tests, ECGs, vital signs, and physical examinations.

The full schedule of assessments for the OLE is provided in Table 3. Scheduled visits may be split over 2 days if required, with a maximum of 5 business days in between visits. Unscheduled visits may be performed if clinically indicated.

## 3.2. RATIONALE OF STUDY DESIGN

### 3.2.1. Rationale of Dose Selection

The placebo-controlled treatment period was designed to evaluate the efficacy of losmapimod for treatment of FSHD at its root cause and the safety of losmapimod over placebo in subjects with FSHD1 over 48 weeks. The OLE was designed to evaluate the safety, tolerability, and efficacy of long-term dosing of losmapimod in subjects with FSHD1. Losmapimod is being developed for the treatment of FSHD based on its robust nonclinical efficacy in inhibiting *DUX4* expression and DUX4-regulated downstream gene transcripts and reducing apoptosis across multiple FSHD cell lines at achievable clinical exposures with minimal impact on myotube differentiation. Based on clinical PK/PD studies (Barbour et al, 2013), it is predicted that the proposed human dose of losmapimod for FSHD clinical trials at 15 mg BID would provide drug concentrations in skeletal muscles sufficient to significantly inhibit p38α/β and reduce aberrant expression of DUX4. The planned dose to be tested is 15 mg BID. Prior results indicate the excellent safety and tolerability of losmapimod for chronic administration in the clinic and include the convenience of oral administration.

Heat shock protein 27 (HSP27) is a phosphorylated substrate of p38α/β that has been demonstrated to be a relevant target engagement marker of p38 inhibition. There is a clear relationship between losmapimod plasma concentrations and target engagement for p38α/β MAPK, as measured by phosphorylated HSP27 (pHSP27). Pharmacokinetic/PD modeling indicates that the 15 mg PO BID dose should result in 40% to 70% pHSP27 reduction (Barbour et al, 2013; Cheriyan et al, 2011, and summarized in the IB). Losmapimod PK in humans has been well characterized, including at the exposure levels expected for the planned dose of 15 mg BID in the proposed studies. Pharmacokinetic/PD modeling has demonstrated that the inhibition of pHSP27 is directly related to the plasma concentration of losmapimod and that as the losmapimod concentration changes with time, the resulting change in pHSP27 occurs almost instantaneously (Barbour et al, 2013). Preclinical data show that this change in pHSP27 correlates with a significant reduction in DUX4 levels and transcriptional activity.

Preclinical in vivo PK/PD studies in non-fasted mice and rats demonstrated that the dose levels of losmapimod that achieved clinically relevant plasma exposures also produced significant skeletal muscle exposure and p38α/β MAPK pathway inhibition (further details provided in the IB). The muscle exposures achieved in rodents that are equivalent to the human 15 mg BID exposures in blood are predicted to result in robust target engagement and a >50% reduction in DUX4-dependent targets in FSHD subjects' skeletal muscle based on the in vitro efficacy data in FSHD myotubes.

Although dosing with 7.5 mg losmapimod BID results in target engagement, it may not be robust, especially at the minimum plasma concentration ($C_{min}$). In COPD subjects dosed for 12 weeks, the target engagement inhibition in predose samples was 21%, while the postdose target engagement inhibition was 39% to 44% (GSK study MKI102428). The trough losmapimod plasma concentrations maintained in that study were generally <20 ng/mL. Importantly, that study did not show any loss of target engagement over 12 weeks of dosing.

Pharmacokinetic/PD analyses of rodent (Studies FULTX-00002, FULTX-00004, FULTX-00005, and FULTX-00006) and human (Barbour et al, 2013) data performed by Fulcrum indicated that robust target engagement in muscle should be achieved when plasma losmapimod concentrations are >30 ng/mL; therefore, significant p38α/β MAPK inhibition would be expected in skeletal muscle with the 15 mg PO BID clinical dose. Although increasing concentrations resulted in increases in target engagement in vitro (Study FULTX-00008), there is no evidence that increasing the dose above 15 mg PO BID will result in significantly greater target engagement. Therefore, clinical dosing beyond 15 mg BID with the current formulation is not warranted (further details are provided in the IB).

Food was found to increase the oral absorption of losmapimod for tablet formulations of the drug. An analysis of $AUC_{0\text{-}inf}$ and $C_{max}$ showed statistically higher systemic exposure in the fed state than in the fasted state. Administration of losmapimod in this study should be performed under fed conditions to reduce the potential for PK variability.

Fulcrum anticipates that a 15 mg BID dosing regimen, as proposed under fed conditions for the planned phase 2 studies in FSHD, will result in mean steady-state $C_{min}$ and $C_{max}$ values of approximately 30 ng/mL and 75 ng/mL, respectively; the corresponding values for a 7.5 mg PO BID dosing regimen are 16 ng/mL and 38 ng/mL, respectively. Thus, the 15 mg BID regimen is expected to maintain steady-state losmapimod plasma concentrations above the optimal level of 30 ng/mL needed for robust target engagement, while the 7.5 mg PO BID dose would fall below that at predose levels. Importantly, at the proposed dose level of 15 mg PO BID, exposures in FSHD subjects are not expected to exceed those previously demonstrated to be safe in humans in multiple previous studies by GSK in healthy volunteers and various patient populations (Barbour et al, 2013; Cheriyan et al, 2011; Pascoe et al, 2017; Watz et al, 2014).

In Study 1821-CLP-101, similar relative bioavailability (AUC) was demonstrated between one 15-mg losmapimod tablet versus two 7.5-mg losmapimod tablets. Peak exposure ($C_{max}$) of losmapimod was reduced by 20% with one 15-mg tablet, although this did not have an impact on target engagement, which was consistent with prior Fulcrum studies.

### 3.2.2. Rationale of Study Design

The placebo-controlled treatment period is a randomized design that includes an active treatment group and a placebo group (Section 3.1). The inclusion of a placebo group is necessary because there is no available standard of care. The use of a placebo group will ensure that any potential for bias is minimized. Additionally, the use of matching placebo tablets to the losmapimod tablets will help maintain blinding of the participants to study treatment. The OLE will evaluate the safety, tolerability, and efficacy of long-term dosing of losmapimod in subjects with FSHD1.

Efficacy of the reduction in the expression of DUX4-regulated gene transcripts endpoints will be assessed with skeletal muscle needle biopsies from lower extremity muscles that meet the criteria for biopsy, are safely accessible, and that have been identified as sites of active disease by MRI. Physicians experienced in skeletal muscle needle biopsy will perform the procedure. In general, these muscle needle biopsies take a short time and are well tolerated, including when done

repeatedly. In one large series, no complications were reported in 400 consecutive skeletal muscle needle biopsies. Superficial infection or hematomas are rare (<1%; Edwards et al, 1983).

Misregulated expression of DUX4 and its downstream transcripts is toxic to muscle and leads to muscle atrophy and death and replacement by fat (Bosnakovski et al, 2014; Vanderplanck et al, 2011; Jones and Jones, 2018). The correlation between MRI characteristics, muscle pathology, and expression of DUX4-regulated transcripts was established and showed that the presence of an elevated MRI short tau inversion recovery (STIR) signal has substantial predictive value in identifying muscles with active disease and DUX4 target gene expression (Wang et al, 2019).

DUX4 protein and mRNA are present at very low levels in FSHD skeletal muscle (Geng et al, 2012; Jones et al, 2012). In contrast, DUX4-regulated transcripts are abundant and stably expressed. They represent the relevant functional readout of DUX4 protein levels and activity. These transcripts are readily measured in skeletal muscle biopsies (Geng et al, 2012; Tasca et al, 2012; Yao et al, 2014; Jagannathan et al, 2016; Whiddon et al, 2017; Chen et al, 2016; Wang et al, 2019). As DUX4-regulated transcripts in skeletal muscle are uniquely and inextricably tied to the expression and function of DUX4, a subset of transcripts will be measured in skeletal muscle biopsies by quantitative reverse transcription polymerase chain reaction (QRT-PCR) as the primary efficacy endpoint to assess treatment effects on aberrant DUX4 activity.

Standardized MRI protocols for imaging of muscle health and disease in neuromuscular disorders, including the measurement of skeletal muscle tissue replacement by fat using the Dixon technique (Dixon 1984), have been recommended as a result of 2 consortia organized by the TREAT-NMD network (Hollingsworth et al, 2012). The MRI technique to be used in this protocol is a standardized, objective, quantitative technique with automatic skeletal muscle segmentation for the 3-dimensional (3D) muscle volumes and fat fraction analyses via robust algorithms using Dixon imaging to measure the extent of skeletal muscle tissue replacement by fat in FSHD patients. Reliable and feasible whole-body MRI acquisition protocols and analysis algorithms are readily available for multicenter clinical studies focused on abdominal and liver fat.

It is anticipated that changes in MRI and clinical assessments will take longer to detect than changes in *DUX4* expression on skeletal muscle biopsy. Evaluation of changes in MRI and clinical assessments throughout the study will inform whether treatment with losmapimod could slow disease progression by protecting and/or restoring skeletal muscle function.

Under FIS-002-2019 protocol version 3.0, the randomized, double-blinded, placebo-controlled portion of the study was scheduled to end at Week 24 with all primary endpoint visits completed by week 16. The COVID-19 pandemic has had a significant impact on the conduct of this clinical trial leading to many missing Week 16 and Week 24 visits and preventing the rolling over to the long-term OLE part of the study. Research site closures and individual study subjects have already missed visits and Fulcrum anticipates that many others will be missed unless rapid corrective actions are implemented. In addition, the necessary pandemic restrictions limit the assessment of long-term safety in the FSHD1 population in the clinic, as well as collection of critically important efficacy data on Week 24 on clinical outcome assessments and MRIs.

Further, the investigational drug delivery that currently takes place during the clinic visits is also now compromised, resulting in the potential for treatment gaps unless home delivery is rapidly enabled.

Protocol version 4.0 (COVID-19 Pandemic Emergency Amendment), which follows the implementation of the ReDUX4 Emergency Guidance Document (31 March 2020), will ensure an adequate assessment of long-term safety of losmapimod compared to placebo, allows subjects to continue on the study with minimal treatment disruption, while preserving the opportunity to participate in an OLE. The amendment additionally enables assessment of the efficacy of losmapimod to treat the underlying cause of FSHD by extending the randomized, double-blinded, placebo-controlled portion of the study from 24 to 48 weeks when sites impacted by COVID-19 will likely be up and running again. Collection of critical data impacted by COVID-19 has been included in additional visits, including muscle biopsy (primary endpoint) and target engagement at Week 36 for subjects who missed the Week 16 visit, and clinical outcome assessments and MRIs at Week 48 for subjects who missed the Week 24 visit. The increase in the duration of the randomized, double-blinded, placebo- controlled portion of the study poses no additional risk to subjects and maintains the ability to safely obtain muscle biopsies in the clinic while monitoring safety parameters at home. It also allows for rolling over to the long-term OLE at the Week 48 visit for those who could not do it at Week 24. The amendment continues to provide subjects with the potential for benefit and the relation of the anticipated benefit to the risk is at least as favorable as that provided by alternatives as there are no approved treatments that can slow, stop, or reverse the effects of FHSD. Additionally, the planned interim analysis will provide an early assessment of the potential treatment effect of losmapimod to treat the underlying cause of FSHD providing timely data to inform future development.

# 4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

## 4.1. SELECTION OF STUDY POPULATION

During the placebo-controlled treatment period, approximately 76 subjects with FSHD1 will be randomized at up to 25 sites. Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria. (Note: Enrollment has completed for this study. A total of 80 subjects have been enrolled.)

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

### 4.1.1. Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Capable of understanding the written informed consent, and providing signed, dated, and witnessed written informed consent.
2. Male or female subjects between the ages of 18 and 65 years, inclusive.
3. Confirmed diagnosis of FSHD1 with 1 to 9 repeats via assessment of the size of the D4Z4 array on chromosome 4. Randomization will be stratified to ensure that treatment allocation is balanced across FSHD repeat number categories (ie, 1 to 3 repeats versus 4 to 9 repeats). Genetic confirmation must be obtained before the subject is randomized and before the baseline muscle biopsy is performed; genetic confirmation can come from previous testing if verified with appropriate documentation from an accredited laboratory. Due to stable transmission of repeat sizes within families, subjects with a clinical diagnosis of FSHD who have a first-degree relative with a genetically confirmed diagnosis of FSHD1 may be entered into the study for screening assessments, including MRI. During screening, a confirmatory genetic diagnosis is conducted. If genetic testing during screening is necessary, the 4-week screening window will not start until the results are obtained and verified by the principal investigator.
4. Clinical severity score of 2 to 4 (RICCI score; range 0-5), inclusive, at screening. Subjects who use a wheelchair or walker for any activity are not permitted to enroll in the study.
5. Has an MRI-eligible muscle for biopsy, as determined by a central reader.
6. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
7. Willing to practice an approved method of birth control:
    - A female subject is eligible to participate if she is of non-child-bearing potential, defined as premenopausal females with permanent sterilization (includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female

subject of any age); or postmenopausal, defined as 12 months of spontaneous amenorrhea; or, if of child-bearing potential, if she is using a highly effective method for avoidance of pregnancy (defined in Section 5.5.1) and will continue to use these methods for the duration of the study and until 90 days after the last dose of study drug. The decision to include or exclude women of child-bearing potential may be made at the discretion of the investigator and in accordance with local practice in relation to adequate contraception.

- Male subjects must agree to use one of the contraception methods listed in Section 5.5.1. This criterion must be followed for the duration of the study and until 90 days after the last dose of study drug.

### 4.1.2. Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Has a history of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject. This may include, but is not limited to, a history of relevant drug or food allergies; history of cardiovascular or central nervous system disease; neuromuscular diseases except FSHD (eg, myopathy, neuropathy, neuromuscular junction disorders); or clinically significant history of mental disease.
2. Previously diagnosed cancer that has not been in complete remission for at least 5 years. Localized carcinomas of the skin and carcinoma in situ of the cervix that have been resected or ablated for cure are not exclusionary.
3. For subjects who are on drug(s) or supplements that may affect muscle function, as determined by the treating physician, or that are included in the list of drugs presented in Appendix 13.2: subjects must be on a stable dose of that drug(s) or supplement for at least 3 months prior to the first dose of study drug and remain on that stable dose for the duration of the study. Changes to the dose or treatment discontinuation during the study can only be done for strict medical reasons by the treating physician with clear documentation and notification to the sponsor.
4. History of febrile illness within 5 days before randomization. Subjects who were healthy during screening but develop febrile illness in the 5 days before randomization need to have the baseline visit postponed until the febrile illness is fully resolved. Once the febrile illness is fully resolved, the subject's baseline visit can be scheduled. The duration of the screening visit in such cases can be extended for up to 35 days.
5. Known active tuberculosis, active opportunistic, or life-threatening infections.
6. Acute or chronic history of liver disease or known to have current alanine aminotransferase ≥2 × upper limit of normal (ULN) or total bilirubin >1.5 × ULN, or known history of hepatitis B or C.
7. Known severe renal impairment (defined as a glomerular filtration rate of <30 mL/min/1.73m$^2$).
8. Positive screen for hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV) antibody, or antibodies against human immunodeficiency virus (HIV)-1 and -2.

9. Standard 12-lead ECG demonstrating QTcF >450 msec for male subjects or QTcF >470 msec for female subjects at screening. If QTcF exceeds 450 msec for males or 470 msec for females, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the subject's eligibility.
10. History of cardiac dysrhythmias requiring anti-arrhythmia treatment(s) or history or evidence of abnormal ECGs that, in the opinion of the investigator or medical monitor, would preclude the subject's participation in the study.
11. Blood donation (of approximately 1 pint [500 mL] or more) or any significant loss of blood within 90 days before the first dose of study drug, as determined by the investigator.
12. Vaccination with a live attenuated vaccine within 6 weeks of randomization and throughout the study.
13. Use of any anticoagulants for at least 1 month and anti-platelet agents for at least 1 week before the baseline biopsy, as they increase the risk of hematomas following skeletal muscle biopsy.
14. Male subjects with a female partner who is planning to become pregnant during the study or within 90 days after the last dose of study drug.
15. Positive pregnancy test or is known to be pregnant or lactating. All female subjects of child-bearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and a negative urine pregnancy test prior to randomization.
16. Alcohol, analgesic/opioid, and/or illicit drug abuse, as defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013), in the last 6 months before screening or a positive test for drugs of abuse at screening.
17. Any current mental condition (psychiatric disorder, senility, or dementia) that, in the opinion of the investigator, may affect study compliance or prevent understanding of the aims, investigational procedures, or possible consequences of the study.
18. Use of another investigational product within 30 days or 5 half-lives (whichever is longer), or according to local regulations, or currently participating in a prospective study with an investigational product, whether it concerns an experimental drug or a medical device. Note: concurrent participation in natural history studies (non-drug, non-device studies) may be acceptable if confirmed in writing by the sponsor.
19. Anticipated inability to comply with any study procedures, including participation in study visits according to the visit schedule.
20. Abnormal laboratory results indicative of any significant medical disease that, in the opinion of the investigator, would preclude the subject's participation in the study.
21. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.
22. Contraindication to needle biopsy.

23. Contraindication to MRI as per clinic standard practice.

## 4.2. WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT AND/OR THE STUDY

The duration of the placebo-controlled treatment period is defined for each subject as the time between the date the written informed consent was signed through 1) the completion of the Week 48 visit if the subject is rolling over into the OLE or 2) the completion of the safety follow-up visit after the end of treatment if the subject is not rolling over into the OLE. The duration of the OLE is defined for each subject as the time after completion of the Week 48 visit through completion of the safety follow-up visit after the end of treatment or discontinuation of the study.

### 4.2.1. Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study, including if a subject decides to prematurely discontinue study treatment. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. The subject does not meet the protocol inclusion or exclusion criteria.
2. The subject is noncompliant with the protocol.
3. The subject has a serious or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study.
4. The subject has laboratory safety results that reveal clinically significant hematological or biochemical changes from the baseline values.
5. The subject has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.
6. The subject is lost to follow-up.
7. Other reasons (eg, pregnancy, development of contraindications of use of study drug).
8. The subject withdraws consent, or the investigator or sponsor decides to discontinue the subject's participation in the study.

The investigator will also withdraw a subject if Fulcrum Therapeutics terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event must continue to be followed to satisfactory resolution as described in Section 6.2.1.10. Any subject may withdraw his or her consent at any time.

### 4.2.2. Handling of Withdrawals

Subjects are free to withdraw from the study or study treatment at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Subjects who discontinue study treatment or active participation in the study will no longer receive study drug. When a subject withdraws from the study treatment or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF).

If a subject prematurely discontinues study treatment, they will be encouraged to remain in the study and continue with all other aspects of the study.

If a subject decides to prematurely discontinue study treatment and not continue with all other aspects of the study, they will be considered to have withdrawn from the study. If a subject withdraws from the study, they will be asked to complete the early termination (ET) visit as soon as possible after the decision to terminate study participation and to complete the safety follow-up visit 7 (±3) days after their last dose of study drug. If the ET visit will be scheduled more than 7 days after the last dose of study drug, the safety follow-up and ET visits may be combined, with no duplication of assessments required.

Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. In the case of subjects being lost to follow-up, at least 3 documented attempts to contact the subject must be made.

It is vital to obtain follow-up data on any subject withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

### 4.2.3. Replacements

Subjects who withdraw or discontinue will not be replaced.

# 5. STUDY TREATMENTS

## 5.1. METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

During the placebo-controlled treatment period, subjects will be randomly assigned at the baseline visit (Day 1) to receive losmapimod (active drug) or placebo using a 1:1 allocation ratio. Randomization will be stratified to ensure that treatment allocation is balanced across FSHD repeat number categories (ie, 1 to 3 repeats versus 4 to 9 repeats).

An Interactive Response Technology (IRT) system will be used to administer the randomization schedule. A designated unblinded statistician separate from the study team will generate the randomization schedule using SAS software Version 9.3 or later (SAS Institute, Cary, NC) for IRT, which will link sequential subject randomization numbers to treatment codes. The randomization will use an appropriate block size, which will not be revealed.

Subjects can be randomized only once.

During the OLE, all subjects will receive open-label losmapimod.

## 5.2. TREATMENTS ADMINISTERED

Study drug tablets in the placebo-controlled treatment period (losmapimod or placebo) and the OLE (losmapimod) will be dispensed to subjects at the visits detailed in Table 2 and Table 3, respectively. Subjects may be provided additional study drug via a courier service, as applicable.

During the placebo-controlled treatment period, subjects will receive 15 mg losmapimod BID or placebo BID. In the OLE, subjects will receive 15 mg losmapimod BID.

For subjects who rolled over to the OLE under protocol version 3.0, prior to the COVID-19 pandemic, during the 24-week placebo-controlled treatment period these subjects received 15 mg losmapimod BID or placebo BID. These subjects will continue on open-label treatment with 15 mg losmapimod BID. At their next clinic visits, these specific subjects will follow the assessments for the Week 36 visit followed by the Week 48 visit in the placebo-controlled portion of the study under the COVID-19 Pandemic Emergency protocol version 4.0.

Study drug (losmapimod or placebo) should be taken with food.

If a subject misses a dose and it is more than 6 hours until the next planned dose, the subject will be instructed to take the missed dose and resume study drug dosing as normal. If it is less than 6 hours until the next planned dose, the subject will be instructed to skip the missed dose and then resume study drug dosing as normal.

## 5.3. IDENTITY OF INVESTIGATIONAL PRODUCT

Losmapimod tablets for oral administration are available as white, round, biconvex, plain, film-coated tablets containing losmapimod as the micronized freebase. Losmapimod tablets also contain the inactive excipients microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, and povidone K29/32, and the Opadry White OY-S-28876 film coat contains hypromellulose, titanium dioxide (E171), and polyethylene glycol.

Placebo tablets are identical in appearance to losmapimod and are manufactured using commonly used and recognized tablet excipients that are also employed in the active tablets.

The sponsor will ensure that the study site is provided with adequate supplies of blinded losmapimod and placebo (placebo-controlled treatment period) or open-label losmapimod (OLE) and that no expired tablets will be dispensed to study subjects.

## 5.4. MANAGEMENT OF CLINICAL SUPPLIES

### 5.4.1. Study Drug Packaging and Storage

All tablets are packed in white high-density polyethylene bottles with a child-resistant closure and include an induction-sealed liner.

During the placebo-controlled treatment period, each dispensation will contain a blinded dosage for 1 subject with a sufficient quantity to cover until the next scheduled visit plus additional tablets to cover the visit window. If needed, subjects may be provided additional study drug via a courier service, as applicable. Study drug will be packaged and labelled in accordance with regulatory requirements and in a manner to retain the study blind.

During the OLE, subjects will be supplied with a sufficient quantity of losmapimod to last until the next scheduled visit plus additional tablets to cover the visit window or will be provided additional study drug via a courier, as applicable. Open-label losmapimod will be packaged and labelled in accordance with regulatory requirements.

Further details of study drug packaging, labeling, and distribution of the study medication will be provided in the study reference manual.

Study drug must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at a controlled room temperature not to exceed 30°C.

### 5.4.2. Study Drug Accountability

During the study, each subject will be provided a sufficient quantity of study drug to allow for dosing until their next scheduled visit plus additional tablets to cover the visit window. If needed, subjects may be provided additional study drug via a courier service, as applicable. At the next scheduled clinic visit, subjects must return their bottles for accountability.

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

### 5.4.3. Medication Errors and Overdose

No specific antidote for losmapimod is known. In case of overdose or medication errors, subjects should be observed and be provided with a supportive standard of care.

## 5.5. LIFESTYLE RESTRICTIONS

Any nutrients known to modulate cytochrome P450 enzyme activity (eg, grapefruit- or Seville orange-containing products or quinine containing drinks [tonic water or bitter lemon]) should be avoided 3 days before the first dose of study drug until after the last dose of study drug.

Strenuous physical activity (eg, heavy lifting, weight or fitness training) should be avoided for 48 hours prior to each study visit. Routine ambulatory and other activities (eg, walking at normal pace) will be permitted, with the level of activities kept as similar as possible on all days of the study. This is especially important on the day of the muscle biopsies and the days before it.

For the screening visit, subjects will be required to fast for at least 4 hours prior to laboratory blood samples being taken. For some study visits, if possible, subjects will be asked to take the morning medication in the clinic to enable blood sampling before and at specific times after taking the study drug.

### 5.5.1. Contraception Requirements

Subjects of child-bearing potential must be willing to practice an approved method of birth control for the duration of the study and until 90 days after the last dose of study drug.

A female subject is eligible to participate if she is of non-child-bearing potential, defined as premenopausal females with permanent sterilization (includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age); or postmenopausal, defined as 12 months of spontaneous amenorrhea; or, if of child-bearing potential, if she is using a highly effective method for avoidance of pregnancy and will continue to use these methods for the duration of the study and until 90 days after the last dose of study drug.

Male subjects must agree to use one of the contraception methods listed below for the duration of the study and until 90 days after the last dose of study drug.

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy in females of child-bearing potential (ie, the methods have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label) (Hatcher et al, 2007):

- Complete abstinence from penile-vaginal intercourse when this is the preferred and usual lifestyle
- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Estrogenic vaginal ring

- Percutaneous contraceptive patches
- Intrauterine device or intrauterine system
- Tubal sterilization
- Essure micro-insert system (provided confirmation of success 3 months after procedure)
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. The information on the male sterility can come from the site personnel's review of the subject's medical records; medical examination of the subject, and/or semen analysis; or interview with the subject on his medical history. Sterilized males (vasectomy with documentation of azoospermia) must use condoms until 90 days after last dose of study drug.
- Male condom combined with a female diaphragm, either with or without a vaginal spermicidal (foam, gel, film, cream, or suppository). Nonoxynol-9 is the critical component in most spermicides.

## 5.6. BLINDING

The placebo-controlled treatment period will be performed in a double-blind fashion. The investigator, study staff, subjects, and monitor will remain blinded to subject-level treatment assignment until study closure. The sponsor and/or its designee will remain blinded to the subject-level treatment assignment until after all subjects have completed the Week 48 visit (or have discontinued) and the database from the placebo-controlled treatment period has been locked for statistical analyses, after which time they will be unblinded. For the interim analysis (IA), DUX4 and demographics data will be presented to the Sponsor as group-level summaries, along with associated p-values.

The study drug and its matching placebo are indistinguishable and will be packaged in the same way. There are no tolerability issues that could unblind drug versus placebo.

A subject's treatment assignment will not be broken until the end of the study unless medical treatment of the subject depends on knowing the study treatment the subject received. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's treatment allocation without the sponsor's prior agreement. As soon as possible, the investigator should contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that subject.

For medical emergencies, the treatment assignment will be unblinded through the IRT. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

During the OLE, no blinding will be performed (subjects will receive open-label losmapimod); however, the investigator, study staff, subjects, and monitor will remain blinded to the original subject-level treatment assignment from the placebo-controlled treatment period for the duration

of the study. The sponsor and/or its designee will be unblinded after all subjects have completed the Week 48 visit (or have discontinued) and the database from the placebo-controlled treatment period has been locked for statistical analyses.

## 5.7. TREATMENT COMPLIANCE

Subject compliance will be monitored by tablet counts in the clinic. In addition, subject diaries may only be used for a portion of the placebo-controlled portion of the trial to record the date and time of each dose taken. This information may also be used to calculate compliance. Site staff should encourage the proper use of study drug for those subjects who are not compliant.

## 5.8. PRIOR AND CONCOMITANT THERAPY

Use of all concomitant medications taken within 28 days before screening through the safety follow-up visit (either at the end of the placebo-controlled treatment period or at the end of the OLE, as applicable) will be recorded in the subject's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the subject's eCRF.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

The use of the following medications is prohibited in this study:

- Vaccination with a live attenuated vaccine from 6 weeks prior to randomization until the safety follow-up visit (either at the end of the placebo-controlled treatment period or at the end of the OLE, as applicable)
- Use of any anticoagulants for at least 1 month and anti-platelet agents for at least 1 week before each biopsy because these treatments increase the risk of hematomas following skeletal muscle needle biopsy

Subjects who are on drug(s) or supplements that may affect muscle function, as determined by the treating physician, or that are included in the list of drugs presented in (Appendix 13.2) must be on a stable dose of that drug(s) or supplement for at least 3 months prior to the first dose of study drug and remain on that stable dose for the duration of the study. Changes to the dose or treatment discontinuation during the study can only be done for strict medical reasons by the treating physician with clear documentation and notification to the sponsor.

# 6. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential subjects will sign an informed consent form (ICF). Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator or designee will also sign the ICF.

Study visits and the timing of assessments for the placebo-controlled treatment period or the OLE are detailed in the schedule of events (Table 2 and Table 3, respectively).

Prior to the COVID-19 pandemic, subjects who reached the Week 24 visit had the option to roll over into the OLE. Subjects that have already rolled over to the OLE prior to the COVID-19 pandemic will remain on open-label treatment. Their next clinic visits will follow the assessments for the Week 36 and Week 48 visit in the placebo-controlled portion of the study in the COVID-19 Pandemic Emergency protocol version 4.0. These subjects will not undergo the Week 36 biopsy. Subjects who did not roll over prior to the COVID-19 pandemic will roll over into the OLE at the Week 48 visit as described in the COVID-19 Pandemic Emergency protocol version 4.0.

## 6.1. EFFICACY ASSESSMENTS

### 6.1.1. Skeletal Muscle Needle Biopsy

The choice of the muscle(s) to be biopsied in this study will be determined by the investigator, informed by skeletal muscle MRI during screening. The bilateral vastus lateralis, vastus medialis, lateral gastrocnemius, medial gastrocnemius, and tibialis anterior will be evaluated for eligibility by MRI using a central reader. Only those muscles that are STIR positive with the predetermined range of MFF will be eligible for biopsy. This information will be communicated to the sites that will select the muscle or muscles for biopsy. Sites will select the best muscle(s) that meet the MRI criteria based on their own experience with muscle needle biopsy. The Week 16 or Week 36 muscle needle biopsies (for those subjects unable to have the Week 16 muscle biopsy due to the COVID-19 pandemic), will be performed in the same approximate muscle region as the pretreatment (Day 1) muscle biopsy.

The muscle tissue collected at each biopsy will be analyzed for DUX4 activity using a molecular panel of DUX4-regulated gene transcripts and for drug concentration and target engagement by central laboratories. The tissue will be used to measure other gene transcripts and may be used to measure proteins related to the pathology of FSHD as part of exploratory biomarker endpoints.

The specific details of the biopsy procedures, materials to be provided, materials to be resourced locally, personnel qualification, and methods for tissue collection, processing, and analysis will be specified in the study reference manual.

### 6.1.2. Skeletal Muscle Magnetic Resonance Imaging

Whole-body Dixon MRI for MFF, LMV, and MFI will be performed at the visits noted in Table 2. Subjects will be screened for any contraindications to MRI as per clinic standard practice.

Details will be described in the study MRI manual. The study MRI manual will also describe, in detail, all of the steps involved in the acquisition, transmission, quality evaluation, and analysis of MRI images between the study site and the central reader.

## 6.2. SAFETY AND TOLERABILITY ASSESSMENTS

### 6.2.1. Adverse Events

#### 6.2.1.1. Definitions of Adverse Events

The investigator is responsible for reporting all treatment-emergent AEs (TEAEs) that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study, regardless of its causal relationship to study drug. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event that was not present before exposure to study drug or any event that was already present but worsens in either intensity or frequency after exposure to study drug.

#### 6.2.1.2. Serious Adverse Events

An SAE is defined as any event that

- results in death
- is immediately life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### 6.2.1.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Adverse events of special interest for this study include liver tests that meet the criteria for potential drug-induced liver injury (DILI), in accordance with the US Food and Drug Administration (FDA) "Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation."

**Liver Tests and Stopping Criteria**

The following 3 laboratory value criteria must be met for potential DILI, or "Hy's Law":

- An elevated alanine transaminase or aspartate transaminase laboratory value that is ≥3 × ULN
- An elevated total bilirubin laboratory value that is ≥2 × ULN
- An alkaline phosphatase laboratory value that is <2 × ULN

Study drug should be discontinued for subjects who meet the laboratory criteria for potential DILI as a result of within-protocol specific testing or unscheduled testing. This AESI must be reported to the sponsor within 24 hours of awareness. Further safety steps should be taken to closely observe and follow-up the event until resolution. These steps include, but are not limited to:

- Making every reasonable attempt to have the subject return to the clinic within 24 hours for repeat liver tests
- Obtaining a more detailed history of symptoms and prior or concurrent disease, concomitant medication use, alcohol use, recreational drug use, and special diets
- Repeating liver enzyme and serum bilirubin tests twice weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic
- Obtaining viral hepatitis serology
- Considering liver imaging and/or hepatology consultation

#### 6.2.1.4. Eliciting and Documenting Adverse Events

Adverse events and SAEs will be assessed from the time the subject signs the ICF through the safety follow-up visit (either at the end of the placebo-controlled treatment period or at the end of the OLE, as applicable). Any SAE that occurs after these time periods and that is believed to be related to study drug should be reported by the investigator (as described in Section 6.2.1.6).

At every study visit, subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs identified from any study data (eg, clinically significant laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to subject safety will be documented on the AE page in the eCRF.

#### 6.2.1.5. Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- drug treatment
- dose
- event term
- time of onset
- investigator-specified assessment of severity and relationship to study drug
- time of resolution of the event
- seriousness
- any required treatment or evaluations
- outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states (if unexpected worsening beyond normal disease progression based on investigator's assessment) must also be reported. All AEs must continue to be followed to satisfactory resolution as described in Section 6.2.1.10. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Please refer to the ReDUX4 Emergency Guidance Document (31 March 2020) for reporting of AEs related to the COVID-19 pandemic.

Reporting for AESIs is described in Section 6.2.1.3.

#### 6.2.1.6. Reporting Serious Adverse Events

The investigator must report any AE that meets the SAE criteria (Section 6.2.1.2) to [redacted] immediately (ie, within 24 hours after the site personnel first learn about the event) via electronic data capture (EDC). In the event that EDC entry is not possible (eg, system failure or access problems), the study site staff should complete the paper SAE report form and fax the form to [redacted] Pharmacovigilance within 24 hours of awareness or call the [redacted] safety hotline to report. The study site staff should update the EDC system as soon as it is available.

A full description of every SAE will need to be provided to [redacted] Pharmacovigilance. The following contact information should be used if reporting SAEs via fax or phone:

**Pharmacovigilance**

US:

[redacted]

Rest of world:

[redacted]

#### 6.2.1.7. Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all suspected unexpected serious adverse reactions (SUSARs) against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and applicable regulatory authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the sponsor will assess the expectedness of these events using the IB.

The sponsor will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the IB.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

#### 6.2.1.8. Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: An event that is usually transient in nature and generally does not interfere with normal activities.

Moderate: An AE that is sufficiently discomforting to interfere with normal activities.

Severe: An AE that is incapacitating and prevents normal activities.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of the onset and duration of each episode.

#### 6.2.1.9. Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Not related: This relationship suggests that there is no association between the study drug and the reported event.

Unlikely: This relationship suggests that the event is most likely produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs administered to the subject, and does not follow a known response pattern to the study drug, or the temporal relationship of the event to study drug administration makes a causal relationship unlikely.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

#### 6.2.1.10. Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable.

### 6.2.2. Laboratory Analyses

Samples for serum chemistry, hematology, coagulation, and urinalysis will be collected at the time points specified in Table 2 and Table 3. Processing, storage, and shipping procedures for all clinical laboratory samples are provided in a laboratory manual. Sample collection details are presented in Section 6.7.

For the screening visit, subjects will be required to fast for at least 4 hours prior to laboratory blood samples being taken.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements), including those that worsen from baseline (ie, prior to first dose in the placebo-controlled treatment period) and are felt to be clinically significant in the medical and scientific judgment of the investigator, are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs. Clinically significant abnormal laboratory test results will be reviewed by the investigator and recorded as AEs or SAEs on the appropriate page in the eCRF.

Blood and other biological samples will be collected for the following clinical laboratory tests:

| | |
|---|---|
| Serum chemistry | Glucose, sodium, potassium, calcium, inorganic phosphate, total protein, albumin, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, creatine phosphokinase |
| Hematology | Hemoglobin (including mean corpuscular volume), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hematocrit, red blood cell count, total white blood cell count, platelet count<br>Differential blood counts, including basophils, eosinophils, neutrophils, lymphocytes, and monocytes |
| Coagulation | International normalized ratio, prothrombin time, partial thromboplastin time |
| Urinalysis | Leucocytes, blood, nitrite, protein, urobilinogen, bilirubin, pH, specific gravity, ketones, glucose<br>If there is a clinically significant positive result, urine will be sent for microscopy and/or culture. |
| Pregnancy | Serum β-hCG (all female subjects of child-bearing potential), serum<br>follicle-stimulating hormone (suspected postmenopausal female subjects only [defined in Section 5.5.1]), urine pregnancy test |
| Serology testing | HbsAg, HCV antibody, HIV-1/HIV-2 antibodies |
| Urine drug screen | Cocaine, amphetamines, opiates (morphine), benzodiazepines, and cannabinoids |

### 6.2.3. Medical History

Medical history will be recorded at screening and will be reviewed at baseline to ensure no changes have occurred since the screening visit. Clinically relevant findings that are present prior to study drug initiation must be recorded on the Medical History page in the eCRF. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded on the AE page in the eCRF.

FSHD-specific history will be recorded at screening or at a subject's next scheduled study visit, if not previously recorded.

### 6.2.4. Vital Signs

Vital sign (pulse rate, respiration rate, blood pressure, and temperature) assessments will be performed at the time points specified in Table 2 and Table 3. Assessments will be taken after the subject has been seated or recumbent for at least 5 minutes and before any 12-lead ECG assessment or blood sampling is performed.

### 6.2.5. Physical Examinations

Physical examinations will be performed at the time points specified in Table 2 and Table 3.

Physical examinations at the screening visit and the safety follow-up visit will include an evaluation of body systems, including but not limited to the following: skin; head, eyes, ears, nose, and throat; respiratory system; cardiovascular system; abdomen (liver, spleen); lymph nodes; neurological system; and MSK system.

Symptom-directed physical examinations can occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

Weight (kg) will be recorded at screening and throughout the study at the time points specified in Table 2 and Table 3.

Height (cm) will be recorded and body mass index (BMI) calculated at screening and once yearly during the OLE: BMI ($kg/m^2$)=weight (kg)/(height [cm]/100)$^2$. Weight and height will be measured with shoes off and preferably with the same balance at each visit.

### 6.2.6. Twelve-Lead Electrocardiograms

Twelve-lead ECGs will be performed at the time points specified in Table 2 and Table 3. The primary ECG tracings will be locally read by the investigator. Any ECGs found to have abnormalities will be referred for a second opinion by a central reader.

Twelve-lead ECGs will be performed after subjects have been recumbent for at least 5 minutes. The ECGs should be performed after the measurement of vital signs and before any procedures that may affect heart rate (eg, blood sampling).

At the screening visit, if QTcF exceeds 450 msec for males or 470 msec for females, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the subject's eligibility for the study.

Any clinically significant changes from baseline should be reported as AEs or SAEs, if applicable.

## 6.3. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

### 6.3.1. Pharmacokinetic Assessments

During the placebo-controlled treatment period, blood samples will be collected to measure the plasma concentrations of losmapimod at Day 1 (baseline), Week 4, Week 16, and Week 36 at the

following time points: immediately predose and 4 hours (±30 minutes) after administration of the study dose. Blood samples will also be taken, when feasible, after dosing during the Week 12, Week 24, and Week 48 visits, preferably ≥1 hour after dosing (Table 2). During the OLE, blood samples will be collected to measure the plasma concentration of losmapimod after dosing at the Week 144 visit, preferably ≥1 hour after dosing (Table 3).

For each plasma PK sample, approximately 3 mL of blood will be collected via an intravenous catheter placed in an antecubital vein in the arm into a 3 mL, lavender-capped vacutainer tube containing K2-EDTA. The indwelling catheter will be kept patent by saline flush after each blood sampling. The exact actual clock time of withdrawal of the blood sample will be recorded.

Skeletal muscle biopsies will be taken at Day 1 (baseline; predose) and at Week 16 or Week 36 to assess the losmapimod concentrations in muscle during the placebo-controlled treatment period (Table 2). Skeletal muscle biopsy procedures are described in Section 6.1.1.

Further detailed handling, processing, storage, and shipping procedures for plasma and skeletal muscle biopsy PK samples are described in laboratory manuals.

### 6.3.2. Pharmacodynamic Assessments

During the placebo-controlled treatment period, samples for assessing the target engagement estimates of losmapimod in peripheral blood will be collected at Day 1 (baseline) and Week 16 or Week 36 if it was not possible to collect the sample due to the COVID-19 pandemic, at the following time points: immediately predose and 4 hours (±30 minutes) after taking the study dose (Table 2).

For drug target engagement measurements in skeletal muscle tissue during the placebo-controlled treatment period, each biopsy will be analyzed for pHSP27/total HSP27. Target engagement estimates of losmapimod in skeletal muscle biopsy will be taken at Day 1 (baseline; predose) and at Week 16 or Week 36 (Table 2). Skeletal muscle biopsy procedures are described in Section 6.1.1. Target engagement in muscle will be compared to target engagement in blood collected on the same day.

Further detailed handling, processing, storage, and shipping procedures for target engagement samples are described in a laboratory manual.

## 6.4. OTHER ASSESSMENTS

### 6.4.1. Reachable Workspace

The RWS Microsoft Kinect-based movement sensor system will be used at the visits noted in Table 2 to determine the subjects' RWS.

The RWS is a 3D sensor-based system (using a single depth-ranging sensor) that can unobtrusively detect an individual's RWS and reflects individual global upper extremity function, including shoulder and proximal arm. Previous and ongoing evaluation of the hardware

and software system using a commercially available and cost-effective single sensor platform (Microsoft Kinect sensor) has demonstrated its high reliability, repeatability, face validity, feasibility, sensitivity to change, and promise as a COA for FSHD and other neuromuscular disorders (Han et al, 2015).

During the evaluation, subjects will be seated in front of the Microsoft Kinect sensor and will undergo a standardized upper extremity movement protocol under the supervision of a study clinical evaluator while looking at a TV monitor. The evaluation will be performed with and without weights and on both the right and left arms. The Kinect sensor will track the 3D upper limb trajectory and transform the movements into a body-centric coordinate system. Each individual's RWS envelope will be reconstructed in a graphical output. Each side's RWS envelope will be divided into 4 quadrants, with the shoulder joint serving as the origin. The absolute total RWS surface envelope area ($m^2$) as well as areas for each of the quadrants will be calculated. Scaling of the data by each person's arm length will allow normalization for comparison between subjects (Han et al, 2015). RWS includes the functional workspace, where patients are instructed to touch certain parts of their body and are rated on their ability to complete this task.

Instructions for equipment assembly, setup, testing, and site certification; a manual of operation; and a quick reference guide will be described in a RWS manual. A central reader will be responsible for training, quality control, data analysis, and standardization of the RWS across all sites in the study.

### 6.4.2. Timed Up and Go

The classic and FSHD TUG test will be performed at the visits noted in Table 2.

The TUG test is a simple test that is used to assess a person's mobility and requires both static and dynamic balance. It measures the time that a person takes to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down. The optimized TUG test is the classic TUG but adds the component of getting up from a laying position on a bed-like table in the clinic at the start of the test and laying back down on his or her back at the end of the test. The test will be done twice per visit.

A manual of operation, traditional TUG source documents, and FSHD TUG source document will be described in a TUG manual. A central reader will be responsible for training, quality control, data analysis, and standardization of the TUG and FSHD TUG across all sites in the study.

### 6.4.3. Dynamometry

Dynamometry will be performed at the visits noted in Table 2.

Quantitative isometric dynamometry (hand-held dynamometer) will be used to assess the skeletal muscle strength of study subjects in both the upper and lower limbs bilaterally. Shoulders, flexors and extensors in the elbow, knees, and ankles as well as the grip will be measured at each

applicable visit. Isometric dynamometry measures the static muscle strength without any movement.

Further details of the assessment will be provided in a study reference manual. All sites will use the same equipment and standardized testing procedure.

### 6.4.4. Motor Function Measure Domain 1

The MFM scale Domain 1 assessment will be performed at the visits noted in Table 2.

The MFM scale assesses the severity of the motor deficit as determined by an experienced physical therapist (Bérard et al, 2005). The score is reproducible, the coefficients of the interrater reliability are good or excellent. Domain 1 of the MFM provides a clinician's assessment of functional impairment for standing and transfers.

Instructions for performing the MFM scale Domain 1 assessment will be provided in a study reference manual.

### 6.4.5. FSHD Health Index

The FSHD-HI will be performed at the visits noted in Table 2.

The FSHD-HI is an FSHD-specific patient-reported measure of disease burden on activities of daily living, quality of life, and symptom prevalence and severity. It consists of a questionnaire with 116 items developed from qualitative interviews of patients followed by a national cross-sectional validation study. The measure consists of 14 subscales that measure a patient's perception of their ambulation and mobility, hand function, shoulder and arm function, emotional health, back/chest/abdomen strength, fatigue, pain, eating function, ability to do activities, communication ability, satisfaction in social situations, performance in social situations, body image and cognition. Scoring is performed centrally by the developer.

### 6.4.6. Patients' Global Impression of Change

The PGIC will be performed at the visits noted in Table 2 to obtain the subjects' rating of overall improvement.

### 6.4.7. Genetic Confirmation of FSHD1

Genetic testing for FSHD1 is highly sensitive and specific. The finding of a D4Z4 contraction on chromosome 4q35 likely has a sensitivity of 93% and a specificity of 98% for the diagnosis of clinically defined FSHD. Healthy individuals possess at least 11 D4Z4 repeats, yielding a DNA fragment >38 kb on standard genetic testing. Affected individuals possess between 1 and 10 repeats, yielding DNA fragments ranging from 10 to 38 kb in size. Measurement of the size of the residual D4Z4 sequence on 4q35 forms the basis for genetic testing in FSHD (Tawil et al, 2015). For this study, only subjects with 1 to 9 repeats will be enrolled. The number of repeats will be calculated by a diagnostic laboratory using the size of the D4Z4 bands on Southern blot testing. The site will enter the number of repeats into the IRT system. Subjects with 10 repeats

will be excluded from the study because such individuals tend to have slower progression and are more variable due to the presence of genetic modifiers.

Genetic confirmation must be obtained before the subject is randomized and before the baseline muscle biopsy is performed. Genetic confirmation can come from previous testing, if verified with appropriate documentation from an accredited laboratory. If genetic testing is necessary, the 4-week screening window and activities will not start until the results are obtained and verified by the principal investigator.

Due to the stable transmission of repeat sizes within families, subjects with a clinical diagnosis of FSHD who have a first-degree relative with a genetically confirmed diagnosis of FSHD1 may be entered into the study for screening assessments including MRI. During screening, a confirmatory genetic diagnosis will be conducted. If genetic testing during screening is necessary, the 4-week screening window will not start until the results are obtained and verified by the principal investigator.

Further detailed handling, processing, storage, and shipping procedures for genetic testing samples are described in a laboratory manual.

## 6.5. SAFETY REVIEW COMMITTEE

As detailed in Section 11.1.1, a safety review committee (SRC) will review safety data from the study.

## 6.6. PREGNANCY

Pregnancy is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported as an SAE. Study staff should complete the paper Pregnancy Initial Report Form and fax the form to [redacted] Pharmacovigilance within 24 hours of awareness or call the [redacted] safety hotline to report. To ensure subject safety, irrespective of the treatment received by the subject, any pregnancy occurring during study drug administration or until follow-up must be reported within 24 hours of the investigator's knowledge of the event to the sponsor.

If a woman becomes pregnant while on study drug, the study drug must be discontinued immediately. The investigator must counsel the subject and discuss the potential risks to the pregnancy and the possible effects on the embryo or fetus. The pregnancy must be followed up to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy that is brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study drug must be promptly reported to [redacted] and Fulcrum Therapeutics.

## 6.7. SAMPLE COLLECTIONS

Processing, storage, and shipping procedures for all clinical laboratory, PK, and target engagement samples are provided in a laboratory manual.

# 7. STATISTICAL AND ANALYTICAL PLAN

Details regarding the statistical methods and definitions will be provided in statistical analysis plan(s) (SAP[s]). Separate SAPs will be prepared for each treatment period of the study. The SAP for the placebo-controlled treatment period will be finalized prior to database lock/freeze for the IA.

Any deviations from the SAP(s) are to be justified in the clinical study reports. Statistical analyses will be performed using Version 9.3 or higher of SAS (SAS Institute, Cary, NC).

Analyses will be generated separately for the placebo-controlled treatment period and the OLE.

## 7.1. PLACEBO-CONTROLLED TREATMENT PERIOD

### 7.1.1. Primary Endpoint

The primary endpoint of the placebo-controlled treatment period is the change from baseline in DUX4 activity in affected skeletal muscle at Week 16 or Week 36, as measured by QRT-PCR in a panel of DUX4-regulated gene transcripts.

### 7.1.2. Secondary Endpoints

The secondary endpoints of the placebo-controlled treatment period are as follows:

- Safety and tolerability of losmapimod as defined by the following:
  - Type, frequency, severity, seriousness, and relationship of AEs to losmapimod
  - Incidence of AESIs
  - Number of subjects who prematurely discontinue study drug due to an AE
  - Frequency of clinically significant changes in laboratory test, ECG, vital sign, and physical examination results
- Change from baseline in MFF, LMV, and MFI at Week 12, Week 24 (if applicable) and Week 48
- Plasma concentrations of losmapimod at Week 4, Week 12, Week 16, Week 24, Week 36, and Week 48
- Concentrations of losmapimod in skeletal muscle biopsy at steady state at Week 16 or Week 36
- Target engagement parameters in blood, and skeletal muscle biopsy at Week 16 or Week 36

### 7.1.3. Exploratory Endpoints

The exploratory endpoints of the placebo-controlled treatment period are as follows:

- Change from baseline in COAs, including
  - RWS with and without weights at Week 4, Week 12, Week 24, and Week 36

- Classic and FSHD TUG at Week 4, Week 12, Week 24, and Week 36
- Muscle strength by hand-held quantitative dynamometry at Week 4,
- Week 12, Week 24, Week 36, and Week 48
- MFM Domain 1 at Week 12, Week 24, Week 36, and Week 48
- FSHD-HI at Week 4, Week 12, Week 24, Week 36, and Week 48
- PGIC at Week 4, Week 12, Week 16, Week 24, Week 36, and Week 48

- Change from baseline in inflammatory, immune, apoptotic, and other muscle disease transcripts may be conducted in muscle biopsy at Week 16 or Week 36 and in circulating proteins in plasma and serum at Week 4, Week 12, Week 16, Week 24, Week 36, and Week 48.

## 7.2. OPEN-LABEL EXTENSION

### 7.2.1. Primary Endpoint

The primary endpoint of the OLE is the safety and tolerability of long-term treatment of losmapimod based on AEs, clinical laboratory tests, ECGs, vital signs, and physical examination.

### 7.2.2. Secondary Endpoint

The secondary endpoint of the OLE is the plasma concentrations of losmapimod after long-term dosing (at every-12-week time points).

## 7.3. SAMPLE SIZE CALCULATIONS

Assuming an effect size of 0.70, a sample size of 68 subjects (34 subjects per group) will be needed to provide 80% power with a 2-sided test at a 0.05 significance level to detect a difference between losmapimod and placebo in change from baseline in DUX4 activity in affected skeletal muscle after 16 or 36 weeks (depending upon when the muscle biopsy was performed) during the placebo-controlled treatment period. Assuming that approximately 10% of subjects will be non-evaluable, approximately 76 subjects will be randomly assigned at a 1:1 ratio to losmapimod and placebo (38 subjects per group).

## 7.4. ANALYSIS SETS

The following analysis sets will be used in the statistical analyses.

Full analysis set (FAS): The FAS will consist of all subjects who are randomly assigned to receive double-blind study drug in the placebo-controlled treatment period. All analyses using the FAS will group subjects according to randomized treatment. The FAS is the main analysis population for key study endpoints (Section 7.6.1). For the secondary and exploratory endpoints, subjects who already transitioned into the OLE portion under protocol version 3.0 will be analyzed as randomized, in this analysis population.

Per-protocol set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria and do not have any significant protocol deviations. All analyses using the PPS will group subjects according to randomized treatment. PPS analyses will be conducted for key study endpoints (Section 7.6.1) to assess robustness of key study inferences.

Safety analysis set: The safety analysis set will consist of all subjects who receive any study drug. All analyses using the safety analysis set will group subjects according to treatment actually received.

Pharmacokinetic analysis set: The PK analysis set will consist of all subjects who receive at least 1 dose of losmapimod and have evaluable PK data for losmapimod.

Pharmacodynamic analysis set: The PD analysis set will consist of all subjects who receive at least 1 dose of losmapimod and have evaluable PD data for losmapimod.

Open-label losmapimod (Pre-COVID-19) analysis set: This analysis set will consist of subjects who were already transitioned into open-label losmapimod under version 3.0 of the protocol. This analysis set will be used for sensitivity analysis, to assess secondary/exploratory endpoints in this subset of subjects.

Open-label analysis set: The open-label analysis set will consist of all subjects who complete 24 weeks of treatment in the placebo-controlled treatment period and receive at least 1 dose of open-label losmapimod in the OLE. Safety and efficacy analyses in the OLE will be based on this analysis set.

## 7.5. DESCRIPTION OF SUBGROUPS TO BE ANALYZED

Any planned subgroup analyses will be described in the SAP(s).

## 7.6. STATISTICAL ANALYSIS METHODOLOGY

Continuous variables will be summarized using the mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions are described in the SAP(s). All statistical tests will be 2-sided and performed using a 0.05 significance level.

Details of multiplicity adjustment, if any, will be fully described in the SAP(s).

### 7.6.1. Hypothesis Testing on Key Study Endpoints

Hypothesis testing on key study endpoints will be conducted using the FAS.

A sequential testing procedure will be used to control for Type I Error to test the following key study endpoints:

- DUX4 change from baseline (Week 16 or Week 36)
- LMV change from baseline (Week 48)

- FSHD TUG (Week 48)

The testing hierarchy will be provided in the SAP. Each endpoint will be tested at approximately 5% alpha in a hierarchical manner, using the final test-alpha obtained from O'Brien-Fleming Spending Function (Section 7.6.8).

### 7.6.2. Analysis of Primary Endpoints

The primary endpoint of the placebo-controlled treatment period is the change from baseline in DUX4 activity in affected skeletal muscle at Week 16 or Week 36, as measured by QRT-PCR in a panel of DUX4-regulated gene transcripts. An analysis of covariance (ANCOVA) model will be used to analyze the change from baseline in DUX4 activity in affected skeletal muscle, with repeat number category and treatment group as fixed effects and baseline DUX4 activity in affected skeletal muscle as a covariate. Least-square (LS) mean, standard error, and 95% CI of the LS mean will be provided for each treatment group. The difference in LS means between treatment groups and the 95% CI of the difference will also be calculated. The final p-value will be compared against the significance level of approximately 0.05 (Section 7.6.8). All available data will be used. Details will be provided in the SAP(s).

The FAS will be used for the primary analysis for the placebo-controlled treatment period.

The analysis for the primary endpoint for the OLE is described in Section 7.6.6.

### 7.6.3. Analysis of Secondary Endpoints

Secondary endpoints (detailed in Section 7.1.2 and Section 7.2.2) will be summarized using descriptive statistics.

Continuous endpoints with multiple post-baseline assessments will be analyzed using mixed-effect model for repeated measures (MMRM) methods including repeat number category, treatment group, visit, and treatment-by-visit interaction as fixed effects and baseline value as a covariate. Continuous endpoints with a single post-baseline assessment will be analyzed using ANCOVA methods, with repeat number category and treatment group as fixed effects and baseline value as a covariate. Secondary endpoints in the OLE will be summarized according to the treatment assigned at randomization. For all subjects, changes in measurements will be calculated relative to measurements obtained at baseline (ie, prior to first dose in the placebo-controlled treatment period).

Further details of these endpoints are presented in Section 7.6.5, Section 7.6.6, and the SAP(s).

### 7.6.4. Analyses of Exploratory Endpoints

Exploratory endpoints (detailed in Section 7.1.3) will be summarized using descriptive statistics. Confidence intervals will be included as appropriate. When appropriate, continuous exploratory endpoints will also be analyzed using ANCOVA or MMRM methods similar to those used for the primary and secondary endpoints. Any treatment group comparisons will be in the nature of hypothesis generation, and any statistical inference will not have any confirmatory value.

Exploratory endpoints in the OLE will be summarized according to the treatment assigned at randomization.

### 7.6.5. Pharmacokinetic and Pharmacodynamic Analyses

Plasma PK concentrations at each time point for losmapimod will be presented in listings and summarized in tables. Losmapimod concentrations in skeletal muscle biopsy at each time point will also be presented in listings and summarized in tables. The summary tables will display the following descriptive statistics: n, mean, standard deviation, coefficient of variation, median, minimum, and maximum.

The individual and mean plasma concentrations and the individual and mean concentrations in skeletal muscle biopsies will be presented by collection time in figures on linear scales.

The target engagement estimates of losmapimod in peripheral blood and skeletal muscle biopsies will be presented in listings and summarized in tables. The summary tables will display the following descriptive statistics: n, mean, standard deviation, coefficient of variation, median, minimum, and maximum. Within-group LS means, the associated standard errors and 2-sided 95% CIs, treatment differences in LS means and the associated 2-sided 95% CIs, and 2-sided p-values will be derived from the ANCOVA model and presented in the tables.

Population PK and PK/PD models may be developed to address program objectives that require an integrative interpretation of these study results. These may include investigations of the nature of the PK/PD relationship and the use of these study results as part of a larger model-based data analysis. If population PK and PK/PD analyses are performed, those results will be reported separately from the results of this study.

### 7.6.6. Safety Analyses

Safety data in the placebo-controlled treatment period will be analyzed using the safety analysis set and summarized by treatment group and visit (if applicable) using descriptive statistics. Safety data in the OLE will be analyzed using the open-label analysis set.

Treatment-emergent AEs will be summarized by MedDRA system organ class and preferred term; separate summaries will be produced for treatment-related AEs, AESIs, SAEs, and discontinuations due to AEs. Laboratory tests, vital signs, findings from physical examinations, and ECGs will be summarized for changes over time during treatment using descriptive statistics.

### 7.6.7. Other Analyses

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the placebo-controlled treatment period and by treatment assigned at randomization and entry point in the OLE.

Efficacy data will be summarized at each scheduled visit in the OLE, and subjects will be grouped according to initial treatment assigned at randomization and entry point of OLE.

Descriptive statistics will include the number of non-missing observations, mean, standard deviation, median, minimum, and maximum for quantitative data. For qualitative data, frequency counts and percentage will be determined. A full description of demographic variables will be included in the SAP(s).

Individual subject demographics and baseline information will be provided in data listings.

Medical history will be coded using MedDRA at the time of each database lock and will be summarized using the number of observations and percentages of subjects reporting each category and listed for each subject.

A list of protocol deviations (major or minor) will be finalized prior to each database lock.

### 7.6.8. Interim Analyses

One IA will be performed when a minimum of 22 paired muscle biopsies are completed. A group sequential method (O'Brien-Fleming Spending Function) will be used to ensure an overall significance level of 0.05 (double-sided) due to multiple looks at the DUX4 primary endpoint, if the IA is deemed necessary by the Sponsor.

- With a sample size of approximately 22 subjects at IA, the test alpha at IA is approximately 0.001, and the final test alpha is 0.05. If the p-value from the test is <0.001, then the study may be stopped for efficacy, or continue as planned as decided by the Sponsor. Cumulative exit probability under the alternative hypothesis is approximately 2.3% and approximately 82.3% at the IA and final analysis, respectively (SAS Version 9.4; nQuery 8 – Power and Sample Size for Group Sequential Trials, Version 8.5.1.0).
- With a sample size of 32 subjects at IA, the test alpha at IA is approximately 0.004, and the final test alpha is 0.048. If the p-value from the test is <0.004, then the trial may be stopped for efficacy, or continue as planned as decided by Sponsor. Cumulative exit probability under the alternative hypothesis is approximately 13.9% and approximately 82.2% at the IA and final analysis, respectively (SAS Version 9.4; nQuery 8 – Power and Sample Size for Group Sequential Trials, Version 8.5.1.0).

The alphas at the time of the IA for sample sizes ranging from 22 to 32 are provided in Table 1.

**Table 1: Alpha At Interim Analysis and Final Analysis for Different Sample Sizes At Interim Analysis (O'Brien-Fleming Method)**

| Interim Analysis Sample Size | Alpha at Interim Analysis | Alpha at Final |
|---|---|---|
| 22 | 0.000567 | 0.049755 |
| 23 | 0.000736 | 0.049685 |
| 24 | 0.000951 | 0.049596 |
| 25 | 0.001203 | 0.049493 |
| 26 | 0.001474 | 0.049384 |
| 27 | 0.001803 | 0.049253 |

| Interim Analysis Sample Size | Alpha at Interim Analysis | Alpha at Final |
|---|---|---|
| 28 | 0.002173 | 0.049107 |
| 29 | 0.002556 | 0.048959 |
| 30 | 0.003005 | 0.048787 |
| 31 | 0.003496 | 0.048602 |
| 32 | 0.004027 | 0.048405 |

# 8. DATA QUALITY ASSURANCE

This study will be conducted according to the International Council for Harmonisation (ICH) E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

## 8.1. DATA MANAGEMENT

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

Study site personnel will enter subject data into Medidata RAVE® (the eCRF program). The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable [redacted] standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After final database lock, each study site will receive a CD-ROM containing all of their site specific eCRF data as entered into the Medidata RAVE system for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. [redacted] will maintain a duplicate CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

# 9. ETHICS

## 9.1. INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date on which approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

## 9.2. ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

## 9.3. SUBJECT INFORMATION AND CONSENT

A written informed consent approved by the sponsor and by the IEC/IRB in compliance with applicable regulatory authority regulations shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject or legal guardian.

# 10. INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

## 10.1. CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.

To ensure privacy, directly identifying information of study subjects will not be attached to records or samples released to the sponsor and its service providers for research purposes.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. Additional confidentiality requirements and obligations will be set forth in the clinical trial agreement to be entered into by the sponsor, the principal investigator, and the institution.

## 10.2. FINANCIAL DISCLOSURE AND OBLIGATIONS

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required by applicable regulatory authorities. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the subject's disease.

## 10.3. INVESTIGATOR DOCUMENTATION

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and, for US sites, Title 21 of the Code of Federal Regulations by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol

- For US sites, Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- For non-US sites, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may request. For US sites, a curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required by applicable regulatory authorities. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site.

## 10.4. STUDY CONDUCT

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

## 10.5. ADHERENCE TO PROTOCOL

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

## 10.6. ADVERSE EVENTS AND STUDY REPORT REQUIREMENTS

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

## 10.7. INVESTIGATOR'S FINAL REPORT

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

## 10.8. RECORDS RETENTION

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a

longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

## 10.9. PUBLICATIONS

After completion of the study, the data will be submitted for reporting at a scientific meeting and for publication in a peer-reviewed scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld. Further terms concerning publication will be set forth in the clinical trial agreement entered into by the sponsor, the principal investigator, any vendors, and the institution.

# 11. STUDY MANAGEMENT

The administrative structure will include an SRC.

## 11.1. MONITORING

### 11.1.1. Safety Review Committee

An SRC will be formed to review safety data for all subjects at regular intervals throughout the study.

The SRC charter will describe the processes for unblinding subject- or study-level data if the SRC requests unblinding. Details on the composition of the SRC and the schedule of SRC meetings and data reviews will be presented in the SRC charter.

### 11.1.2. Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

### 11.1.3. Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

## 11.2. MANAGEMENT OF PROTOCOL AMENDMENTS AND DEVIATIONS

### 11.2.1. Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

### 11.2.2. Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from or a change of the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines and will lead to the subject being withdrawn from the study (Section 4.2). A list of major protocol deviations will be compiled prior to the start of the study.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

## 11.3. STUDY TERMINATION

Although Fulcrum Therapeutics has every intention of completing the study, Fulcrum reserves the right to discontinue the study at any time for clinical or administrative reasons. Should termination of the study be required, the sponsor will promptly inform the investigator and the IRB/IEC and provide them with a detailed written explanation. Fulcrum and the investigator will assure that adequate consideration is given to the protection of the subjects' interests. The sponsor has no plans to provide study drug to subjects after study closure or termination. The obligations to provide study results for subjects and reports to IRB/IEC shall continue as required by applicable laws and regulations.

At any time, the sponsor, the investigators, or the IRBs/IECs may terminate this study for reasonable cause. Conditions that may lead to reasonable cause and warrant termination include, but are not limited to the following:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the regulatory authority

Written notification that includes the reason for the clinical study termination is required.

The end of the study is defined as the date on which the last subject completes the last visit (includes the safety follow-up visit).

## 11.4. FINAL REPORT

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study reports. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study reports, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

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# 13. APPENDICES

## 13.1. APPENDIX: SCHEDULES OF EVENTS

## Table 2: Schedule of Events: Placebo-Controlled Treatment Period

| Procedure | Screening | Baseline | Week 4 | Week 12 | Week 16 | Week 24 | Week 36 | Week 48 End of Placebo-Controlled Treatment Period/Start of OLE[a] | ET Visit[b] | Safety Follow-Up 7 Days After the Last Dose of Study Drug[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **-** | **8** |
| **Visit Window (days)[d]** | **–28 to –1** | **Day 1** | **±5** | **±5** | **±5** | **±5** | **±14[aa]** | **±5** | | **±3** |
| Informed consent | X | | | | | | | | | |
| Confirm eligibility via inclusion/exclusion criteria | X | X | | | | | | | | |
| Randomization | | X | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Height and BMI[e] | X | | | | | | | | | |
| Medical history | X | X[f] | | | | | | | | |
| FSHD-specific history[g] | X | | | | | | | | | |
| Serology (HBsAg, HCV, HIV1/HIV2) | X | | | | | | | | | |
| Urine drug screen[h] | X | | | | | | | | | |
| Genetic confirmation of FSHD1[i] | X | | | | | | | | | |
| [redacted] | | | | | | | | | | |
| Serum β-hCG[k] | X | | | | | | | | | |
| Serum follicle-stimulating hormone[l] | X | | | | | | | | | |
| Urine pregnancy test[m] | | X | X | X | X | X | X | X | X | X |
| Weight[e] | X | X | | | | | | X | X | X |
| Vital signs[n] | X | X | X | X | X | X | X | X | X | X |
| Physical examination[o] | X | | | | | | | | | X |

| Procedure | Screening | Baseline | Week 4 | Week 12 | Week 16 | Week 24 | Week 36 | Week 48 End of Placebo-Controlled Treatment Period/Start of OLE[a] | ET Visit[b] | Safety Follow-Up 7 Days After the Last Dose of Study Drug[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **-** | **8** |
| **Visit Window (days)[d]** | **–28 to –1** | **Day 1** | **±5** | **±5** | **±5** | **±5** | **±14[aa]** | **±5** | | **±3** |
| Standard 12-lead ECG[p] | X | X | X | | | | | X | X | X |
| Serum chemistry | X[q] | X | X | X | X | X | X | X | X | X |
| Hematology | X[q] | X | X | X | X | X | X | X | X | X |
| Blood sample for coagulation[bb] | X[q] | | | | | | X | | | |
| Urinalysis | X | | | | | | | X | X | X |
| MSK MRI[r] | X | | | X | | | | X | X[s] | |
| Muscle needle biopsy[t] | | X | | | X | | X[t] | | | |
| PK sampling[u] | | X | X | X | X | X | X | X | X | |
| Target engagement sampling[v] | | X | | | X | | X | | | |
| [redacted] | | | | | | | | | | |
| RWS | | X | X | X | | X | X | X | X | X |
| TUG (classic and FSHD) | | X | X | X | | X | X | X | X | X |
| Manual dynamometry | | X | X | X | | X | X | X | X | X |
| MFM Domain 1 | | X | | X | | X | X | X | X | |
| FSHD-HI questionnaire | | X | X | X | | X | X | X | X | X |
| PGIC questionnaire | | | X | X | X | X | X | X | X | X |
| Clinic visit | X | X | X | X | X | X | X | X | X | X |
| Study drug dispensation[x] | | X | X | X | X | X[y] | X | X | | |
| Study drug count | | X | X | X | X | X | X | X | X | |

| Procedure | Screening | Baseline | Week 4 | Week 12 | Week 16 | Week 24 | Week 36 | Week 48 End of Placebo-Controlled Treatment Period/Start of OLE[a] | ET Visit[b] | Safety Follow-Up 7 Days After the Last Dose of Study Drug[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **-** | **8** |
| **Visit Window (days)[d]** | **–28 to –1** | **Day 1** | **±5** | **±5** | **±5** | **±5** | **±14[aa]** | **±5** | | **±3** |
| Concomitant medications[z] | *Continuous from signing the ICF through the safety follow-up visit* | | | | | | | | | |
| Concomitant treatments and procedures | *Continuous from signing the ICF through the safety follow-up visit* | | | | | | | | | |
| Adverse event monitoring | *Continuous from signing the ICF through the safety follow-up visit* | | | | | | | | | |

Abbreviations: β-hCG, beta human chorionic gonadotropin; BMI, body mass index; ECG, electrocardiogram; ET, early termination; FSHD, facioscapulohumeral muscular dystrophy; FSHD-HI, Facioscapulohumeral Muscular Dystrophy Health Index; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; MFM, Motor Function Measure; MRI, magnetic resonance imaging; MSK, musculoskeletal; OLE, open-label extension; PGIC, Patients' Global Impression of Change; PK, pharmacokinetic(s); RWS, Reachable Workspace; STIR, short tau inversion recovery; TUG, Timed Up and Go.

**Note: Some procedures may not have been performed due to the COVID-19 pandemic. Please refer to the ReDUX4 Emergency Guidance document.**

[a] Prior to the COVID-19 pandemic, subjects who reached the Week 24 visit had the option to roll over into the OLE. For subjects who had already rolled over, their next clinic visits will follow the assessments for the Week 36 and Week 48 visit in the placebo-controlled portion of the study in the COVID-19 Pandemic Emergency protocol version 4.0; however, these specific subjects will not undergo the Week 36 biopsy. Those subjects who rolled over before the COVID-19 pandemic protocol version 4.0 was implemented will remain on open-label treatment. Subjects who did not roll over prior to the COVID-19 pandemic will roll over when they reach Week 48. Subjects who roll over into the OLE should not complete the ET visit or safety follow-up visit from the placebo-controlled treatment period.

[b] If a subject prematurely discontinues study treatment during the placebo-controlled treatment period, they will be encouraged to remain in the study and continue with all other aspects of the study. If a subject decides to prematurely discontinue study treatment during the placebo-controlled treatment period and not continue with all other aspects of the study, they will be considered to have withdrawn from the study. If a subject withdraws from the study during the placebo-controlled treatment period, they will be asked to complete an ET visit as soon as possible after the decision to terminate study participation and to complete the safety follow-up visit 7 (±3) days after their last dose of study drug. If the ET visit will be scheduled more than 7 days after the last dose of study drug, the safety follow-up and ET visits may be combined, with no duplication of assessments required.

[c] The safety follow-up visit 7 (±3) days after the last dose of study drug should only be completed by subjects who are not rolling over into the OLE.

[d] Scheduled visits may be split over 2 days if required, with a maximum of 5 business days in between visits. Unscheduled visits may be performed if clinically indicated. Subjects can travel for MRI or muscle biopsy if needed, but the use of a study-approved MRI scanner should be consistent during the trial.

[e] Weight and height will be measured with shoes off and preferably with the same balance at each visit. Body mass index will be calculated at Screening.

[f] Medical history will be reviewed at baseline to ensure no changes have occurred since the screening visit.

[g] FSHD-specific history will be recorded at screening or at a subject's next scheduled study visit, if not previously recorded.

[h] Urine drug screen for drugs of abuse including cocaine, amphetamines, opiates (morphine), benzodiazepines, and cannabinoids.

[i] Genetic confirmation must be obtained before the subject is randomized and before the baseline muscle biopsy is performed; genetic confirmation can come from previous testing if verified with appropriate documentation from an accredited laboratory. Due to the stable transmission of repeat sizes within families, subjects with a clinical diagnosis of FSHD who have a first-degree relative with a genetically confirmed diagnosis of FSHD1 may be entered into the study for screening assessments, including MRI. During screening, a confirmatory genetic diagnosis will be conducted. If genetic testing is necessary, the 4-week screening window and activities will not start until the results are obtained and verified by the principal investigator.

[redacted]

[k] Serum pregnancy tests will be performed at screening for all female subjects of child-bearing potential.

[l] Serum follicle-stimulating hormone testing is required for suspected postmenopausal female subjects only.

[m] Urine pregnancy tests will be performed for all female subjects of child-bearing potential before randomization at all other visits. If pregnancy is found, subjects must be terminated from the study effective immediately.

[n] Vital signs (pulse rate, respiration rate, blood pressure, and temperature) will be collected after the subject has been seated or recumbent for at least 5 minutes and before any 12-lead ECG assessment or blood sampling is performed.

[o] Physical examination at the screening visit and the safety follow-up visit include an evaluation of body systems, including but not limited to the following: skin; head, eyes, ears, nose, and throat; respiratory system; cardiovascular system; abdomen (liver, spleen); lymph nodes; neurological system; and MSK system. Symptom-directed physical examinations can occur at any time during the study if triggered by adverse events or if deemed necessary by the investigator.

[p] Twelve-lead ECGs will be performed after subjects have been recumbent for at least 5 minutes. Twelve-lead ECGs will be performed after the measurement of vital signs and before any procedures that may affect heart rate (eg, blood sampling).

[q] For the screening visit, subjects will be required to fast for at least 4 hours prior to laboratory blood samples being taken.

[r] Subjects will be screened for any contraindications to MRI as per clinic standard practice.

[s] The MRI at the ET visit will not be repeated if an MRI was completed during the previous 8 weeks.

[t] The choice of the muscle(s) to be biopsied in this study will be determined by the investigator, informed by skeletal muscle MRI during screening. The bilateral vastus lateralis, vastus medialis, lateral gastrocnemius, medial gastrocnemius, and tibialis anterior will be evaluated for eligibility by MRI using a central reader. Only those muscles that are STIR positive with the predetermined range of muscle fat fraction will be eligible for biopsy. The 12 patients who rolled over at Week 24 will not undergo the Week 36 muscle biopsy.

[u] Blood samples for PK will be collected at Day 1 (baseline), Week 4, Week 16, and Week 36 at the following time points: immediately predose and 4 hours (±30 minutes) after administration of the study dose. Blood samples will also be taken, when feasible, after dosing during the Week 12, Week 24, and Week 48 visits, preferably ≥1 hour after dosing.

[v] Blood samples for target engagement will be collected on Day 1 (baseline), and Week 16 or Week 36, at the following time points: immediately predose and 4 hours (±30 minutes) after administration of the study dose.

[redacted]

[x] The appropriate amount of study drug supply (losmapimod or placebo) will be given to the subject at each applicable visit to allow for dosing until their next scheduled study visit plus additional tablets to cover the visit window. Study drug (losmapimod or placebo) will be administered as 2 tablets taken twice daily and should be taken with food. Subject diaries may only be used for a portion of the placebo-controlled portion of the trial to record the date and time of each dose taken. This information may also be used to calculate compliance. Subjects will record the date and time of each dose of study drug taken (losmapimod or placebo) in the subject diary. Subjects may be provided additional study drug via courier service, as applicable.

[y] Subjects who are rolling over into the OLE will be dispensed open-label losmapimod at the time of the rollover visit. Subjects may be provided open-label losmapimod via courier or shipping service, as applicable.
[z] All medications taken within 28 days before screening through the safety follow-up visit will be recorded.
[aa] Large window given to accommodate the COVID-19 pandemic.
[bb] It is optional to perform coagulation studies prior to muscle biopsies. Refer to your institutional guidelines.

**Table 3: Schedule of Events: Open-Label Extension (Visits Will Occur Quarterly Until 90 Days After Commercial Drug Availability Post Regulatory Approval or Study is Discontinued)**

| **Procedure** | **Week 60<br>Week 108<br>Week 156<br>Week 204 etc.** | **Week 72<br>Week 120<br>Week 168<br>Week 216 etc.** | **Week 84<br>Week 132<br>Week 180 etc.** | **Week 96<br>Week 144<br>Week 192 etc.** | **ET Visit[a]** | **Safety Follow-Up 7 Days After the Last Dose of Study Drug** |
|---|---|---|---|---|---|---|
| **Visit Window (days)[b]** | **±7** | **±7** | **±7** | **±7** | | **±3** |
| Weight, height, and BMI[c] | | X | | | | |
| [redacted] | | | | | | |
| Urine pregnancy test[e] | X | X | X | X | X | X |
| Vital signs[f] | X | X | X | X | X | X |
| Physical examination[g] | | | | | | X |
| Standard 12-lead ECG[h] | X | X | X | X | X | X |
| Serum chemistry | X | X | X | X | X | X |
| Hematology | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X |
| PK sampling[i] | | | | X | X | |
| Clinic visit | X | X | X | X | X | X |
| Study drug dispensation[j] | X | X | X | X | | |
| Study drug count | X | X | X | X | X | |
| Concomitant medications[k] | *Continuous from signing the ICF through the safety follow-up visit* | | | | | |
| Concomitant treatments and procedures | *Continuous from signing the ICF through the safety follow-up visit* | | | | | |
| Adverse event monitoring | *Continuous from signing the ICF through the safety follow-up visit* | | | | | |

Abbreviations: BMI, body mass index; ECG, electrocardiogram; ET, early termination; ICF, informed consent form; MRI, magnetic resonance imaging; MSK, musculoskeletal; OLE, open-label extension; PK, pharmacokinetic(s).

[a] If a subject prematurely discontinues study treatment during the OLE, they will be encouraged to remain in the study and continue with all other aspects of the study. If a subject decides to prematurely discontinue study treatment during the OLE and not continue with all other aspects of the study, they will be considered to have withdrawn from the study. If a subject withdraws from the study during the OLE, they will be asked to complete the ET visit as soon as

possible after the decision to terminate study participation and to complete the safety follow-up visit 7 (±3) days after their last dose of study drug. If the ET visit will be scheduled more than 7 days after the last dose of study drug, the safety follow-up and ET visits may be combined, with no duplication of assessments required.

[b] Scheduled visits may be split over 2 days if required, with a maximum of 5 business days in between visits. Unscheduled visits may be performed if clinically indicated. Subjects can travel for MRI or muscle biopsy if needed, but the use of a study-approved MRI scanner should be consistent during the trial.

[c] Weight and height will be measured and BMI will be calculated once a year (ie, Week 72, Week 120, Week 168, Week 216, etc.). Weight and height will be measured with shoes off and preferably with the same balance.

[redacted]

[e] Urine pregnancy tests will be performed for all female subjects of child-bearing potential before dispensation of study drug. If pregnancy is found, subjects must be terminated from the study effective immediately.

[f] Vital signs (pulse rate, respiration rate, blood pressure, and temperature) will be collected after the subject has been seated or recumbent for at least 5 minutes and before any 12-lead ECG assessment or blood sampling is performed.

[g] Physical examination at the safety follow-up visit includes an evaluation of body systems, including but not limited to the following: skin; head, eyes, ears, nose, and throat; respiratory system; cardiovascular system; abdomen (liver, spleen); lymph nodes; neurological system; and MSK system. Symptom-directed physical examinations can occur at any time during the study if triggered by adverse events or if deemed necessary by the investigator.

[h] Twelve-lead ECGs will be performed after subjects have been recumbent for at least 5 minutes. Twelve-lead ECGs will be performed after the measurement of vital signs and before any procedures that may affect heart rate (eg, blood sampling).

[i] Blood samples for PK will be collected after dosing at the Week 144 clinic visit only, preferably ≥1 hour after dosing.

[j] The appropriate amount of study drug supply (losmapimod) will be given to the subject at each applicable visit to allow for dosing until their next scheduled study visit plus additional tablets to cover the visit window or additional study drug will be provided to the subject via a courier, as applicable. Study drug (losmapimod) will be taken twice daily and should be taken with food.

[k] All medications taken within 28 days before screening through the safety follow-up visit will be recorded.

## 13.2. APPENDIX: DRUGS POTENTIALLY AFFECTING MUSCLE FUNCTION

List of drug(s) or supplements that potentially may affect muscle function includes, but is not limited to, the following:

1. Statins
2. Steroids
3. Testosterone or other growth hormone agonists
4. Beta-agonists
5. Creatine
6. Colchicine
7. Benzylpenicillin