CLINICAL STUDY PROTOCOL

IND: 138739

EUDRACT: 2022-000389-16

A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Patients with Facioscapulohumeral Muscular Dystrophy (REACH)

PROTOCOL 1821-FSH-301

Sponsor:
Fulcrum Therapeutics
26 Landsdowne Street
Cambridge, MA 02139 USA

Sponsor Contact:
[redacted], MD
Vice President, Clinical Development, Neuromuscular
Fulcrum Therapeutics
26 Landsdowne Street
Cambridge, MA 02139 USA
Telephone: 617-678-4980

Version of Protocol: Version 5.1

Date of Protocol: 21 December 2023

Compound Name: Losmapimod

Study Phase: Phase 3

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title	A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Patients with Facioscapulohumeral Muscular Dystrophy (FSHD) (REACH)
Protocol Number and Version	1821-FSH-301, Version 5.1
Protocol Date	21 December 2023

Protocol accepted and approved by:

Name and Title	Signature	Date
[redacted], PhD Vice President, Biometrics Fulcrum Therapeutics, Inc.	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 12/21/2023 | 1:41:27 PM EST [redacted]	12/21/2023
[redacted], MD Vice President, Clinical Development, Neuromuscular Fulcrum Therapeutics, Inc.	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 12/21/2023 | 12:57:36 PM EST [redacted]	12/21/2023
[redacted], MD Executive Medical Director, Drug Safety and PV Medical Sciences Fulcrum Therapeutics, Inc.	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I have reviewed this document Signing Time: 12/21/2023 | 12:40:22 PM EST [redacted]	12/21/2023

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Patients with Facioscapulohumeral Muscular Dystrophy (FSHD) (REACH)" and the current losmapimod 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 5.1, dated 21 December 2023, 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

SUMMARY OF CHANGES TO THE PROTOCOL

The previous version of this protocol (Version 4.0, 01 March 2023) was amended to create the current version (Version 5.1, 21 December 2023). The protocol history is below:

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 17 February 2022	Original version
Version 2.0, 03 March 2022	Global amendment
Version 3.0, 08 August 2022	Global amendment
Version 4.0, 01 March 2023	Global amendment
Version 5.1, 21 December 2023	Global amendment

Country/region-specific differences are defined in Appendix 2 and cross-referenced throughout.

Key changes made in the current version of the protocol are summarized below.

Typographical and administrative changes were also made to improve the clarity of the document.

Change and Rationale	**Affected Sections**
Study objectives and endpoints for Part A were updated; primary endpoint will assess RSA as the average of both arms instead of dominant arm only and an exploratory endpoint was added to assess RSA in dominant or non-dominant arms separately. This change was made to provide a more robust assessment of shoulder mobility. Shoulder strength assessed by hand-held quantitative dynamometry was changed from an exploratory to a secondary endpoint. Statistical analyses were updated as appropriate.	Synopsis, Section 2.1, Section 9.1
Oral CYP3A4, OAT3, and MATE substrates are no longer systematically prohibited as concomitant medications. This change is based on the results of the recently completed drug-drug interaction study (1821-CLP-102). Only those concomitant medications that are substrates of OAT1/OAT3 and have a narrow therapeutic index may need to have their blood levels monitored when coadministered with losmapimod. The following changes were made: • Background sections were updated (Section 1.3.4) • Exclusion criteria were updated for Part A (EC #3 and #4) and for Part B (EC #2) (Section 4.1) • Concomitant medications were updated (Section 5.8) • Contraception guidelines were updated; oral combined	Section 1.3.4, Section 4.1, Section 5.5, Section 5.5.1, Section 5.8, Appendix 4

Change and Rationale	Affected Sections
hormonal methods are now allowed (Section 5.5.1). • List of CYP3A4, OAT1, and OAT3 substrates in Appendix 3 was deleted and a list of OAT1/OAT3 substrates with narrow therapeutic index (NTI) was added as a new Appendix 4. • Lifestyle restrictions were updated; subjects no longer have to avoid nutrients known to modulate CYP enzyme activity (Section 5.5).	
Clarified the study duration of Part B (OLE). The OLE will last for approximately 2 years, according to the visits defined in the OLE schedule of assessments (Table 8). Any plans to extend the study duration will be executed in a future amendment. The phrase "until after commercial drug is available post regulatory approval" was also deleted.	Synopsis, Section 3.1, Section 3.1.2, Appendix 1
Added clarification for safety follow-up visits for clarity; only subjects that do not continue to the OLE will complete the safety follow-up visits in Part A.	Synopsis, Section 3.1.1, Appendix 1
Background sections were updated to align with most recent version of the losmapimod Investigator's Brochure.	Section 1.2.3, Section 1.2.4, Section 1.3.2
Clarified guidance on use of statins as concomitant medications	Section 5.8, Appendix 3
Added clarification for direct bilirubin testing per Protocol Clarification Letter dated 01 Sep 2023	Section 6.1.5
Clarified procedures for clinically significant abnormal laboratory test results.	Section 6.1.5
Deleted incorrect statement referring to a central reader for electrocardiograms; a central reader is not being utilized for this study.	Section 6.1.9
Updated safety reporting information to account for a vendor change.	Section 7.3.2
Clarified adverse event follow-up procedures by removing redundant language	Section 7.4
Clarified safety procedures in the case of an overdose.	Section 7.8.1
Updated pregnancy testing to follow local regulations; this change eliminates the need for a UK-specific protocol version to allow for more frequent pregnancy testing.	Section 6.1.5, Appendix 1
Added new appendix to define any country/region-specific differences and allow for a harmonized protocol	Appendix 2

TABLE OF CONTENTS

PROTOCOL APPROVAL – SPONSOR SIGNATORY 2
DECLARATION OF INVESTIGATOR 3
SUMMARY OF CHANGES TO THE PROTOCOL 4
TABLE OF CONTENTS 6
LIST OF ABBREVIATIONS 13
PROTOCOL SYNOPSIS 16
1. BACKGROUND 22
1.1. Nonclinical Studies 23
1.2. Clinical Studies 24
1.2.1. Pharmacokinetics 24
1.2.2. Pharmacodynamics 25
1.2.3. Safety 26
1.2.4. Efficacy 26
1.3. Benefit Risk 28
1.3.1. Identified Risks 28
1.3.2. Potential Risks 28
1.3.2.1. Hepatotoxicity 28
1.3.2.2. Immune Function 29
1.3.3. Contraindications 30
1.3.4. Interactions 30
1.3.4.1. Drug Interactions 30
1.3.4.2. Food Interactions 31
1.3.5. Other Clinically Relevant Information 31
1.3.5.1. Effects on Serum Creatinine 32
1.3.5.2. Thorough QT Study 32
2. STUDY OBJECTIVES AND ENDPOINTS 33
2.1. Part A: Placebo-Controlled Treatment Period 33
2.1.1. Primary Objective and Endpoint 33
2.1.2. Secondary Objectives and Endpoints 33

2.1.3. Exploratory Objectives and Endpoints 34
2.2. Part B: Open-Label Extension 35
2.2.1. Primary Objectives and Endpoints 35
2.2.2. Secondary Objectives and Endpoints 35
2.2.3. Exploratory Objectives and Endpoints 35
3. INVESTIGATIONAL PLAN 36
3.1. Study Design 36
3.1.1. Part A: Placebo-Controlled Treatment Period 36
3.1.2. Part B: Open-Label Extension 37
3.2. Rationale of Study Design 38
3.2.1. Rationale of Dose Selection 38
3.2.2. Rationale of Study Design 38
4. PARTICIPANT SELECTION AND WITHDRAWAL CRITERIA 41
4.1. Selection of Study Participants 41
4.1.1. Part A: Placebo-Controlled Treatment Period 41
4.1.1.1. Inclusion Criteria 41
4.1.1.2. Exclusion Criteria 42
4.1.2. Part B: Open-Label Extension 44
4.1.2.1. Inclusion Criteria 44
4.1.2.2. Exclusion Criteria 44
4.2. Rescreening of Study Participants 44
4.3. Withdrawal of Patients from Study Treatment and/or the Study 45
4.3.1. Reasons for Withdrawal/Discontinuation 45
4.3.2. Handling of Withdrawals 46
4.3.3. Replacements 46
5. STUDY TREATMENTS 47
5.1. Part A: Placebo-Controlled Treatment Period 47
5.1.1. Method of Assigning Participants to Treatment Groups 47
5.1.2. Treatments Administered 47
5.2. Part B: Open-Label Extension 47

5.2.1. Treatments Administered 47
5.3. Identity of Investigational Product 48
5.4. Management of Clinical Supplies 48
5.4.1. Study Drug Packaging and Storage 48
5.4.2. Study Drug Accountability 48
5.5. Lifestyle Restrictions 49
5.5.1. Contraception Requirements 49
5.5.1.1. Highly Effective Methods for Avoiding Pregnancy in Females of Childbearing Potential 49
5.6. Blinding 50
5.6.1. Part A: Placebo-Controlled Treatment Period 50
5.6.2. Part B: Open-Label Extension 51
5.7. Treatment Compliance 51
5.8. Prior and Concomitant Therapy 51
6. STUDY ASSESSMENTS AND PROCEDURES 52
6.1. Efficacy and Safety Assessments 52
6.1.1. Reachable Workspace 52
6.1.2. Skeletal Muscle Magnetic Resonance Imaging 53
6.1.3. Hand-Held Dynamometry 53
6.1.4. Eliciting and Documenting Adverse Events 53
6.1.5. Laboratory Analyses 54
6.1.6. Medical History 55
6.1.7. Vital Signs 55
6.1.8. Physical Examinations 56
6.1.9. Twelve-Lead Electrocardiograms 56
6.2. Other Assessments 56
6.2.1. Genetic Confirmation of FSHD 56
[redacted]
6.2.5. Patient Global Impression of Change 58

[redacted]

6.2.8. Neuro-QoL Upper Extremity Patient Reported Outcome 58

[redacted]

6.2.12. Qualitative Exit Interview 59

[redacted]

6.2.14. Sample Collections 60
7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 61
7.1. Definitions 61
7.1.1. Definition of Adverse Event 61
7.1.2. Definition of Treatment-Emergent Adverse Event 61
7.1.3. Definition of Serious Adverse Event 61
7.1.3.1. Definition of Terms 62
7.1.4. Definition of Suspected Unexpected Serious Adverse Reaction 62
7.1.5. Reference Safety Information 62
7.2. Classification of Adverse Events 63
7.2.1. Assessment of Intensity/Severity 63
7.2.2. Assessment of Causality 63
7.2.3. Outcome 64
7.2.4. Action Taken 64
7.3. Reporting Guidelines 64
7.3.1. Reporting Adverse Events 64
7.3.2. Reporting Serious Adverse Events 65
7.3.3. Expectedness of an Adverse Event 65
7.3.4. Reporting Suspected Unexpected Serious Adverse Reactions 65
7.4. Adverse Event Follow-up 66
7.5. Adverse Events of Special Interest 66
7.6. Adverse Events of Significance 66

7.7. Clinical Laboratory Changes 67
7.8. Special Situations 67
7.8.1. Overdose 67
7.8.2. Death 67
7.8.3. Pregnancy 67
7.8.4. Medication Error 68
7.8.5. Unblinding Due to Medical Emergency 68
8. INVESTIGATIONAL PRODUCT COMPLAINTS 69
8.1. Definition of Investigational Product Complaints 69
8.2. Reporting of Investigational Product Complaints 69
9. STATISTICAL CONSIDERATIONS 70
9.1. Part A: Placebo-Controlled Treatment Period 70
9.1.1. Estimands and Intercurrent Events 70
9.1.2. Statistical Hypothesis 70
9.1.3. Sample Size Determination 71
9.1.4. Analysis Sets 71
9.1.5. Description of Subgroups to Be Analyzed 71
9.1.6. Statistical Analysis Methodology 71
9.1.6.1. General Considerations 71
9.1.6.2. Overview of Statistical Methods: Estimation of Estimands and Sensitivity Analyses 72
9.1.6.3. Analysis of Primary Endpoint 72
9.1.6.4. Analysis of Secondary Efficacy Endpoints 72
[redacted]
9.1.6.6. Pharmacokinetic Analyses 73
9.1.6.7. Safety Analyses 73
9.1.6.8. Other Analyses 73
9.1.6.9. Handling of Missing Data 74
9.1.6.10. Independent Data Monitoring Committee 74
9.2. Part B: Open-Label Extension 74
9.2.1. Statistical Hypotheses 74

9.2.2. Sample Size Determination 74
9.2.3. Analysis Sets 74
9.2.4. Description of Subgroups to be Analyzed 74
9.2.5. Statistical Analysis Methodology 75
9.2.5.1. General Considerations 75
9.2.5.2. Safety Analyses 75
9.2.5.3. Other Analyses 75
9.2.6. Handing of Missing Data 75
9.3. Interim Analyses 76
10. DATA QUALITY ASSURANCE 77
10.1. Data Management 77
11. ETHICS 78
11.1. Independent Ethics Committee or Institutional Review Board 78
11.2. Ethical Conduct of the Study 78
11.3. Patient Information and Consent 78
12. INVESTIGATOR'S OBLIGATIONS 80
12.1. Confidentiality 80
12.2. Financial Disclosure and Obligations 80
12.3. Investigator Documentation 80
12.4. Study Conduct 81
12.5. Adherence to Protocol 81
12.6. Adverse Events and Study Report Requirements 81
12.7. Investigator's Final Report 81
12.8. Records Retention 82
12.9. Publications 82
13. STUDY MANAGEMENT 83
13.1. Monitoring 83
13.1.1. Sponsor Safety Review 83
13.1.2. Monitoring of the Study 83
13.1.3. Inspection of Records 83

13.2. Management of Protocol Amendments and Deviations....83
13.2.1. Modification of the Protocol....83
13.2.2. Protocol Deviations....84
13.3. Study Termination....84
13.4. Final Report....85
14. REFERENCES....86
APPENDIX 1. SCHEDULES OF ASSESSMENTS....90
APPENDIX 2. COUNTRY/REGION-SPECIFIC DIFFERENCES....96
APPENDIX 3. DRUGS POTENTIALLY AFFECTING MUSCLE FUNCTION....97
APPENDIX 4. LIST OF OAT1/OAT3 SUBSTRATES WITH A NARROW THERAPEUTIC INDEX....98

LIST OF TABLES

Table 1: Primary Objective and Endpoint (Part A)....33
Table 2: Secondary Objectives and Endpoints (Part A)....33
Table 3: Exploratory Objectives and Endpoints (Part A)....34
Table 4: Primary Objectives and Endpoints (Part B)....35
Table 5: Exploratory Objectives and Endpoints (Part B)....35
Table 6: Protocol-Required Laboratory Tests....54
Table 7: Part A: Placebo-Controlled Treatment Period Schedule of Assessments....90
Table 8: Part B: Open-Label Extension Schedule of Assessments....94

LIST OF FIGURES

Figure 1: Study Schematic....36

LIST OF ABBREVIATIONS

Abbreviation	Definition
3D	3-dimensional
ACS	acute coronary syndrome
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
C_{max}	maximum plasma concentration
COA	clinical outcome assessments
CYP	cytochrome P450
DILI	drug-induced liver injury
DUX4	double homeobox 4
ECG	electrocardiogram
eCRF	electronic case report form
EMEA	Europe, Middle East, and Africa
[redacted]	[redacted]
ET	early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSHD	facioscapulohumeral muscular dystrophy
FSHD1	facioscapulohumeral muscular dystrophy type 1
FSHD2	facioscapulohumeral muscular dystrophy type 2
GCP	Good Clinical Practice
HSP27	heat shock protein 27
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IPC	investigational product complaint
IRB	Institutional Review Board
IRT	interactive response technology
KLH	keyhole limpet hemocyanin
LME	linear mixed-effects model
LMV	lean muscle volume
LS	least squares
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MFF	muscle fat fraction
MFI	muscle fat infiltration
MMRM	mixed-effects model for repeated measures
MRI	magnetic resonance imaging
Neuro-QoL	Quality of Life in Neurologic Disorders
[redacted]	[redacted]
OAT	organic anion transporter
OLE	open-label extension
OLS	open-label study
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
[redacted]	[redacted]
pHSP27	phosphorylated heat shock protein 27
PI	Principle Investigator
PK	pharmacokinetic(s)
PO	orally
PRO	patient-reported outcome
PVG	pharmacovigilance
Q	quintant/quadrant

Abbreviation	Definition
QTc	QT interval corrected
QTcF	QT interval corrected for heart rate by Fridericia's formula
RSA	relative surface area
RWS	reachable workspace
SAE	serious adverse event
SAP	statistical analysis plan
SMCHD1	structural maintenance of chromosomes flexible hinge domain 1
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TDAR	T–cell-dependent antibody response
TEAE	treatment-emergent adverse event
UE	upper extremity
ULN	upper limit of normal
WB	whole-body

PROTOCOL SYNOPSIS

Protocol Number:	1821-FSH-301
Title:	A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Patients with Facioscapulohumeral Muscular Dystrophy (FSHD) (REACH)
Sponsor:	Fulcrum Therapeutics, Inc. 26 Landsdowne Street, 5th Floor Cambridge, MA 02139 USA
Study Phase:	3
Study Sites:	Approximately 36 sites in North America and Europe
Indication:	FSHD
Rationale:	Treatment of FSHD with losmapimod has demonstrated evidence of slowing of disease progression and/or improvement on clinical outcome assessments in people living with FSHD. Nonclinical studies have shown that losmapimod reduces the aberrant expression of double homeobox 4 (DUX4); the underlying cause of FSHD. Two Phase 2 clinical studies, a 48-week randomized controlled study (ReDUX4, FIS-002-2019) and a 52-week open-label study (OLS, FIS-001-2019) demonstrate evidence of benefit of treatment with losmapimod on structural and FSHD-relevant clinical endpoints that is recognized by patients, and a favorable safety and tolerability profile supporting continued development.
Objectives:	***Part A: Placebo-Controlled Treatment Period*** **Primary Objective:** • To evaluate the efficacy of losmapimod for the treatment of FSHD on disease progression assessed by reachable workspace quantification of total relative surface area (RSA) Q1-Q5 with 500 g wrist weight, averaged over both arms **Secondary Objectives:** • To evaluate Patient Global Impression of Change (PGIC) relative to placebo • To evaluate efficacy of losmapimod to slow accumulation of fat in muscle-by-muscle fat infiltration (MFI) with whole-body (WB) musculoskeletal (MSK) magnetic resonance imaging (MRI) relative to placebo • To evaluate relative change from baseline in shoulder strength by hand-held quantitative dynamometry relative to placebo • To evaluate the change in Quality of Life in Neurological Disorders: Upper Extremities (Neuro-QoL UE) relative to placebo

	• To assess safety and tolerability of losmapimod in patients with FSHD **Exploratory Objectives:** [redacted] • To evaluate relative change from baseline in muscle strength by handheld quantitative dynamometry, relative to placebo [redacted] ***Part B: Open-Label Extension*** **Primary Objective:** • To assess the long-term safety and tolerability of losmapimod in patients with FSHD **Exploratory Objectives:** [redacted]
Endpoints:	***Part A: Placebo-Controlled Treatment Period*** **Primary Endpoints:** • Change from baseline in average total RSA Q1--Q5 with 500 g wrist weight at Week 48, where average is applied over both arms **Secondary Endpoints:** • PGIC at Week 48 • Change from baseline in WB longitudinal composite MFI of B muscles

at Week 48

- Relative change from baseline in average shoulder abductor strength by hand-held quantitative dynamometry at Week 48
- Change from baseline in Neuro-QoL UE at Week 48
- Safety and tolerability, based on the assessment of adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations

Exploratory Endpoints:

- Change from baseline in WB longitudinal composite MFF at Week 48

- Relative change from baseline in muscle strength by hand-held quantitative dynamometry at Week 48

Part B: Open-Label Extension

Primary Endpoint:

- Safety and tolerability of long-term treatment with losmapimod, based on the assessment of AEs, clinical laboratory tests, ECGs, vital signs, and physical examinations

Exploratory Endpoints:

	• [redacted]
Study Population:	**Part A:** Males and females between the ages of 18 to 65 years, inclusive, with a diagnosis of FSHD1 or FSHD2 verified by genetic testing and a Clinical Severity Score of 2 to 4 (Ricci score; range 0 to 5), with no contraindications to MRI. **Part B:** Patients who have completed Part A of this study.
Study Design:	Part A of Study 1821-FSH-301 is a global, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Efficacy and safety of losmapimod will be evaluated in patients with FSHD over a 48-week treatment period. A total of approximately 230 patients with FSHD will be randomized 1:1 to receive losmapimod or placebo. Upon completion of Part A, patients will have the option to rollover into Part B, the open-label extension. The long-term safety, tolerability, and efficacy of losmapimod will be evaluated in patients.
Duration of Treatment:	**Part A: Placebo-Controlled Treatment Period** Patients will participate in the randomized, controlled treatment period, including the following: • [redacted] • A 48-week placebo-controlled treatment period. • Safety follow-up visits [redacted] days and [redacted] days after last dose (only for patients who discontinue from treatment early or who do not rollover into Part B). – For patients who rollover into Part B, the Week 48 visit will be the end of study visit for Part A. • Patients will have the opportunity to rollover into Part B (open-label extension) after completing Part A. Approval from the Medical Monitor will be required if patients do not rollover without interruption after completing the Week 48 assessments. If a patient rolls over more than 7 days after the last dose in Part A, they may be required to repeat selected Week 48 assessments at the discretion of the Medical Monitor. **Part B: Open-Label Extension** • Patients may participate in the open-label extension after completing Part A. • All patients in Part B will be eligible to receive losmapimod 15 mg orally twice daily (BID) from the time they complete Part A of this study and for the duration of the study as specified in the Schedule of Assessments for Part B or until the study is discontinued by the sponsor. • Patients will have safety follow-up visits [redacted] and [redacted] days after the last dose.
Details of Applicable Monitoring	In Part A only, an Independent Data Monitoring Committee (IDMC) will conduct periodic planned safety reviews of study data, as outlined in the IDMC

Committee:	charter.
Investigational Product, Dosage, and Route of Administration:	**Part A: Placebo-Controlled Treatment Period** Losmapimod 15 mg will be administered orally BID with food. Placebo tablets (Part A only) will be identical in appearance to losmapimod tablets and will have the same excipients as the active tablets. **Part B: Open-Label Extension** Losmapimod 15 mg will be administered orally BID with food for the duration of the study as specified in the Schedule of Assessments for Part B or until the study is discontinued by the sponsor.
Sample Size:	**Part A: Placebo-Controlled Treatment Period** Approximately 210 patients with genetically confirmed FSHD1 and 20 patients with genetically confirmed FSHD2 will be enrolled. All previous FSHD studies of losmapimod have been conducted in patients with FSHD1; therefore, sample size calculations are based on patients with FSHD1 genotype. Additional patients with FSHD2 genotype will be enrolled to explore safety and efficacy in this subgroup. Assuming the within-group SD of change is 0.08 and that 10% of the study population has missing Week 48 data, a sample size of 210 patients with FSHD1 (105 patients per group) will be needed to provide at least 95% power with a 2-sided test at 0.05 significance level to detect a difference of 0.05 between losmapimod and placebo in change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48. An additional approximately 20 patients with FSHD2 will be recruited. **Part B: Open-Label Extension** Patients who complete Part A will be given the opportunity to participate in Part B. The sample size is not based on any formal statistical assumptions. Up to 230 patients may be enrolled in Part B.
Statistical Methods:	**Part A: Placebo-Controlled Treatment Period** The primary endpoint of absolute change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 will be formally tested only during the final analysis, when all patients complete Part A participation. The full analysis set (FAS) will be used for the primary analysis in the placebo-controlled treatment period. The FAS will consist of all patients with FSHD1 and FSHD2 who are randomized and receive at least 1 dose of study drug in the placebo-controlled treatment period. The analysis of the absolute change from baseline in average total RSA will be based on a mixed-effects model for repeated measures with the absolute change from baseline at post-baseline visits up to Week 48 as the dependent variable. The model will include terms for treatment group, visit, treatment group by visit interaction, baseline value, baseline value by visit interaction, region, and FSHD repeat number category, where appropriate. An unstructured covariance matrix will be used to model the correlations between repeated measurements within each patient. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. **Part B: Open-Label Extension** The open-label analysis set will be used for all analyses, unless otherwise

	specified, for Part B. It will consist of all patients who receive at least 1 dose of losmapimod in the open-label extension portion. All statistical analyses will be descriptive. The statistical methods are described in Section 9.2.5 and in the Statistical Analysis Plan.
Version and Date of Protocol	Version 5.1, 21 December 2023

1. BACKGROUND

Fulcrum Therapeutics Inc. (Fulcrum) is developing losmapimod for the treatment of facioscapulohumeral muscular dystrophy (FSHD). Losmapimod is an orally bioavailable small molecule inhibitor of the p38α/β mitogen-activated protein kinase (MAPK) that specifically reduces double homeobox 4 (DUX4) protein expression and its downstream transcriptional targets. Losmapimod is not authorized for marketing in any country worldwide at this time.

FSHD is a serious, rare, progressive and debilitating neuromuscular disease, with a prevalence of approximately 16,000 to 38,000 diagnosed individuals in the United States (Deenen et al. 2014; Preston, Tawil, and Wang 2020). Symptoms of FSHD typically appear in the second decade of life but can begin at any age (Tawil et al. 2015); however, earlier onset typically manifests in more severe progression (Chen, Wu, and Tseng 2020; Goselink et al. 2019). About two-thirds of cases are familial-inherited in an autosomal dominant fashion, and one-third of cases are sporadic. During a June 2020 FSHD Externally Led Patient-Focused Drug Development virtual meeting with the US Food and Drug Administration (FDA), patients, caregivers, and others, a number of testimonials conveyed a message of suffering, stress, and despair (Arjomand et al. 2020).

FSHD is characterized by muscle weakness and eventual loss of function. It is a relentlessly progressive disease, with accumulation of weakness rostral to caudal, characteristically starting with facial and scapular weakness, followed by lower extremities and trunk. The progression of the disease significantly impacts activities of daily living (ADLs), independence, self-esteem, and mental status, with some experiencing pain and lost ability to function or work. The most prevalent functional motor limitations include difficulty getting up from lying down in bed and difficulty using arms for ADLs (Statland and Tawil 2014). FSHD significantly impacts all quality-of-life domains on the 36-Item Short Form Health Survey, and over half of patients with FSHD report at least mild to moderate pain (Moris et al. 2018; Padua et al. 2009).

The natural history of FSHD disease progression has been captured in a longitudinal assessment of reachable workspace (RWS). Total relative surface area (RSA) quadrants (Q1-Q4) demonstrates an annualized 1.63% RSA decline over 5 years across patients with FSHD assessed without weights and a significant 1.82% RSA decline in total RWS with weights (Hatch, Kim, et al. 2019). Moderately impaired individuals with baseline RSA values between 0.20 and 0.70 (out of 1.0, for quadrants Q1-Q4) were more likely to show predictable declines over time with an annualized total RSA loss of 2.74% (P=0.047) (Hatch, Kim, et al. 2019).

Muscle strength, measured by quantitative muscle testing, decreases at a rate of approximately 1% to 4% per year (Statland and Tawil 2014; Stübgen and Stipp 2010), and a 6-year risk of wheelchair use is 24% (Statland, Shah, et al. 2015). Asymmetry of muscle involvement is common. In the most severe cases, there can be extramuscular manifestations, including retinal vascular changes and hearing loss (Statland and Tawil 2014); cardiac and respiratory muscles are usually spared.

FSHD is caused by aberrant expression of the DUX4 gene, a homeobox transcription factor. DUX4 pathological expression in skeletal muscle in both FSHD type 1 (FSHD1) and FSHD type 2 (FSHD2) leads to the activation of genes usually not expressed in skeletal muscle and almost exclusively found in the early embryo (Bosnakovski et al. 2014; Homma et al. 2015; Jagannathan et al. 2016; Yao et al. 2014). This aberrant *DUX4*-driven gene expression activates complex pathological cell processes including expression of cytokines (Statland, Odrzywolski, et al. 2015), cellular stress, and programmed cell death (apoptosis) with no single process currently defined as driving the pathology (Wang et al. 2019; Wong et al. 2020). The result is myofiber death with skeletal muscle tissue loss, as well as muscle fat infiltration and eventual replacement by fat. This loss of muscle tissue and replacement by fat is responsible for the clinical manifestation of the disease, including progressive loss of muscle strength and strength (muscle weakness), loss of function, and slow accumulation of physical disability.

The primary treatment goal for patients living with FSHD is slowing or stopping disease progression (Arjomand et al. 2020). 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). 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.

1.1. NONCLINICAL STUDIES

In vitro studies, including absorption, distribution, metabolism, and excretion assessments, have demonstrated that losmapimod is a highly selective p38α/β MAPK inhibitor with a limited risk of significant interaction with most 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 muscle cell death 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. Additionally, the PK/PD analysis 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). Fulcrum and others have demonstrated that the

treatment effect of losmapimod on the root cause of FSHD occurs regardless of the genotype of the patient-derived muscle cell models used (Oliva et al. 2019; Rojas et al. 2020).

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). 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 most 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 QT interval corrected (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 no concerns in carcinogenicity studies.

1.2. CLINICAL STUDIES

Fulcrum is evaluating losmapimod for the treatment of patients with FSHD. Previously, losmapimod was evaluated for the treatment of 10 different indications other than FSHD or other muscle disorders; however, losmapimod did not show the desired efficacy in those indications and thus is no longer under investigation for those conditions. Losmapimod was generally well tolerated in those studies. As part of these development programs, safety data are available from >3500 healthy volunteers or patients who have been treated with oral losmapimod.

Fulcrum has completed 3 Phase 1 studies (FIS-001-2018, 1821-CLP-101, and 1821-CLP-102); 2 Phase 1 studies (1821-CLP-103 and 1821-CLP-104) and 2 Phase 2 studies (FIS-001-2019 [open-label study (OLS)] and FIS-002-2019 [ReDUX4]) are currently ongoing. The main parts of the Phase 2 studies have been completed while the open-label extensions portions of these studies are ongoing.

For additional details regarding the clinical studies refer to the current version of the losmapimod Investigator's Brochure.

1.2.1. Pharmacokinetics

Elimination of losmapimod is almost exclusively by metabolism with only 2% of the administered dose recovered as unchanged drug in urine and feces. 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 formation of FTX-5508 was shown to be catalyzed by carboxylesterase-1. The absolute oral bioavailability of the tablet formulation is 62%.

Following a single intravenous dose of losmapimod, the volume of distribution at steady state indicated extensive tissue distribution (Mellion et al. 2021). Food was found to increase the oral absorption of losmapimod for both milled and micronized formulations of losmapimod with up to 60 mg tablets (Studies FIS-001-2018 and 1821-CLP-101).

The PK of losmapimod tablets was evaluated in healthy volunteers and patients with FSHD in Fulcrum's completed Phase 1 study FIS -001-2018 (Barbour et al. 2013; Cheriyan et al. 2011). Single-dose plasma PK profiles of losmapimod in patients with FSHD1 were similar to the PK profiles in healthy patients and multiple-dose plasma PK profiles in patients with FSHD1 were similar to that in published literature (Barbour et al. 2013; Cheriyan et al. 2011). Exposures increased approximately dose proportionally from 7.5 to 15 mg and were generally non-significantly higher than losmapimod exposures described in the literature, which may be due to formulation differences, PK sampling duration differences, and/or food effects.

Exposure at target tissue level, in the muscle, was confirmed by detection of losmapimod in biopsied muscle at levels ranging from 42.10 to 97.16 ng/g after 14 days of 15 mg PO BID dosing; these concentrations exceed the half-maximal inhibitory concentration as determined in blood by Barbour et al (Barbour et al. 2013) of 37.4 ng/mL as well as preclinical concentrations (approximately 30 ng/mL) that resulted in a reduction of aberrant DUX4-driven gene expression and muscle cell death. Approximately dose-proportional levels of losmapimod were observed in muscle in patients with FSHD.

For additional details regarding PK, refer to the current version of the losmapimod Investigator's Brochure.

1.2.2. Pharmacodynamics

Losmapimod is highly selective for p38α and p38β MAPKs, and phosphorylation of heat shock protein 27 (HSP27) is directly related to the activation of p38α (MAPK14) through a downstream kinase, MK2. Therefore, phosphorylated HSP27 (pHSP27) is a relevant surrogate to measure the degree of p38α MAPK inhibition as it is activated by induction of the p38α MAPK signaling pathway, downstream from p38α MAPK itself. Data have shown that the ratio pHSP27/HSP27 is more responsive to single- and multiple-dose treatment compared to pHSP27 or total HSP27 separately.

In Phase 1 and Phase 2 studies conducted by Fulcrum, target engagement was confirmed in blood and muscle based on a decrease in the pHSP27/HSP27 ratio. Levels of pHSP27/total HSP27 in blood after sorbitol stimulation ex vivo showed a percent reduction from baseline of approximately 35% to 65% at maximum plasma concentration (C_{max}; 4 hours postdose) in the losmapimod group, demonstrating target engagement in the Phase 2 ReDUX4 study. Additionally, target engagement was similar for the one 15-mg tablet dose and the two 7.5-mg tablet dose whether it was administered with or without food.

For additional details regarding pharmacodynamics, refer to the current version of the losmapimod Investigator's Brochure.

1.2.3. Safety

Fulcrum has conducted Phase 1 Studies FIS-001-2018 (Part A), 1821-CLP-101, and 1821-CLP-102 in healthy volunteers and evaluated the safety of losmapimod. Also, Fulcrum has evaluated the safety of losmapimod in patients with FSHD in the Phase 1 Study FIS-001-2018 (Parts B and C) and is currently conducting 2 Phase 1 studies (1821-CLP-103 and 1821-CLP-104), 2 Phase 2 studies (FIS-001-2019 and FIS-002-2019 [ReDUX4]), and 1 Phase 3 study (1821-FSH-301 [REACH]).

Additionally, the safety profile of losmapimod has been evaluated previously in >3500 subjects across multiple clinical studies and indications, none of which were FSHD or muscle disorders.

The safety of losmapimod tablets was evaluated in healthy volunteers and in patients with FSHD aged 18 years and above in Fulcrum's completed Phase 1 studies and 2 ongoing Phase 2 studies.

As of 09 January 2022, a total of 208 subjects have received losmapimod in a Fulcrum-sponsored clinical study: 66 healthy volunteers, approximately 120 patients with FSHD, and 22 patients with COVID-19. To date, there were no drug-related serious adverse events (SAEs) or deaths reported. One subject discontinued from the study due to an adverse event (AE) of dizziness considered unrelated to the study drug by the investigator; the patient decided to discontinue treatment and withdrew consent.

Evaluation of treatment-emergent adverse events (TEAEs), vital signs, physical findings, electrocardiograms (ECGs), and safety hematology and chemistry results showed no safety concerns or findings of losmapimod given in tablet formulation to healthy volunteers in single doses of 7.5 and 15 mg and to patients with FSHD receiving 15 mg doses BID for up to 48 weeks. There were no reported deaths, SAEs, or severe AEs throughout the studies. There was no specific pattern of TEAEs discernable across treatments (losmapimod 7.5 mg, losmapimod 15 mg, or placebo). There was no identifiable causal relationship between the use of losmapimod and the occurrence of infections, bleeding events, congestive heart failure AEs, stroke AEs, or skin-related AEs. Despite the pharmacology of p38 MAPK inhibition, there is no clear evidence to suggest clinically relevant immune compromise in subjects taking losmapimod.

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. The potential benefit of losmapimod continues to outweigh the risk following exposure in more than 3500 subjects in GSK and Fulcrum clinical studies.

For additional details regarding safety, refer to the current version of the losmapimod Investigator's Brochure.

1.2.4. Efficacy

Fulcrum is evaluating the efficacy of losmapimod for the treatment of patients with FSHD aged 18 years and above in 2 Phase 2 studies (FIS-001-2019 and FIS-002-2019). The main parts of the studies have been completed, and the open-label extensions are ongoing.

Losmapimod demonstrated disease-modifying properties as evidenced by efficacy on structural, functional, and patient-reported measures of FSHD disease progression in the main parts of the 2 Phase 2 studies. Both studies have ongoing extensions in which all participants are taking losmapimod.

These studies show that treatment with losmapimod resulted in:

- Dose-dependent exposure in plasma and muscle at concentrations predicted by nonclinical models to provide efficacy by reducing DUX4 activity
- Superiority over placebo in maintaining or improving muscle function as assessed by total RWS (a quantitative measure of upper arm mobility and strength), and, importantly, range of motion above the shoulder and behind the back
- Stability or improved muscle strength on hand-held quantitative dynamometry and quantitative muscle testing
- Improvements in ankle dorsiflexion strength supportive of the trends of faster timed up-and-go (TUG)
- Reduction in the progression of muscle fat infiltration (MFI) and muscle fat fraction (MFF) in A and B muscles, suggesting losmapimod has an impact on fat accumulation in muscles that have not yet reached end-stage which has been previously reported to have little remaining functional capacity; muscles were categorized based on MFI and MFF as normal appearing (Category A; MFI <0.10, MFF, <0.50), intermediate (Category B; MFI ≥0.10, MFF <0.05), or late-stage (Category C; MFF ≥0.50)
- Moderate and strong correlations in functional correlation composites of muscles involved in functional assessments of interest (TUG and RWS) with MFI, MFF, and lean muscle volume (LMV)

Importantly, the effect of treatment with losmapimod is recognized by patients (clinically meaningful difference of -0.58 on the Patients' Global Impression of Change [PGIC] scale between losmapimod and placebo groups) in ReDUX4. Of subjects reporting at Week 48 (29 and 31 subjects for the losmapimod and placebo groups, respectively), 27.6% of losmapimod patients and 6.5% of placebo patients reported improvement by PGIC, and 72.4% of losmapimod patients and 93.5% of placebo patients reported not improved.

Even though there is downstream evidence of benefits of reduction in DUX4-driven gene expression, the prespecified population and subgroup analyses (including subgroups by DUX4 repeat category, clinical severity score, sex, fat fraction on muscle MRI, baseline DUX4 score on muscle biopsy, completion of classical or FSHD TUG with use of assisted device) did not show differences in DUX4-driven gene expression in muscle biopsies, between or within groups in either study, due to the variability of DUX4-driven gene expression, which spanned over 1000-fold among patients at baseline. Multiple factors contributed to this large variability, including the stochastic nature of DUX4-driven gene expression, the very transient duration of and relative scarcity of DUX4 expression among myonuclei (which has been shown to be approximately 1/1000 to 1/3000), the heterogeneity in composition of FSHD muscles, and the variability in the muscle biopsy procedure performed across multiple clinical sites.

Additionally, an interim analysis of the ongoing OLE data from Study FIS-002-2019 (ReDUX4) shows stability in annualized total (Q1-5) RSA in the dominant arm with weights in the participants continuing to receive losmapimod (LOS/LOS) during the second year of dosing compared to the first (0.31%/year vs -0.62%/year, respectively) and improvement in placebo participants who converted to losmapimod after the first year of the study (PBO/LOS) (0.98% in the OLE vs -7.49% in the placebo-controlled portion).

For additional details regarding efficacy, refer to the current version of the losmapimod Investigator's Brochure.

1.3. BENEFIT RISK

1.3.1. Identified Risks

Currently, there are no important identified risks for losmapimod.

1.3.2. Potential Risks

This section summarizes the important potential risks that have been recognized during the conduct of the losmapimod clinical development program. For more details, refer to the current version of the losmapimod Investigator's Brochure.

1.3.2.1. Hepatotoxicity

Evidence of hepatotoxicity typified by increased concentrations of transaminases, with or without hyperbilirubinemia, has been noted after repeat dose administration of some other p38 MAPK inhibitors. The mechanism of liver injury for these compounds is not known. Patients receiving losmapimod have not demonstrated clinically apparent hepatotoxicity in studies to date. Reasons for this apparent difference may include different selectivity, a lower total daily dose, less than complete inhibition of p38 MAPK (as demonstrated by pHSP27 inhibition), and the absence of active metabolites.

Based on consolidated data from 11 repeat-dose clinical studies across patient populations conducted by GSK, the proportion of subjects who experienced alanine aminotransferase (ALT) ≥3×ULN was 0.9% in those receiving losmapimod and 0.5% in those receiving placebo. ALT elevations were generally reversible following drug discontinuation, although follow-up is not available in all cases. There was a slightly higher incidence of ALT elevation in the non-ST-segment elevation myocardial infarction (NSTEMI) study (Study PM1111810), in which ALT ≥3×ULN occurred in 8/391 (2%) of those receiving losmapimod and 1/135 (0.7%) of those receiving placebo. In the acute coronary syndrome (ACS) Phase 3 study (Study PM1116197), 5/1724 subjects in the losmapimod group and 4/1752 subjects in the placebo group experienced simultaneous ALT ≥3× ULN and total bilirubin ≥2×ULN.

Factors that likely contributed to the rise in ALT and bilirubin in these cases included the underlying ACS event, concomitant high dose statin administration, cholecystitis, and/or a history of autoimmune hepatitis.

In studies in patients with FSHD, the following was observed in terms of liver function evaluations:

In the open-label Study FIS-001-2019, 5/14 (35.7%) patients had an AE of ALT increased (defined as ALT values > ULN) and 3/14 (25.4%) patients had an AE of aspartate aminotransferase (AST) increased (defined as AST values >ULN). All cases of ALT increased, and AST increased resolved with continued dosing, and all cases were considered mild in severity. The mean change (SD) from baseline at Week 52 of treatment was 6.8 (7.20) U/L for ALT and 6.1 (4.25) U/L for AST.

In the randomized, placebo-controlled portion of Study FIS-002-2019 (ReDUX4), 2/40 patients randomized to losmapimod experienced AEs of increased ALT levels (defined as ALT values >ULN); all events were considered mild in severity and resolved with continued dosing. None of the 40 subjects randomized to placebo experienced increased ALT levels during the placebo-controlled period. No other patients experienced clinically notable liver-related laboratory values or drug-induced liver injury (DILI).

Cumulatively, there have been no reported SAEs or adverse events of special interest in Fulcrum-sponsored FSHD clinical studies, in relation to the potential risk of hepatotoxicity.

The liver effects in patients with FSHD are consistent with the safety profile of losmapimod in patients with other clinical conditions.

The liver safety data available to date support the enrollment of patients with stable liver disease in clinical trials, provided there is no evidence of clinically relevant active liver dysfunction.

1.3.2.2. Immune Function

Based on the pharmacology of p38 MAPK inhibition, losmapimod theoretically may have an impact on immunity and be associated with an increased risk of infection. To date, there is no evidence to suggest an increased risk of infection based on exposure to losmapimod. However, this drug class has demonstrated a modest but broad influence on various cytokines. It should also be noted that at a clinical dose of 15 mg orally, losmapimod only partially inhibits the p38 MAPK pathway (approximately 60% at C_{max}), as estimated by inhibition of HSP27 phosphorylation (Study PM1113022). In addition, losmapimod does not inhibit neutrophil response to a variety of stimuli. Further, clinical studies to date have not demonstrated an increase in the incidence, type, or severity of infections in patients who have received losmapimod when compared to those who received placebo. Thus, the degree of impact of losmapimod will continue to be monitored.

Of note, additional nonclinical investigation has shown marked reductions in immunoglobulin (Ig)M and IgG responses to keyhole limpet hemocyanin (KLH) at maximal inhibitory doses (300 mg/kg/day) in the rat T–cell-dependent antibody response (TDAR) model. These findings were reversible after a 4-week recovery period. No clear dose- or sex-dependent reductions in IgM or IgG responses to KLH were noted at lower doses (≤3 mg/kg/day). The reduction in TDAR response is consistent with the known pharmacology of p38 kinase inhibition (Khiem et al. 2008) when using doses that produce maximal inhibition.

In considering the totality of nonclinical and clinical data for losmapimod to date, there may be clinical circumstances under which the theoretical risk of administration of losmapimod outweighs the benefit, particularly due to limited or no prior experience in certain populations. This includes the co-administration of losmapimod and cytotoxic chemotherapy for cancer, as data in this population are not available. In addition, administration of losmapimod during active opportunistic infection and tuberculosis, as well as other active, life-threatening infections, may carry theoretical risks. The rat immunotoxicology study showed that reductions in T–cell-dependent antigen response (with large safety margins) were reversible once losmapimod administration was stopped.

It is theoretically possible that losmapimod could diminish the efficacy of immunizations if given during the same period of time. Attenuated live vaccines should not be administered shortly prior to, during, or shortly after dosing with losmapimod.

1.3.3. Contraindications

There are no specific disease-related contraindications to the administration of losmapimod.

Losmapimod should not be administered to:

- Pregnant or nursing mothers
- Women of childbearing potential who are not employing adequate contraceptive measures

Teratogenicity and effects on embryo fetal survival were noted in rat and rabbit reproductive toxicity studies with losmapimod. The use of losmapimod is currently limited to females of nonchildbearing potential or to females of childbearing potential who are utilizing adequate contraceptive methods.

Losmapimod is contraindicated in patients who are known to have previously experienced hypersensitivity to losmapimod and patients with known hypersensitivity to any of the excipients [redacted] used in its formulations.

1.3.4. Interactions

1.3.4.1. Drug Interactions

Losmapimod has low potential to cause clinically significant drug interactions with most metabolizing enzymes and transporters studied. Losmapimod is a potent in vitro inhibitor of breast cancer resistance protein (BCRP), but in a clinical study, losmapimod (at 7.5 mg PO BID) did not significantly increase the exposure of rosuvastatin (a substrate of BCRP). However, caution is advised if losmapimod is co-administered with orally administered BCRP substrates with a narrow therapeutic index as high intestinal concentrations of losmapimod may enhance their absorption.

An in vitro study investigating the effect of losmapimod on kidney transporters revealed that losmapimod is an in vitro inhibitor of the multidrug and toxin extrusion (MATE)-1, or MATE2-K, renal transporter. A Phase 1, drug-drug interaction study (1821-CLP-102) was conducted to evaluate the effect of multiple oral doses of losmapimod on the PK profile of midazolam (a known cytochrome P450 [CYP] 3A4 substrate) and separately on the PK profiles of furosemide (a known organic anion transporter [OAT] 1 and OAT3 transporter substrate) and metformin (a known organic cation transporter [OCT] 2, multidrug and toxin extrusion [MATE]-1, and MATE2-K transporter substrate). The results of this study demonstrate that there is no clinically meaningful drug-drug interaction potential of losmapimod or the FTX-5508 metabolite with CYP3A4, MATE, or OAT substrates, with the exception of substrates of OAT1/OAT3 with a narrow therapeutic index; subjects taking such concomitant medications may require monitoring of blood concentrations of these substrates when coadministered with losmapimod (see guidance in Section 5.8).

FTX-5508 does not meet the current drug-drug interaction thresholds of safety concern stipulated in the regulatory guidance (European Medicines Agency guidance, CPMP/EWP/560/95/Rev. 1 Corr. 2 and FDA draft guidance, 2020) for interactions with carboxylesterase [CES]-1, P-glycoprotein, BCRP, organic anion transporting polypeptides (OATP) 1B1/1B3, OAT1/2/4, OCT 2, MATE-1, or MATE2-K and consequently has low potential to cause clinically significant drug interactions via these enzymes or transporters. The major metabolite (FTX-5508) is a potent in vitro inhibitor of OAT3 (see above guidance). FTX-5508 does not inhibit nor induce major CYPs at clinical doses.

Losmapimod and FTX-5508 are unlikely to be victims of inhibitors or inducers of the enzymes and transporters studied.

Patients should be instructed as to the risk of drug-drug interaction and to report any change in medication prescription or usage to the study Investigator.

1.3.4.2. Food Interactions

The food effect on the oral absorption of losmapimod has been investigated. A high-fat meal increased [redacted] of losmapimod (wet granulation formulation) compared to the fasted state at the 15 mg dose. This increase in exposure is not considered clinically significant and, as a result, losmapimod may be taken without regard to meals unless otherwise stated in individual protocols. In this study, losmapimod will be taken with food to reduce PK variability and enhance exposure.

1.3.5. Other Clinically Relevant Information

This section documents safety observations or events that may be potentially relevant in the clinical management of patients receiving losmapimod. A reasonable possibility of a causal association with losmapimod and the potentially medically important observations or events listed below has not been established, and at this time none of these are considered expected for

the purpose of expedited reporting. Further characterization is ongoing. Additional details may be found elsewhere in the losmapimod Investigator's Brochure.

1.3.5.1. Effects on Serum Creatinine

A small increase in (model-adjusted geometric mean) serum creatinine in the combined losmapimod group compared to placebo at Week 12 was noted in Study PM1111810 (ratio 1.07 [95% CI: 1.02, 1.11]). Retrospective statistical analyses for creatinine levels in three other Phase 2 studies demonstrated similar trends (model-adjusted geometric mean ratio: 1.01 to 1.07 at Week 12). This increase appeared to attenuate with continued therapy (to Week 24 in chronic obstructive pulmonary disease) as well as with discontinuation (2 weeks post-treatment in acute coronary syndrome). There was no increase in the incidence of renal insufficiency or related adverse events.

There were no clinically relevant changes in serum creatinine or changes in estimated glomerular filtration rate observed in Fulcrum losmapimod clinical studies.

1.3.5.2. Thorough QT Study

A thorough QT study (PM1116628) was conducted with losmapimod at 7.5 mg BID or 20 mg once daily or placebo administered for 5 days in healthy volunteers. Moxifloxacin (single 400 mg dose) was included as a positive control. The primary PD analysis showed that, at the 20 mg dose of losmapimod, the upper bound of the 90% CI of ΔΔQTcF (change from baseline in QT interval corrected for heart rate by Fridericia's formula [QTcF] compared to that for placebo) exceeded the 10 msec threshold at the 24-hour post-dose time point. For the 7.5 mg 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. PK/PD modeling, using the raw QTcF and plasma concentration data, showed that at plasma losmapimod concentrations 4 times the 7.5 mg BID exposure, 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.

In summary, although the upper bound of the 90% CI exceeded the 10 msec regulatory threshold of concern in the primary PD analysis, it is unlikely that there will be a clinically relevant effect on the QT interval data, 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 supports the lack of a QT effect.

Across the completed and ongoing Fulcrum losmapimod studies, there were no notable or clinically meaningful changes or trends noted in changes from baseline in ECG parameters; this was confirmed by ECG interpretation by visit.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. PART A: PLACEBO-CONTROLLED TREATMENT PERIOD

2.1.1. Primary Objective and Endpoint

The primary objective and endpoint are presented in Table 1.

Table 1: Primary Objective and Endpoint (Part A)

Objectives	Endpoint
• To evaluate the efficacy of losmapimod for the treatment of FSHD on disease progression assessed by RWS quantification of total RSA Q1-Q5 with 500 g wrist weight, averaged over both arms	• Change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48, where average is applied over both arms

Abbreviations: FSHD = facioscapulohumeral muscular dystrophy; Q = quintant/quadrant; RSA = relative surface area; RWS = reachable workspace.

2.1.2. Secondary Objectives and Endpoints

Secondary objectives and endpoints are presented in Table 2.

Table 2: Secondary Objectives and Endpoints (Part A)

Objectives	Endpoints
• To evaluate PGIC relative to placebo • To evaluate efficacy of losmapimod to slow accumulation of fat in muscle by MFI with WB MSK MRI relative to placebo • To evaluate relative change from baseline in shoulder strength by hand-held quantitative dynamometry relative to placebo • To evaluate the change in Neuro-QoL UE relative to placebo • To assess safety and tolerability of losmapimod in patients with FSHD	• PGIC at Week 48 • Change from baseline in WB longitudinal composite MFI of B muscles at Week 48 • Relative change from baseline in average shoulder abductor strength by hand-held quantitative dynamometry at Week 48 • Change from baseline in Neuro-QoL UE at Week 48 • Safety and tolerability, based on the assessment of AEs, clinical laboratory tests, ECGs, vital signs, and physical examinations

Abbreviations: AE = adverse event; ECG = electrocardiogram; FSHD = facioscapulohumeral muscular dystrophy; MFI = muscle fat infiltration; MRI = magnetic resonance imaging; MSK = musculoskeletal; Neuro-QoL-UE = Quality of Life in Neurologic Disorders-upper extremity; PGIC = Patient Global Impression of Change; WB = whole-body.

2.1.3. Exploratory Objectives and Endpoints

Exploratory objectives and endpoints are presented in Table 3.

Table 3: Exploratory Objectives and Endpoints (Part A)

Objectives	Endpoints
[redacted] • To evaluate relative change from baseline in muscle strength by hand-held quantitative dynamometry, relative to placebo [redacted]	[redacted] • Relative change from baseline in muscle strength by hand-held quantitative dynamometry at Week 48 [redacted]

Abbreviations: [redacted]; FSHD = facioscapulohumeral muscular dystrophy; [redacted] MSK = musculoskeletal; NPRS = numeric pain rating scale; [redacted]; PRO = patient-reported outcomes; Q = quadrant/quintant; RSA = relative surface area; WB = whole-body.

2.2. PART B: OPEN-LABEL EXTENSION

2.2.1. Primary Objectives and Endpoints

The primary objectives and endpoints are presented in Table 4.

Table 4: Primary Objectives and Endpoints (Part B)

Objectives	Endpoint
• To assess the long-term safety and tolerability of losmapimod in patients with FSHD	• Safety and tolerability of long-term treatment with losmapimod, based on the assessment of AEs, clinical laboratory tests, ECGs, vital signs, and physical examinations

Abbreviations: AE = adverse event; ECG = electrocardiogram; FSHD = facioscapulohumeral muscular dystrophy.

2.2.2. Secondary Objectives and Endpoints

There are no secondary objectives and endpoints in Part B.

2.2.3. Exploratory Objectives and Endpoints

Exploratory objectives and endpoints are presented in Table 5.

Table 5: Exploratory Objectives and Endpoints (Part B)

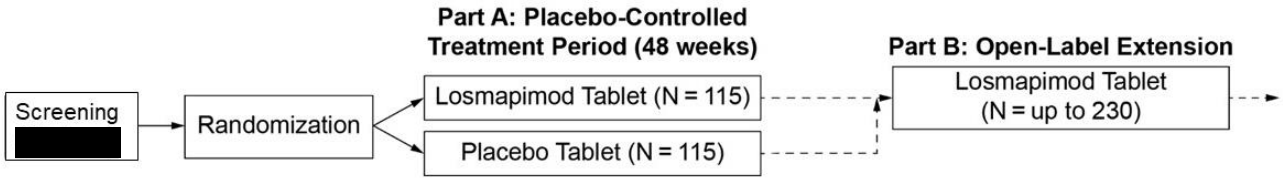
Objectives	Endpoints
[redacted]	

Abbreviations: [redacted] FSHD = facioscapulohumeral muscular dystrophy; [redacted]; RSA = relative surface area; RWS = Reachable Workspace.

3. INVESTIGATIONAL PLAN

3.1. STUDY DESIGN

Figure 1: Study Schematic



Patients will have the opportunity to rollover into Part B after completing Part A. Approval from the Medical Monitor will be required if patients do not rollover without interruption after completing the Week 48 assessments. If a patient rolls over more than 7 days after the last dose in Part A, they may be required to repeat selected Week 48 assessments at the discretion of the Medical Monitor. Losmapimod will be administered continuously for the duration of the study as specified in the Schedule of Assessments for Part B or until the study is discontinued by the sponsor.

3.1.1. Part A: Placebo-Controlled Treatment Period

Part A of Study 1821-FSH-301 is a global, randomized, double-blind, placebo-controlled, parallel-group, multicenter study with a [redacted] screening period, a 48-week treatment period, and safety follow-up visits [redacted] days and [redacted] days after last dose (for patients who discontinue from treatment early or who do not rollover into Part B).

During the placebo-controlled treatment period, a total of approximately 230 patients with FSHD will be randomized 1:1 to receive 15 mg PO of losmapimod (n=115) or placebo (n=115) tablets BID with food for 48 weeks (Figure 1).

Patients will complete a [redacted] screening period followed by a 48-week placebo-controlled treatment period. After Week 48 patients will have the option to participate in Part B: Open-Label Extension (Section 3.1.2).

- Patients will have the opportunity to rollover into Part B after completing Part A. Approval from the Medical Monitor will be required if patients do not rollover without interruption after completing the Week 48 assessments. If a patient rolls over more than 7 days after the last dose in Part A, they may be required to repeat selected Week 48 assessments at the discretion of the Medical Monitor.
- For patients who rollover into Part B, the Week 48 visit will be the end of study visit for Part A.
- All patients who discontinue from treatment early or who do not rollover into Part B will return for a complete safety follow-up visit [redacted] days after the last dose of study drug and will complete a safety follow-up phone screen [redacted] days after the last dose of study drug.

During the treatment period, patients will be asked to attend the study clinic at each scheduled visit (Table 7).

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 7. Scheduled visits may be split over 2 days, if required, and must be completed within the protocol-defined visit windows (Table 7). Unscheduled visits may be performed if clinically indicated.

3.1.2. Part B: Open-Label Extension

Upon completion of Part A at Week 48, patients will have the option to rollover into Part B, the open-label extension (Figure 1). Patients should be prepared to rollover into Part B as soon as possible after the last dose of study drug in Part A (Week 48 visit). Approval from the Medical Monitor will be required if patients do not rollover without interruption after completing the Week 48 assessments. If a patient does not rollover within 7 days of the last dose of study drug in Part A, they may be required to repeat selected Week 48 assessments (at the discretion of the Medical Monitor) to establish baseline for Part B. Study drug will not be administered in Part B until all assessments for Part A have been completed.

As outlined in Table 8, the Day 1 visit of Part B (baseline) may occur on the same day as the Week 48 visit of Part A. If the patient rolls over within 7 days of the Week 48 visit, the Week 48 assessments will not be repeated at the beginning of Part B. Patients will provide informed consent before any Part B–specific assessments are performed.

Patients will remain blinded to their Part A treatment assignment (losmapimod or placebo) through completion of Part B. During Part B, all patients will receive 15 mg PO losmapimod tablets BID with food. Patients may continue to receive study drug in Part B for the duration of the study as specified in the visit schedule (Table 8) or until the study is discontinued by the sponsor. Any planned treatment interruptions (e.g., scheduled surgery) during Part B may be permitted on a case-by-case basis with approval from the Medical Monitor.

Part B will consist of in-person clinic visits at baseline (Week 48) and at Weeks [redacted]. After the [redacted] visit and for the remainder of the study, in-person clinic visits will occur [redacted]. All patients who complete or discontinue from treatment will return for a complete safety follow-up visit [redacted] days after the last dose of study drug and will complete a safety follow-up phone call [redacted] days after the last dose of study drug.

Safety and tolerability of long-term treatment with losmapimod will be evaluated based on the assessment of AEs, clinical laboratory tests, ECGs, vital signs, and physical examinations. Long-term efficacy [redacted]) will be evaluated as exploratory endpoints. The full schedule of assessments is provided in Table 8. Unscheduled visits may be performed if clinically indicated.

3.2. RATIONALE OF STUDY DESIGN

3.2.1. Rationale of Dose Selection

Losmapimod is a small molecule inhibitor of the p38α/β MAPK that specifically reduces DUX4 protein expression and its downstream transcriptional targets. 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 PO BID would provide drug concentrations in skeletal muscles sufficient to significantly inhibit p38α/β and reduce aberrant expression of DUX4 and DUX4-driven gene expression.

HSP27 is a phosphorylated substrate of p38α/β MAPK 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 pHSP27.

PK/PD modeling indicates that losmapimod dosed at 15 mg PO BID should result in 40% to 70% pHSP27 reduction (Barbour et al. 2013; Cheriyan et al. 2011; Mellion et al. 2021). Target engagement in the Phase 1 and Phase 2 studies confirm that there is a 40% to 70% reduction in pHSP27:total HSP27.

Fulcrum has shown that a 15 mg PO BID with food dosing regimen, as proposed, results in mean steady-state C_{min} and C_{max} values of approximately 30 ng/mL and 75 ng/mL, respectively. The 15 mg PO BID regimen maintains steady state losmapimod plasma concentrations above the minimal level of 30 ng/mL needed for robust target engagement. Importantly, at the proposed dose level of 15 mg PO BID, exposures in FSHD patients does not exceed those previously demonstrated to be safe in humans in multiple previous studies in healthy volunteers and various patient populations (Barbour et al. 2013; Cheriyan et al. 2011; Kools et al. 2021; Mellion et al. 2021; Pascoe et al. 2017; Tawil et al. 2021; Watz et al. 2014).

In Part A: Placebo-Controlled Treatment Period and in Part B: Open-Label Extension, losmapimod will be administered 15 mg PO BID with food.

3.2.2. Rationale of Study Design

Part A: Placebo-Controlled Treatment Period

This study is designed to demonstrate that treatment with losmapimod will slow the progression of disease and/or improve function in patients with FSHD. The study will evaluate the efficacy, safety, and tolerability of losmapimod. The placebo-controlled treatment period is a randomized design that includes an active treatment group and a placebo group (Section 3.1.1). The inclusion of a placebo group is necessary because there is clinical equipoise. 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 patients to study treatment.

The selection of study objectives and endpoints was informed by the Phase 2 study results. The primary objective of this study is to evaluate the efficacy of losmapimod for the treatment of

FSHD on disease progression assessed by RWS quantification of total relative surface area (RSA) Q1-Q5 with 500 g wrist weight, averaged over both arms relative to placebo. RWS is a sensitive and quantitative evaluation of function and is a relevant and suitable outcome measure to assess clinical efficacy. RWS can distinguish between healthy volunteers and people living with FSHD and can identify those patients more likely to decline over time. It is sensitive to change and quantitatively tracks progressive change in upper extremity (UE) function. Importantly, assessment of RWS (by measuring RSA) provides a functional clinical outcome that can track disability accumulation throughout a patient's lifespan. It is a reliable and sensitive clinical outcome assessment (COA) that characterizes not just the presence, but also the extent, of dysfunction, which strongly correlates with and predicts impact on important quality of life measures by providing not only an assessment of absolute change, but also a quantification of the change in the slope of disease progression over time.

RWS is a clinical outcome assessment that is sensitive to disease progression and responsive to treatment. This primary endpoint provides a robust representation of the effect of losmapimod on slowing of disease progression in FSHD. Selection of RWS is supported by findings from the ReDUX4 and OLS studies. For further details regarding RWS in clinical studies, refer to the current losmapimod Investigator's Brochure.

The secondary objectives were selected to inform interpretation and support clinical meaningfulness of the RWS as well as provide additional support for the efficacy of losmapimod to slow disease progression in FSHD. The patient reported outcome Quality of Life in Neurologic Disorders (Neuro-QoL) item bank "Upper Extremity function - fine motor, ADL" (Neuro-QoL UE) is a validated assessment that evaluates one's ability to carry out various activities involving digital, manual, and reach-related functions, ranging from fine motor to self-care (ADL). A prior study showed that there are moderate to strong correlations between the total score with an even slightly higher correlation with the 5 proximal- and shoulder-related items. Additionally, this study identified cut-off values for risk of dependence. Individuals with total RSA (Q1-Q4) values of less than 0.7 are more likely to be dependent in all 5 proximal and shoulder Neuro-QoL questions. An RSA value of 0.7 has a positive predictive value of 83% and negative predictive value of 100% (Hatch et al. 2020).

In Study FIS-001-2019, we observed that the RWS assessment was able to quantify meaningful change captured by PGIC. Looking across the scale, as the PGIC score increases we observe there was a directional and measurable association between change in PGIC and percent change in RSA. This demonstrates that PGIC-recognized improvement, stability or worsening was also captured in RWS assessments over this same time period.

The secondary endpoint to support efficacy includes assessment of change from baseline in the whole-body longitudinal composite MFI. The magnetic resonance imaging (MRI) technique to be used in this protocol is a standardized, objective, quantitative technique with automatic skeletal muscle segmentation for the 3-dimensional (3D) [redacted] volumes and [redacted] analyses via robust algorithms using Dixon imaging to measure the extent of skeletal muscle tissue replacement by fat in FSHD patients. MFI provides an assessment of fatty changes in functional muscle tissue, the most proximal target of pathology (Dahlqvist et al. 2020). MFI is

the fat fraction calculated within voxels with less than 50% fat (West et al. 2018). This measurement is a representation of the fat content in parts of the muscle that are not fat-replaced and is analogous to the use of magnetic resonance spectroscopy (Aisen and Chenevert 1989) to measure [redacted]. In ReDUX4, losmapimod preserved muscle structure, assessed by MFI, relative to placebo, which demonstrated increased MFI, over the course of 48 weeks; this assessment also showed moderate to strong cross-sectional correlations with RWS. For further details regarding the secondary endpoints, refer to the current losmapimod Investigator's Brochure.

The Sponsor will continue to expand and contribute to the understanding and evaluation of FSHD through selected exploratory endpoints and additional pre-specified analyses.

Additionally, a patient advisory board reviewed and provided feedback on the design of this study.

Part B: Open-Label Extension

The Part B open-label extension (Section 3.1.2) will allow patients to continue to receive losmapimod and will provide long-term safety and tolerability data.

4. PARTICIPANT SELECTION AND WITHDRAWAL CRITERIA

4.1. SELECTION OF STUDY PARTICIPANTS

Approximately 210 patients with genetically confirmed FSHD1 and 20 patients with genetically confirmed FSHD2 will be enrolled at approximately 36 sites in North America and Europe. Eligibility will be reviewed and documented by an appropriately qualified member of the Investigator's team before patients are enrolled. Patients will be assigned to study treatment only if they meet all the inclusion criteria and none of the exclusion criteria.

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

4.1.1. Part A: Placebo-Controlled Treatment Period

4.1.1.1. Inclusion Criteria

1. Patient will sign and date an informed consent form (ICF).
2. Patients will have a diagnosis of FSHD1 or FSHD2 verified by genetic testing (see Section 6.2.1).
   - Randomization will be stratified for FSHD1 to ensure that treatment allocation is balanced across FSHD repeat number categories (ie, 1 to 3 repeats versus 4 to 9 repeats).
   - Randomization will be stratified for FSHD2 to ensure that an equal number of patients will be allocated to treatment and placebo.
3. Patients will have a Clinical Severity Score of 2 to 4 (Ricci score; range 0 to 5) at screening. Patients who are wheelchair-dependent or dependent on walker or wheelchair for activities are not permitted to enroll in the study.
4. Patients with screening total RSA (Q1-Q4) without weight in the dominant UE assessed by RWS ≥ 0.2 and ≤ 0.7.
5. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
6. No contraindications to MRI.
7. Patients (male and female) will be between the ages of 18 and 65 years at the time of consent, inclusive.
   - A female patient is eligible to participate if she is of non-childbearing potential, defined as pre-menopausal females with a documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy; if she is postmenopausal, defined as no menses for 12 months without an alternative medical cause; OR

- If of child-bearing potential, she is using a highly effective method for avoidance of pregnancy for the duration of dosing and until 90 days after the last dose. For details regarding contraception requirements, refer to Section 5.5.1.1.
- Male patients must agree to use one of the contraception methods listed in Section 5.5.1. This criterion must be followed from the time of the first dose of study medication and until 90 days after the last dose of study drug.

4.1.1.2. Exclusion Criteria

1. 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 patient. This may include, but is not limited to, history of relevant drug or food allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology; 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 patients who are on drug(s) or supplements that may affect muscle function, as determined by the Investigator, or that are included in the list of drugs presented in Appendix 3: patients 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 the first study drug dose. Patients 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 (fever-free without the use of antipyretic agents for 24 hours). Once the febrile illness is fully resolved, the patient's baseline visit can be scheduled. The duration of the screening period in such cases can be extended to up to 35 days.
5. Known active opportunistic or life-threatening infections including HIV and hepatitis B or C.
6. Known active or inactive tuberculosis infection.
7. Current acute liver disease or chronic liver disease as defined by any of the following:
   - Current ALT $\geq 2 \times$ upper limit of normal (ULN) or total bilirubin $> 1.5 \times$ ULN (unless participant has Gilbert's syndrome characterized by the combination of total bilirubin $< 3 \times$ ULN, direct bilirubin within the normal range and normal ALT and AST, or the presence of mutations in the UDP-glucuronosyltransferase 1 gene, indicative of Gilbert's syndrome).
   - Positive for hepatitis B surface antigen.

- Positive for hepatitis C antibody unless additional testing for hepatitis C viral RNA is negative, ALT is < 2 × ULN and total bilirubin is ≤ 1.5 × ULN, indicating inactive/resolved hepatitis C infection.

8. Known severe renal impairment (defined as a glomerular filtration rate of < 30 mL/min/1.73 m^2).
9. Standard 12-lead ECG demonstrating QTcF >450 msec for male patients and QTcF >470 msec for female patients 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 patient'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 patient's participation in the study.
11. Male patients with a female partner who is planning to become pregnant during the study or within 90 days after the last study drug dose.
12. Concomitant use of cytotoxic chemotherapy for cancer or known ongoing or anticipated use of chronic severe immunosuppressive agents.
13. Positive pregnancy test, known to be pregnant or lactating, or planning to become pregnant during study drug administration and until 90 days after last dose.
14. Any current mental condition (psychiatric disorder, senility or dementia) that may affect study compliance or prevent understanding of the aims, investigational procedures, or possible consequences of the study.
15. Patient has any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy, or other gastrointestinal tract surgery, except appendectomy).
16. History of alcohol, analgesic/opioid, and/or illicit drug abuse, as defined by the 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. Use of CBD/THC is permitted.
17. 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 study of an investigational device.
18. Current or anticipated participation in a natural history study. Previous participation is allowed but patients cannot continue after enrollment in Study 1821-FSH-301.
19. Known hypersensitivity or intolerance to losmapimod or any of its excipients.
20. Previous participation in a Fulcrum-sponsored FSHD losmapimod study (FIS-001-2019 or FIS-002-2019).
21. Anticipated inability to comply with any study procedures, including participation in study visits according to the visit schedule through 48 weeks.
22. Abnormal laboratory results indicative of any significant medical disease that, in the opinion of the Investigator, would preclude the patient's participation in the study.

23. Patient, or close relative of the patient, 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.
24. Patient is vulnerable (i.e., deprived of freedom), including inmates of psychiatric wards and prison or state institutions, patients with commitments to an institution, or a patient who is detained or committed to an institution by a law court or by legal authorities.
25. ***For Italy only:*** Vaccination with a live attenuated vaccine within 6 weeks prior to randomization until the safety follow-up visit (see Appendix 2 for all country-specific differences)

4.1.2. Part B: Open-Label Extension

4.1.2.1. Inclusion Criteria

1. Patient completed 48 weeks of treatment during Part A.
2. Patient will sign and date an ICF.
3. Patient is willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
4. Patient agrees to the following methods of contraception:
   - Female patients of childbearing potential agree to continue using a highly effective method for avoidance of pregnancy for the duration of dosing and until 90 days after the last dose. For details regarding contraception requirements, refer to Section 5.5.1.
   - Male patients must agree to use one of the contraception methods listed in Section 5.5.1. This criterion must be followed from the time of the first dose of study medication and until 90 days after the last dose of study drug.

4.1.2.2. Exclusion Criteria

1. 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 patient.
2. Male patients with a female partner who is planning to become pregnant during the study or within 90 days after the last study drug dose.
3. Anticipated inability to comply with any study procedures, including participation in study visits.

4.2. RESCREENING OF STUDY PARTICIPANTS

Participants who are not enrolled within the screening period will be considered screen failures. Rescreening of participants for Part A is permitted with approval of the Medical Monitor. Participants can only be rescreened once and must be reconsented at the time of rescreening. Rescreened participants will be assigned the same screening number assigned at initial screening.

Rescreening of participants is not permitted if the reason for screen failure includes any of the following:

- Did not have a Clinical Severity Score of 2 to 4 (Ricci score; range 0 to 5) at screening (failure to meet inclusion criterion 3)
- Did not have a screening total RSA (Q1-Q4) without weight in the dominant UE assessed by RWS ≥ 0.2 and ≤ 0.7 (failure to meet inclusion criterion 4)
- Meets any of the exclusion criteria

Participants who are rescreened may not be required to repeat the MRI imaging if performed less than 60 days prior to study treatment administration.

Rescreening is not applicable for the Open-Label Extension (Part B).

4.3. WITHDRAWAL OF PATIENTS FROM STUDY TREATMENT AND/OR THE STUDY

4.3.1. Reasons for Withdrawal/Discontinuation

Patients 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 patients in the study, including if a patient decides to prematurely discontinue study treatment (see Section 4.3.2). The reasons for a patient not completing the study will be recorded. A patient may be withdrawn from the study drug for any of the following reasons:

1. The patient does not meet the protocol inclusion or exclusion criteria.
2. The patient is noncompliant with the protocol.
3. The patient has laboratory safety results that reveal clinically significant hematological or biochemical changes from the baseline values.
4. The patient has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.
5. The patient is lost to follow-up.
6. Other reasons (eg, development of contraindications of use of study drug).

A patient must be withdrawn from the study drug for any of the following reasons:

1. The patient has a serious or intolerable AE(s) that, in the Investigator's opinion, requires withdrawal from the study.
2. The patient withdraws consent, or the Investigator or Sponsor decides to discontinue the patient's participation in the study.
3. The patient becomes pregnant.

The Investigator will also withdraw a patient if Fulcrum terminates the study. Upon occurrence of a serious or intolerable AE, the Investigator will confer with the Sponsor. If a patient is

discontinued because of an AE, the event must continue to be followed to satisfactory resolution as described in Section 7.4. Any patient may withdraw his or her consent at any time.

4.3.2. Handling of Withdrawals

Patients are free to withdraw from the study or study treatment at any time upon request. Patient participation in the study may be stopped at any time at the discretion of the Investigator or at the request of the Sponsor.

Patients who discontinue study treatment or active participation in the study will no longer receive study drug. When a patient 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 patient prematurely discontinues study treatment, they will be encouraged to remain in the study and continue with all other aspects of the study. If appropriate, patients can restart study drug at the Investigator's discretion (depending on the reason for discontinuation of study treatment), after approval from the Sponsor.

If a patient 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 patient 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 [redacted] days and a safety phone screen [redacted] 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.

Patients 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 patients being lost to follow-up, at least 3 documented attempts to contact the patient must be made.

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

4.3.3. Replacements

Patients who withdraw or discontinue will not be replaced.

5. STUDY TREATMENTS

5.1. PART A: PLACEBO-CONTROLLED TREATMENT PERIOD

5.1.1. Method of Assigning Participants to Treatment Groups

Patients 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) and by FSHD Type (FSHD1 versus FSHD2).

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 the latest version of SAS software (SAS Institute, Cary, NC) for IRT, which will link sequential patient randomization numbers to treatment codes. The randomization will use an appropriate block size, which will not be revealed.

Patients can be randomized only once.

5.1.2. Treatments Administered

Study drug tablets (losmapimod or placebo) will be dispensed to patients at the visits detailed in Table 7.

During the 48-week placebo-controlled treatment period, patients will receive 15 mg losmapimod PO BID or placebo BID with food.

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

On visit days during which blood collection will occur for PK assessment (see Table 7), patients should wait to take their dose in the clinic.

5.2. PART B: OPEN-LABEL EXTENSION

5.2.1. Treatments Administered

Losmapimod will be dispensed to patients at the visits detailed in Table 8. Patients are not to receive study drug until all assessments for Part A have been completed.

While on study, patients will receive 15 mg losmapimod tablets PO BID with food.

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

Any planned treatment interruptions (e.g., scheduled surgery) during Part B may be permitted on a case-by-case basis with approval from the Medical Monitor.

5.3. IDENTITY OF INVESTIGATIONAL PRODUCT

Losmapimod tablets for oral administration are available as [redacted] tablets containing 15 mg of losmapimod as the [redacted] free base. Losmapimod tablets also contain the inactive excipients [redacted]

Placebo tablets (Part A only) are identical in appearance to losmapimod and are manufactured using commonly used and recognized tablet excipients that are also used in the active tablets.

An IRT system will be used to ensure that the study site is provided with adequate supplies of blinded losmapimod and placebo (Part A only) or losmapimod (Part B only) and that no expired tablets will be dispensed to study patients.

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.

Each dispensation will contain a blinded (Part A only) or labeled (Part B only) dosage for 1 patient with a sufficient quantity to cover until the next scheduled visit plus additional tablets to cover the visit window. If needed, patients may be provided additional study drug via a courier service, as applicable. Study drug will be packaged and labeled in accordance with regulatory requirements. In Part A only, study drug will be packaged and labeled in a manner to retain the study blind.

Further details of study drug packaging, labeling, and distribution of the study medication will be provided in the Pharmacy Manual. For information on proper storage of the study drug, refer to the current losmapimod Investigator's Brochure or Pharmacy Manual.

5.4.2. Study Drug Accountability

During the study, each patient 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, patients may be provided additional study drug via a courier service, as applicable. At the next scheduled clinic visit, patients must return their bottles of study drug 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 patient 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.

5.5. LIFESTYLE RESTRICTIONS

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.

For the screening visit in Part A and the baseline visit in Part B, patients will be required to fast for at least 4 hours prior to laboratory blood samples being taken.

5.5.1. Contraception Requirements

A female patient of childbearing potential is eligible to participate if she is using or willing to use a highly effective method for avoidance of pregnancy for the duration of dosing and until [redacted] after the last dose of study drug.

Women of childbearing potential and male patients with female partners of childbearing potential must agree to use one of the contraception methods listed in Section 5.5.1.1. This criterion must be followed from the time of the first dose of study medication until [redacted] after the last dose of study drug.

5.5.1.1. Highly Effective Methods for Avoiding Pregnancy in Females of Childbearing Potential

The following is the all-inclusive list of highly effective methods for avoiding pregnancy (ie, 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 2007):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

- Vasectomized partner, provided that the partner is the sole sexual partner of the WOCBP trial patient and that the vasectomized partner has received medical assessment of the surgical success
- Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.)

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action), male or female condom with or without spermicide, and cap, diaphragm or sponge with spermicide are not considered as highly effective. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are not considered highly effective, birth control methods.

5.6. BLINDING

5.6.1. Part A: Placebo-Controlled Treatment Period

The placebo-controlled treatment period will be performed in a double-blind fashion. The Investigator, study staff, patients, and monitor will remain blinded to patient-level treatment assignment until study closure. The Sponsor and/or its designee will remain blinded to the treatment until after all patients have completed Part A of the study and the database has been locked for statistical analyses, after which time they will be unblinded.

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 patient's treatment assignment will not be broken until the end of the study unless medical treatment of the patient depends on knowing the study treatment the patient received. In the event that the blind needs to be broken because of a medical emergency, the Investigator may unblind an individual patient'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 patient.

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.

Patients who continue to Part B will remain blinded to their Part A treatment condition through completion of Part B.

5.6.2. Part B: Open-Label Extension

Neither patients nor study staff will be unblinded to Part A treatment condition. Patients will not be blinded in Part B.

5.7. TREATMENT COMPLIANCE

Patient compliance will be monitored by tablet counts in the clinic. In addition, patient diaries may be used 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 patients 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 visits will be recorded in the patient'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 patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient 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 restricted or prohibited in this study:

- Vaccination with a live attenuated vaccine from 6 weeks prior to randomization until the safety follow-up visits.
- Patients who are on drug(s) or supplements that may affect muscle function, as determined by the Investigator, or that are included in the list of drugs presented in Appendix 3 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. Treatment with a statin can be initiated during the study if it is medically required. In this case, preference should be given to hydrophilic statins (e.g., pravastatin, rosuvastatin, fluvastatin) over lipophilic statins (e.g., simvastatin, atorvastatin, lovastatin.) Particular attention should be paid to creatine phosphokinase (already part of the laboratory safety monitoring) in patients who start treatment with a statin during the study.

Subjects who take concomitant medications that are OAT1/OAT3 substrates and have a narrow therapeutic index may need to have their blood levels monitored for levels of the OAT1/OAT3 substrates after losmapimod dosing (see Appendix 4).

6. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential patients will sign an ICF. Patients will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the patient. The Investigator or designee will also sign the ICF.

Patients continuing to Part B will sign and date an ICF before performing any study procedures for Part B of this protocol. Patient numbers will be maintained from Part A.

Study visits and the timing of assessments for the screening period or the treatment and follow-up periods are detailed in the schedules of assessments (Table 7 and Table 8).

6.1. EFFICACY AND SAFETY ASSESSMENTS

Efficacy assessments will be performed during Part A and select efficacy assessments will also be performed during Part B [redacted] Select safety assessments (Eliciting and Documenting Adverse Events, Laboratory Analyses, Vital Signs, Physical Examinations, Twelve-Lead Electrocardiograms) will also be performed during Part B.

6.1.1. Reachable Workspace

The RWS Microsoft Kinect-based movement sensor system will be used at the visits noted in Table 7 and Table 8 to determine the patient's 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 UE 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). Moderately impaired individuals with baseline RSA values between 0.20 and 0.70 (out of 1.0, for quadrants Q1-Q4) were more likely to show predictable declines over time with an annualized total RSA loss of 2.74% (P=0.047) (Hatch, Chan, et al. 2019). This study includes an inclusion criteria of screening total RSA (Q1-4) without weight between 0.20 and 0.70 to enrich for a population that is likely to change over a 1-year period.

During the evaluation, patients 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 video monitor. The evaluation will be performed with and without weights and on both the dominant and non-dominant 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 body side's RWS envelope will be divided into 5 quintants, 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 patients (Han et al. 2015).

Instructions for equipment assembly, setup, testing, and site certification; a manual of operation; and a quick reference guide will be described in an 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.

6.1.2. Skeletal Muscle Magnetic Resonance Imaging

Whole-body Dixon MRI for MFF, LMV, and MFI will be performed at the visits noted in Table 7. Patients will be screened for any contraindications to MRI as per clinic standard practice. Patients can travel for MRI if needed, but the use of a study-approved MRI scanner should be consistent during the trial.

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

6.1.3. Hand-Held Dynamometry

Dynamometry will be performed at the visits noted in Table 7 and Table 8. Quantitative isometric dynamometry (hand-held dynamometer) will be used to assess the skeletal muscle strength. 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.

6.1.4. Eliciting and Documenting Adverse Events

AEs and SAEs will be assessed from the time the patient signs the ICF (for Part A and Part B) up to the last study visit, or up to 30 days after the patient has stopped study treatment, whichever is later, and SAEs must be reported to the Sponsor (or designee) by the Investigator without undue delay, but not later than 24 hours of obtaining knowledge of its occurrence (as described in Section 7.3.2). Any SAEs experienced after this period should be reported to the Sponsor (or designee) only if the Investigator suspects a causal relationship to the study drug.

At every study visit, patients 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 patient 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 patient safety will be documented on the AE page in the eCRF.

AEs that occur during Part A will continue to be monitored until they are resolved or the patient is lost to follow-up. For those patients who rollover to Part B, ongoing AEs will continue to be monitored during Part B.

6.1.5. Laboratory Analyses

Samples for serum chemistry, hematology, and urinalysis will be collected at the time points specified in Table 7 and Table 8. Processing, storage, and shipping procedures for all clinical laboratory samples are provided in a laboratory manual. Sample collection details are presented in Section 6.2.14. For the screening visit in Part A and the baseline visit in Part B, patients 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) 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 patient'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.

If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). In most cases, clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with clinically significantly abnormal results during participation in the study or within 7 days after the last dose of investigational product should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.

All protocol-required laboratory assessments (Table 6) must be conducted in accordance with the laboratory manual and the Schedules of Assessments. If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the eCRF.

Blood and other biological samples will be collected for the clinical laboratory tests in Table 6.

Table 6: Protocol-Required Laboratory Tests

Serum chemistry	Glucose, sodium, potassium, calcium, inorganic phosphate, total protein, albumin, blood urea nitrogen, creatinine, total bilirubin, direct bilirubin*, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, creatine phosphokinase *Direct bilirubin will only be tested in instances where total bilirubin is elevated. Direct bilirubin will be measured automatically by the central lab on the sample where total bilirubin is elevated. An additional sample is not required to be collected.

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 Differential blood counts, including basophils, eosinophils, neutrophils, lymphocytes, and monocytes
Urinalysis	Leukocytes, blood, nitrite, protein, urobilinogen, bilirubin, pH, specific gravity, ketones, glucose If there is a clinically significant positive result, urine will be sent for microscopy and/or culture.
Pregnancy	Serum beta human chorionic gonadotropin (all female patients of child-bearing potential), serum follicle-stimulating hormone (suspected postmenopausal female patients only [defined in Section 5.5.1]), urine pregnancy test (as required by local regulations)
Serology testing	Hepatitis B surface antigen, hepatitis C virus antibody, HIV-1/HIV-2 antibodies; tuberculosis will also be tested locally by QuantiFERON-TB Gold at ***Italian sites only*** (Appendix 2). Patients with a known history of hepatitis infection must be tested to confirm active infection. All patients will be tested for hepatitis B surface antigen and, if positive, will not be allowed to enroll in the study. All patients will also be tested for hepatitis C antibody and, if positive, should be tested for viral RNA. If the viral RNA test is negative, indicating inactive/resolved hepatitis C infection, then the patient can enroll in the study as long as their liver panel is within range of the inclusion and exclusion criteria (Section 4.1). If the viral RNA test is positive, indicating active viral hepatitis C, the patient will not be allowed to enroll in the study.
Urine drug screen	Cocaine, amphetamines, opiates (morphine), benzodiazepines, and cannabinoids Use of CBD/THC is permitted.

6.1.6. 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.

6.1.7. Vital Signs

Vital sign (pulse rate, respiration rate, blood pressure, and temperature) assessments will be performed at the time points specified in Table 7 and Table 8. Assessments will be taken after the patient has been seated or recumbent for at least 5 minutes and before any 12-lead ECG assessment or blood sampling is performed.

6.1.8. Physical Examinations

Physical examinations will be performed at the time points specified in Table 7 and Table 8.

Physical examinations at screening and safety follow-up 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 musculoskeletal 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 7 and Table 8.

Height (cm) will be recorded and body mass index (BMI) calculated at screening: 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.

6.1.9. Twelve-Lead Electrocardiograms

Single 12-lead ECGs will be performed at the time points specified in Table 7 and Table 8. The primary ECG tracings will be locally read by the Investigator.

Twelve-lead ECGs will be performed after patients 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 patient's eligibility for the study.

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

6.2. Other Assessments

Assessments, described below, will be performed in Part A. [redacted] will also be performed in Part B.

6.2.1. Genetic Confirmation of FSHD

Genetic testing for FSHD 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 patients 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. Patients with >9 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.

FSHD2 (5% of FSHD) is also the result of hypomethylation of the D4Z4 region of chromosome 4q35. However, in this case, hypomethylation is not associated with a D4Z4 contraction. About 80% of patients with FSHD2 have a separate mutation in SMCHD1 (structural maintenance of chromosomes flexible hinge domain 1), a hypermethylating enzyme with a normal role in X chromosome inactivation. Mutations in SMCHD1 (and presumably other yet-to-be-defined loci) result in hypomethylation of the D4Z4 region, which leads to DUX4 transcript expression.

Genetic confirmation must be obtained before the patient is randomized. Genetic confirmation can come from previous testing, if verified with appropriate documentation from an accredited laboratory. If genetic testing is necessary, the [redacted] screening window and activities will not start until the results are obtained and verified by the Principal Investigator (PI).

Due to the stable transmission of repeat sizes within families, patients with a clinical diagnosis of FSHD who have a first-degree relative with a genetically confirmed diagnosis of FSHD 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 [redacted] screening window will not start until the results are obtained and verified by the PI.

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

[redacted]

[redacted]

6.2.5. Patient Global Impression of Change

The PGIC will be performed at the visits noted in Table 7 to obtain the patients' rating of overall improvement. Patients will be asked to rate their overall status at the start of the study on a scale from 1 (very much improved) to 7 (very much worse). The PGIC scale has been validated in several other indications and is recommended by the FDA for use as a meaningful measure of within-patient change (Gautschi et al. 2016; Chan et al. 2020).

[redacted]

6.2.8. Neuro-QoL Upper Extremity Patient Reported Outcome

The Neuro-QoL UE function measure will be performed at the visits noted in Table 7 to obtain the patients' self-reported rating of quality of life related to upper extremity function (Cella et al. 2012). The Neuro-QoL UE measures ability across fine motor and activities of daily living involving digital, manual and reach-related function and self-care. Responses are divided into 5 ordinal levels (1 = unable to do, 2 = with much difficulty, 3 = with some difficulty, 4 = with a little difficulty, 5 = without any difficulty).

6.2.12. Qualitative Exit Interview

A qualitative exit interview will be conducted in a subset of the patient population at Week 48 as noted in Table 7 to assess the patient's experience during the study.

The purpose of the qualitative exit interview is to capture study participants' subjective experience with treatment, with study participation, and to gather insights to inform interpretation and clinical meaningfulness of the primary endpoint, RWS. Interview topics will include their experience with the disease, associated symptoms, symptom impact/burden and interference on the patient's life, patient perceptions of meaningful changes during the double-blind treatment period, and to explore patient experience with treatment.

The interview will consist of a 1-time telephone interview, lasting approximately 60 minutes. Interviews will be conducted by trained interviewers using a semi-structured interview guide and will be conducted within 7 days of completing the Week 48 visit. Neither failure to complete the interview nor completion outside of the targeted 7-day window will constitute a protocol deviation. All patients enrolling in the study will be invited to participate in the qualitative interview until the targeted subsample of at least 60 patients has been filled. This sample is large enough to accomplish objectives and reasonable for achieving a mix of patients from each treatment arm as well as inclusion of a small number of the patients who will be enrolled with FSHD2. If more study participants are consented than required, the larger pool of interview candidates will be used to select a more diverse sample across countries and/or regions.

Patients will be invited to participate in the qualitative interview substudy as part of the main consenting process at the beginning of the study. Patients already enrolled and randomized at the time of this amendment can be invited later in their treatment period and can re-sign the amended consent form to document their willingness to participate in the substudy. Patients who agree to

participate in the qualitative exit interviews will also be asked to complete a contact information transfer form during the consent process, which gives the clinic site staff permission to provide their contact information to the interview team and allows the interviewers in each country to contact the patients directly to schedule their interview at a convenient date and time. Additionally, the clinic site staff will obtain verbal consent no later than the Week 48 visit (Visit 6) to confirm that the patients are still willing to participate in the exit interview sub-study. Fulcrum has engaged Evidera Patient Centered Research to support the study by providing skilled interview services. Before conducting the interview, Evidera will confirm with the site that the study participant has completed the necessary study procedures for the Week 48 visit to ensure compliance with the exit interview protocol procedures. Evidera personnel are not authorized to contact patients after they complete their exit interview.

Any unfavorable changes or AEs reported by the patients during the conduct of the exit interviews will be communicated to the Investigator or designee by the interviewer within 24 hours (or 1 business day). The Investigator will be responsible for reporting all AEs and SAEs based upon appropriate medical judgement in accordance with this protocol.

6.2.14. Sample Collections

Processing, storage, and shipping procedures for all clinical laboratory samples are provided in the laboratory manual.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The Investigator is responsible for reporting all AEs that are observed or reported during the study regardless of their relationship to study drug or their clinical significance. All AEs from the time of Part A informed consent and assent, if applicable, through the last follow-up visit in Part A or Part B (if applicable) will be recorded in each enrolled patient's eCRF.

7.1. DEFINITIONS

7.1.1. Definition of Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (International Council for Harmonisation [ICH]-E2A). Conditions that were already present at the time of informed consent should be recorded on the Medical History page of the eCRF. Adverse event monitoring should be continued for at least 30 days after the last dose of study drug.

Disease progression should not be regarded or reported as an AE itself, unless it is associated with a separate AE.

Patients will be instructed to contact the Investigator at any time after randomization if any symptoms develop.

7.1.2. Definition of Treatment-Emergent Adverse Event

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

7.1.3. Definition of Serious Adverse Event

An SAE is defined as any event that meets 1 of the following criteria:

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

7.1.3.1. Definition of Terms

Life-threatening: Life-threatening means that the patient was at immediate risk of death from the event as it occurred; ie, it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring in-patient hospitalization or prolongation of an existing hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either “serious” or “non-serious” according to the usual criteria.

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

7.1.4. Definition of Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is defined as an untoward and unintended response to a study drug, which is not listed in the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

7.1.5. Reference Safety Information

No serious adverse reactions are considered expected by the Sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs in the “Cumulative summary tabulations of serious adverse reactions” section of the current Investigator’s Brochure for the investigational medical product.

7.2. CLASSIFICATION OF ADVERSE EVENTS

Each AE, whether non-serious or serious, will be classified by the Investigator according to the following rules and definitions.

7.2.1. Assessment of Intensity/Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient'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.

NOTE: Severity is not the same as "seriousness." The Investigator will assess the severity of all AEs according to the appropriate categories.

7.2.2. Assessment of Causality

For each AE, the Investigator will determine whether there is a reasonable likelihood that the AE may have been caused by study drug according to the categories below. 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 patient's clinical condition, intercurrent illness, or concomitant drugs administered to the patient, 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, 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.

7.2.3. Outcome

The Investigator will provide information regarding the patient outcome of each AE. Outcome categories are as follows: Recovered, Recovered with Sequela, Not Recovered, Fatal, and Unknown.

7.2.4. Action Taken

The Investigator will provide information regarding the action taken with respect to the study treatment in response to the AE. Categories for action taken include:

- Drug withdrawn
- Dose not changed
- Unknown
- Not applicable

7.3. REPORTING GUIDELINES

7.3.1. 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 the Investigator's assessment) must also be reported. All AEs must continue to be followed to satisfactory resolution. The latest version of Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient 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.

Reporting for AESIs is described in Section 7.5.

7.3.2. Reporting Serious Adverse Events

The Investigator (or designee) must report the SAE to the Sponsor or designee without undue delay but no later than 24 hours of obtaining knowledge via the paper SAE Intake Form.

This form should be completed, scanned, and emailed as a PDF attachment to clinicalsafety@propharmagroup.com within 24 hours of SAE awareness. Alternately, the report may be faxed to +1 (866) 681-1063.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an investigational product under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information from the Sponsor will review and then file it as appropriate and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.3. Expectedness of an Adverse Event

The expectedness of all AEs will be determined according to the current version of the losmapimod Investigator's Brochure.

7.3.4. Reporting Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions will be handled by the Sponsor or designee and the Investigator and reported within the required timelines in an unblinded fashion to Regulatory Authorities and the IRB/IEC per the requirements of the concerned Regulatory Authorities. SUSARs will also be reported in a blinded fashion to study investigators. Investigators may request that SUSARs be unblinded.

7.4. ADVERSE EVENT FOLLOW-UP

All AEs will be followed until the resolution of AE, completion of the patient's study participation, or study termination, whichever occurs first.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

7.5. 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 is appropriate. If an AE or the abnormality is an AESI, the event should be reported on an SAE form, regardless of seriousness, and captured in the safety database. Non-serious AESIs will not be reported to the Regulatory Authorities unless required.

Adverse events of special interest for this study include liver tests that meet the criteria for potential drug-induced liver injury, in accordance with the US 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 ALT or aspartate aminotransferase 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 patients 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 the event until resolution. These steps include, but are not limited to:

- Making every reasonable attempt to have the patient return to the clinic within 24 hours for repeat liver enzyme 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 patient is asymptomatic.
- Obtaining viral hepatitis serology.
- Considering liver imaging and/or hepatology consultation.

7.6. ADVERSE EVENTS OF SIGNIFICANCE

If an AE of significance occurs (eg, dose-limiting toxicity AE), the event should be reported on an SAE form, regardless of seriousness, and captured in the safety database. Non-serious AEs of significance will not be reported to the Regulatory Authorities.

7.7. CLINICAL LABORATORY CHANGES

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, vital sign measurements), including those that worsen from baseline (i.e., prior to first dose) and are felt to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded 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.

7.8. SPECIAL SITUATIONS

7.8.1. Overdose

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved losmapimod) that meets SAE criteria (defined in Section 7.1.3) must be communicated to the Sponsor or a specified designee within 24 hours. Overdose with or without associated signs or symptoms must be reported in the AE eCRF. Any signs or symptoms associated with an overdose must also be reported as AEs. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered. No specific antidote for losmapimod is known. In case of overdose, patients should be observed and be provided with a supportive standard of care.

7.8.2. Death

Events that result in death should be recorded and reported on the appropriate eCRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Sponsor or designee's Pharmacovigilance.

7.8.3. Pregnancy

Pregnancies occurring in patients enrolled in a study or in a female partner of a male patient must be reported and followed to outcome. If a female patient inadvertently becomes pregnant while on study treatment, the patient will immediately be removed from the study.

The Investigator should complete the Pregnancy Report Form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Pregnancy Report Form and SAE report form should be completed.

The site will follow-up with the patient until the pregnancy has been completed or terminated. The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. The Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome. If an SAE occurred, then the SAE form must be completed and submitted as well.

In the event the pregnancy outcome occurs following the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor (or designee) within 24 hours after

the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs (per SAE reporting guidelines).

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions, but should be reported to the Sponsor. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

7.8.4. Medication Error

In case of medication errors, patients should be observed and be provided with a supportive standard of care.

Medication errors should be documented as protocol deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list of symptoms) or asymptomatic and the event accidental or intentional.

Dosing detail should be captured on the dosing CRF. If the patient takes a dose of study drug that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE(s) and be reported per Section 7.3.1.

7.8.5. Unblinding Due to Medical Emergency

Any unblinding in Part A should be done only in an emergency that requires the investigational drug be identified for the welfare of the patient. Fulcrum will be notified immediately, and a full, written description explanation will be provided if the blind is broken. Before the investigational drug is unblinded, every attempt should be made to discuss the case with the Investigator. Breaking the code at the study site/center will immediately disqualify the patient from further participation in the study.

For IRT Unblinding:

In an emergency, the PI can obtain the treatment assignment of any patient at his or her study site/center through the IRT. In an emergency, the PI will access the IRT to break the blind.

8. INVESTIGATIONAL PRODUCT COMPLAINTS

8.1. DEFINITION OF INVESTIGATIONAL PRODUCT COMPLAINTS

An Investigational Product Complaint (IPC) means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug after distribution for investigational use. Examples of possible IPCs can be reviewed in the associated Pharmacy Manual.

All product complaints associated with the material packaged, labeled, and released by the Sponsor or its designee will be reported.

The Investigator or his/her designee is responsible for reporting a complete description of the product complaint and any AEs associated via the reporting form or other written communication to Fulcrum.

8.2. REPORTING OF INVESTIGATIONAL PRODUCT COMPLAINTS

IPCs must be reported within 24 hours and details fully documented on the reporting form provided within the Study 1821-FSH-301 Pharmacy Manual. The reporting process is detailed within the Study 1821-FSH-301 Pharmacy Manual.

9. STATISTICAL CONSIDERATIONS

Details regarding the statistical methods and definitions will be provided in statistical analysis plans (SAPs). Separate SAPs will be prepared for Part A and Part B. Any deviations from the SAPs are to be justified in the clinical study report. Statistical analysis will be performed using the latest version of SAS software (SAS Institute, Cary, NC) or other validated software.

9.1. PART A: PLACEBO-CONTROLLED TREATMENT PERIOD

Primary Part A analysis will be conducted when the last patient has completed the [redacted] safety follow-up phone call or 48 weeks of treatment (for those who rollover into Part B). For details of the interim analyses, see Section 9.3.

9.1.1. Estimands and Intercurrent Events

The estimand of the primary analysis is the mean difference of the change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 between treatment groups in the full analysis set (FAS) (as per the ICH E9 (R1)). The FAS will consist of all patients with FSHD1 and FSHD2 who are randomized and receive at least one dose of study drug in the placebo-controlled treatment period. All observed data will be included in the primary analysis, including data collected after intercurrent events (as described in ICH E9 (R1) Addendum 2017), i.e., treatment discontinuation or a change in concomitant use of FSHD symptomatic medication. The change from baseline in average total RSA Q1-Q5 with 500 g wrist weight will be summarized by treatment group at each post-baseline visit. A mixed-effects model for repeated measures (MMRM) will be used as the primary analysis to analyze change from baseline in average total RSA Q1-Q5 with 500 g wrist weight, with terms for treatment group, visit, treatment group by visit interaction, baseline value, baseline value by visit interaction, region, and FSHD repeat number category, where appropriate. An unstructured covariance matrix will be used to model the correlations between repeated measurements within each patient. If the unstructured covariance matrix results in a lack of convergence, the first-order autoregressive covariance structure followed by the compound symmetric covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. In the primary analysis, missing data are assumed to be missing at random (Rubin 1976).

9.1.2. Statistical Hypothesis

The primary endpoint is the absolute change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48.

The null hypothesis for the primary endpoint is that the mean change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 is the same for the 2 treatment groups.

The alternative hypothesis for the primary endpoint is that the mean changes from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 are different between the 2 treatment groups.

9.1.3. Sample Size Determination

The target population for this clinical trial is patients with FSHD1 and FSHD2. The clinical trial will reflect the current epidemiologic information about FSHD, with patients with FSHD1 making up approximately 95% of the study population and the other 5% being people living with FSHD2. However, all studies thus far have been conducted with FSHD1 patients; therefore, this calculation was based on that population. Additional FSHD2 patients will be enrolled to explore safety and efficacy in this subgroup.

Assuming the within-group SD of change is 0.08 and that 10% of the study population has missing Week 48 data, a sample size of 210 patients with FSHD1 (105 patients per group) will be needed to provide at least 95% power with a 2-sided test at 0.05 significance level to detect a difference of 0.05 between losmapimod and placebo in change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48. An additional approximately 20 patients with FSHD2 will be recruited. The primary analysis will include patients with FSHD1 and FSHD2.

9.1.4. Analysis Sets

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

Full analysis set: The FAS will consist of all patients with FSHD1 and FSHD2 who are randomized and receive at least 1 dose of study drug in the placebo-controlled treatment period. All analyses using the FAS will group patients according to randomized treatment.

Safety analysis set: The safety analysis set will consist of all patients who receive any study drug in the placebo-controlled treatment period. All analyses using the safety analysis set will group patients according to treatment actually received.

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

9.1.5. Description of Subgroups to Be Analyzed

Any planned subgroup analyses will be described in the SAP for Part A. Subgroups will include a subgroup of patients with FSHD2 and subgroups of region, sex, and age.

9.1.6. Statistical Analysis Methodology

Details of the statistical analyses, methods, and data conventions will be described in the SAP for Part A.

9.1.6.1. General Considerations

Continuous variables will be summarized using the mean, standard deviation, standard error, median, first quartile, third quartile, minimum value, and maximum value. Categorical variables

will be summarized using frequency counts and percentages. Data will be presented in data listings.

All statistical tests will be 2-sided and performed using a 0.05 significance level, unless otherwise specified.

9.1.6.2. Overview of Statistical Methods: Estimation of Estimands and Sensitivity Analyses

See Section 9.1.1 for the estimand of the primary endpoint. Sensitivity analysis of the primary and selected secondary endpoints will be described in the SAP for Part A.

9.1.6.3. Analysis of Primary Endpoint

The primary endpoint of the placebo-controlled treatment period is the change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48. An MMRM will be used to analyze the primary endpoint, with the change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at each post-baseline visit as the dependent variable. The model will include terms for treatment group, visit, treatment group by visit interaction, baseline value, baseline value by visit interaction, region, and FSHD repeat number category, where appropriate. An unstructured covariance matrix will be used to model the correlations between repeated measurements within each patient. If the unstructured covariance matrix results in a lack of convergence, the first-order autoregressive covariance structure followed by the compound symmetric covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Least squares (LS) mean, standard error, and 95% CI 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 primary endpoint of absolute change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 will be formally tested only during the final analysis when all patients complete Part A study participation. All available data will be used.

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

In addition, a linear mixed-effects model (LME) will be used to analyze data on average total RSA Q1-Q5 with 500 g wrist weight over the placebo-controlled treatment period to estimate the slope of trend line and % change/year for each treatment group, and differences of estimated slopes and % changes/year between treatment groups.

9.1.6.4. Analysis of Secondary Efficacy Endpoints

Secondary endpoints (detailed in Section 2.1.2) will be summarized using descriptive statistics.

Continuous endpoints with multiple post-baseline assessments will be analyzed using an MMRM model analogous to the one used for the primary analysis of the primary endpoint based on the FAS. They will also be analyzed using an LME model analogous to the linear trend analysis in Section 9.1.6.3 based on the FAS, where appropriate. Relative changes from baseline will be analyzed using the Wilcoxon rank-sum test, stratified by the FSHD repeat number category. The Hodges-Lehmann estimate of the associated treatment difference and asymptotic nonparametric

95% confidence interval will be computed. For all patients, changes in measurements will be calculated relative to measurements obtained at baseline.

Further details of these endpoints and analyses are presented in Section 2.1.2 and the SAP for Part A.

9.1.6.6. Pharmacokinetic Analyses

Plasma PK concentrations at each time point for losmapimod 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.

The individual and mean plasma concentrations will be presented by nominal collection time in figures on linear and semi-log scales.

Population PK 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.

9.1.6.7. 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.

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.

9.1.6.8. Other Analyses

Descriptive statistics will be provided for demographics, medical history, physical examinations, and baseline characteristics.

Medical history will be coded using MedDRA and summarized by treatment group.

9.1.6.9. Handling of Missing Data

For the primary analysis of the primary endpoint, with a mixed-effects model based on restricted maximum likelihood estimation and assuming that, conditional on fixed and random effects, data are missing at random, no imputation of missing data will be performed.

Sensitivity analysis will be described in the SAP for Part A.

9.1.6.10. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be formed before study initiation, and it will be set up according to EMEA/CHMP/EWP/5872/03 Corr. The IDMC is an independent and external multidisciplinary group consisting of at least 2 physicians (one of which will serve as Chair) and a statistician that, collectively, have experience in the management of relevant patients and in the conduct and monitoring of clinical trials. IDMC membership is to be for the duration of the trial. If any member would leave the IDMC during the trial, the Sponsor may promptly appoint their replacement.

The IDMC is responsible for periodically reviewing selected data for the purpose of ensuring patient safety and maintaining the overall integrity of the trial. The IDMC has the responsibility to ensure that any safety and/or efficacy issues and/or recommendations regarding the ongoing conduct of the study realized from its review are fairly and expeditiously reported to the Sponsor.

Full details will be described in a separate IDMC Charter, which will be finalized before the first patient is screened in the study.

9.2. PART B: OPEN-LABEL EXTENSION

9.2.1. Statistical Hypotheses

9.2.2. Sample Size Determination

Patients from Part A who meet the entry criteria may participate in Part B. The sample size is not based on any formal statistical assumptions. Up to 230 patients will be enrolled in Part B.

9.2.3. Analysis Sets

The open-label analysis set will consist of all patients who received at least 1 dose of losmapimod in Part B. The open-label analysis set will be used for all analyses, unless otherwise specified.

9.2.4. Description of Subgroups to be Analyzed

Any planned subgroup analyses will be described in the SAP for Part B. Subgroups will include a subgroup of patients with FSHD2.

9.2.5. Statistical Analysis Methodology

Details of the statistical analyses, methods, and data conventions will be described in the SAP for Part B.

9.2.5.1. General Considerations

Continuous variables will be summarized using n (number of patients with non-missing data), mean, standard deviation, standard error, median, first quartile, third quartile, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be presented in data listings.

Data will be summarized according to sequence of treatment assignment:

- Losmapimod 15 mg BID/Losmapimod 15 mg BID: This will include patients who are assigned to losmapimod at baseline in Part A and continue to losmapimod 15 mg BID in Part B.
- Placebo BID/Losmapimod 15 mg BID: This will include patients who are assigned to placebo at baseline in Part A and switch to losmapimod 15 mg BID in Part B.

9.2.5.2. Safety Analyses

Safety data will be analyzed using the open-label analysis set and summarized by treatment sequence and visit (if applicable) using descriptive statistics.

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

9.2.5.3. Other Analyses

All other endpoints (detailed in Section 2) will be summarized using descriptive statistics. Linear mixed-effects models may be used to analyze continuous longitudinal data to estimate the slopes of trend lines and % changes/year, and to explore the possibility that earlier treatment with losmapimod is better than delayed treatment and that the placebo group's progression slows after treatment with losmapimod.

Further details of these endpoints and analyses are presented in Section 2.2 and the SAP for Part B.

Descriptive statistics will be provided for demographics, baseline characteristics, and medical history.

Medical history will be coded using MedDRA and summarized by treatment sequence.

9.2.6. Handing of Missing Data

Missing values for individual data points will remain as missing, unless otherwise specified.

9.3. INTERIM ANALYSES

No formal interim analyses are planned for Part A aside from those safety analyses required to support the IDMC (as described in Section 9.1.6.10).

Once all subjects have completed Part A, primary statistical analyses of Part A data as specified in Section 9.1 will be performed.

The Investigator, study staff, patients, and monitor will remain blinded to patient-level treatment assignment until study closure. The Sponsor and/or its designee will remain blinded to the treatment until after all patients have completed Part A of the study and the database has been locked for statistical analyses of Part A data, after which time they will be unblinded.

For Part B, the Sponsor may perform periodic safety, PRO reviews, and interim analysis at any time to facilitate Sponsor decision-making and communications with health authorities and other stakeholders as needed. These reviews and analyses will be performed such that the ongoing study integrity is maintained.

Patients who continue to Part B will remain blinded to their Part A treatment assignment through completion of Part B.

10. DATA QUALITY ASSURANCE

This study will be conducted according to the 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. The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

10.1. DATA MANAGEMENT

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients 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 patient data into 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 Sponsor or designee's standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. AE terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

All personal data collected related to patients, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in accordance with local data protection law.

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

After final database lock, each study site will receive a CD-ROM or other acceptable transfer method containing all of their site specific eCRF data as entered into the eCRF program for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy or other acceptable storage of all of the study site's data from the study will be created and sent to the Sponsor for storage. The Contract Research Organization will maintain a duplicate CD-ROM copy or other acceptable storage for their records. In all cases, patient initials will not be collected or transmitted to the Sponsor.

11. ETHICS

11.1. 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 patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH 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 patients.

11.2. 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.

11.3. PATIENT 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 patient before entering the study (for both Part A and Part B) or performing any unusual or nonroutine procedure that involves risk to the patient. 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 patients must sign the revised form.

Before recruitment and enrollment, each prospective patient 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 patient/legal guardian understands the implications of

participating in the study, the patient/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 patient or legal guardian.

12. INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study but may be patient 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.

12.1. CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient 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 patient (or the patient'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 patients 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 PI, and the institution.

12.2. 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 designee 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 designee is financially responsible for further treatment of the patient's disease.

12.3. 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 patient or legal guardian.
- Laboratory certifications and normal ranges for any local laboratories used by the site.

12.4. 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 patients begins.

12.5. 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.

12.6. ADVERSE EVENTS AND STUDY REPORT REQUIREMENTS

By participating in this study, the Investigator agrees to submit reports of SAEs to the Sponsor according to the timeline and method outlined in the protocol. The Contract Research Organization or site (per local country regulations) will submit annual reports to the study site IRB/IEC as appropriate.

12.7. 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.

12.8. 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. No records may be transferred to another location or party without written notification to the Sponsor.

12.9. PUBLICATIONS

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a 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 PI, any vendors, and the institution.

13. STUDY MANAGEMENT

The administrative structure will include a Safety Review Committee (SRC).

13.1. MONITORING

13.1.1. Sponsor Safety Review

All safety data will be evaluated on an ongoing basis in accordance with the applicable Sponsor and/or designee SOPs. During the conduct of the clinical trial, cumulative safety data will be collected and reviewed monthly or on an ad-hoc basis as needed.

13.1.2. 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.

13.1.3. 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 designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

13.2. MANAGEMENT OF PROTOCOL AMENDMENTS AND DEVIATIONS

13.2.1. Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, 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 patients can be enrolled into an amended protocol.

13.2.2. Protocol Deviations

The Investigator or designee must document and explain in the patient'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 patients 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 patient or Investigator that affects important efficacy and safety assessments (as applicable), the safety or mental integrity of a patient, or the scientific value of the trial/project. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines and may lead to the patient 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.

13.3. 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 patients' interests. The Sponsor has no plans to provide study drug to patients after study closure or termination. The obligations to provide study results for patients 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:

- Patient or Investigator noncompliance
- Unsatisfactory patient enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study patients
- 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 patient completes the last visit (includes the safety follow-up visit).

13.4. FINAL REPORT

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study report is 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 patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

Irrespective of the outcome of the clinical trial, the Sponsor shall submit a summary of the results of the clinical trial to the EU database within 1 year from the end of the trial in all Member States concerned.

14. REFERENCES

Aisen, A. M., and T. L. Chenevert. 1989. 'MR spectroscopy: clinical perspective', *Radiology*, 173: 593-9.

Arjomand, Jamshid, Lisa Bain, June Kinoshita, and Mark Stone. 2020. "Facioscapulohumeral Muscular Dystrophy (FSHD) Voice of the Patient Report." In.: FSHD Society.

Barbour, A. M., M. Magee, B. Shaddinger, N. Arya, L. Tombs, W. Tao, B. R. Patel, M. J. Fossler, and R. Glaser. 2015. 'Utility of concentration-effect modeling and simulation in a thorough QT study of losmapimod', *J Clin Pharmacol*, 55: 661-70.

Barbour, A. M., L. Sarov-Blat, G. Cai, M. J. Fossler, D. L. Sprecher, J. Graggaber, A. T. McGeoch, J. Maison, and J. Cheriyan. 2013. 'Safety, tolerability, pharmacokinetics and pharmacodynamics of losmapimod following a single intravenous or oral dose in healthy volunteers', *Br J Clin Pharmacol*, 76: 99-106.

Bosnakovski, D., S. H. Choi, J. M. Strasser, E. A. Toso, M. A. Walters, and M. Kyba. 2014. 'High-throughput screening identifies inhibitors of DUX4-induced myoblast toxicity', *Skelet Muscle*, 4: 4.

Cella, D., J. S. Lai, C. J. Nowinski, D. Victorson, A. Peterman, D. Miller, F. Bethoux, A. Heinemann, S. Rubin, J. E. Cavazos, A. T. Reder, R. Sufit, T. Simuni, G. L. Holmes, A. Siderowf, V. Wojna, R. Bode, N. McKinney, T. Podrabsky, K. Wortman, S. Choi, R. Gershon, N. Rothrock, and C. Moy. 2012. 'Neuro-QOL: brief measures of health-related quality of life for clinical research in neurology', *Neurology*, 78: 1860-7.

Chan, V., M. Hatch, G. Kurillo, D. Cadavid, and J. J. Han. 2020. "Abstract: Development of an optimized timed up and go (oTUG) for measurement of changes in mobility impairment in facioscapulohumeral muscular dystrophy (FSHD) clinical trials." In *Annual Meeting of the American Academy of Neurology*. Toronto, Canada [online].

Chen, Tai-Heng, Yan-Zhang Wu, and Yung-Hao Tseng. 2020. 'Early-Onset Infantile Facioscapulohumeral Muscular Dystrophy: A Timely Review', *International Journal of Molecular Sciences*, 21: 7783.

Cheriyan, J., A. J. Webb, L. Sarov-Blat, M. Elkhawad, S. M. Wallace, K. M. Mäki-Petäjä, D. J. Collier, J. Morgan, Z. Fang, R. N. Willette, J. J. Lepore, J. R. Cockcroft, D. L. Sprecher, and I. B. Wilkinson. 2011. 'Inhibition of p38 mitogen-activated protein kinase improves nitric oxide-mediated vasodilatation and reduces inflammation in hypercholesterolemia', *Circulation*, 123: 515-23.

Dahlqvist, J. R., P. Widholm, O. D. Leinhard, and J. Vissing. 2020. 'MRI in neuromuscular diseases: An emerging diagnostic tool and biomarker for prognosis and efficacy', *Ann Neurol*, 88: 669-81.

Deenen, J. C., H. Arnts, S. M. van der Maarel, G. W. Padberg, J. J. Verschuuren, E. Bakker, S. S. Weinreich, A. L. Verbeek, and B. G. van Engelen. 2014. 'Population-based incidence and prevalence of facioscapulohumeral dystrophy', *Neurology*, 83: 1056-9.

Gautschi, O. P., N. R. Smoll, M. V. Corniola, H. Joswig, I. Chau, G. Hildebrandt, K. Schaller, and M. N. Stienen. 2016. 'Validity and Reliability of a Measurement of Objective Functional Impairment in Lumbar Degenerative Disc Disease: The Timed Up and Go (TUG) Test', *Neurosurgery*, 79: 270-8.

Goselink, Rianne J.M., Karlien Mul, Caroline R. van Kernebeek, Richard J.L.F. Lemmers, Silvère M. van der Maarel, Tim H.A. Schreuder, Corrie E. Erasmus, George W. Padberg, Jeffrey M. Statland, Nicol C. Voermans, and Baziel G.M. van Engelen. 2019. 'Early onset

as a marker for disease severity in facioscapulohumeral muscular dystrophy', *Neurology*, 92: e378-e85.

Han, J. J., E. De Bie, A. Nicorici, R. T. Abresch, R. Bajcsy, and G. Kurillo. 2015. 'Reachable workspace reflects dynamometer-measured upper extremity strength in facioscapulohumeral muscular dystrophy', *Muscle Nerve*, 52: 948-55.

Hatch, M. N., K. Kim, G. Kurillo, A. Nicorici, C. M. McDonald, and J. J. Han. 2019. 'Longitudinal study of upper extremity reachable workspace in fascioscapulohumeral muscular dystrophy', *Neuromuscul Disord*, 29: 503-13.

Hatch, Maya N. , Vicky Chan, Alina R. Nicorici, Gregorij Kurillo, Tony Nguyen, Diego Cadavid, and Jay J. Han. 2019. "Abstract S10.3 Development of an optimized Timed-Up-and-Go Test for the FSHD population." In *26th Annual FSHD International Research Congress*, edited by FSH Society Facioscapulohumeral Muscular Dystrophy. Marseille, France.

Hatch, Maya N., Vicky Chan, Diego Cadavid, and Jay J. Han. 2020. "Abstract: Initial Analysis of Responsiveness of an FSHD Optimized Timed Up and Go (oTUG) Across the Disability Spectrum in FSHD." In *Annual Meeting of the American Academy of Neurology*. Toronto, Canada [online].

Hatcher, Robert A. 2007. *Contraceptive technology* (Ardent Media: New York, N.Y).

Homma, S., M. L. Beermann, F. M. Boyce, and J. B. Miller. 2015. 'Expression of FSHD-related DUX4-FL alters proteostasis and induces TDP-43 aggregation', *Ann Clin Transl Neurol*, 2: 151-66.

Jagannathan, S., S. C. Shadle, R. Resnick, L. Snider, R. N. Tawil, S. M. van der Maarel, R. K. Bradley, and S. J. Tapscott. 2016. 'Model systems of DUX4 expression recapitulate the transcriptional profile of FSHD cells', *Hum Mol Genet*, 25: 4419-31.

Janssen, B., N. Voet, A. Geurts, B. van Engelen, and A. Heerschap. 2016. 'Quantitative MRI reveals decelerated fatty infiltration in muscles of active FSHD patients', *Neurology*, 86: 1700-7.

Khiem, D., J. G. Cyster, J. J. Schwarz, and B. L. Black. 2008. 'A p38 MAPK-MEF2C pathway regulates B-cell proliferation', *Proc Natl Acad Sci U S A*, 105: 17067-72.

Kools, J., N. Voermans, K. Mul, L. Ronco, J. Jiang, J. Shoskes, K. Marshall, D. Cadavid, M. Mellion, and B. van Engelen. 2021. "An Open-Label Study of Losmapimod to Evaluate the Safety, Tolerability, and Biomarker and Clinical Outcome Assessment Changes in Subjects with FSHD1." In *World Muscle Society Annual Conference*. Virtual.

Lomas, D. A., D. A. Lipson, B. E. Miller, L. Willits, O. Keene, H. Barnacle, N. C. Barnes, R. Tal-Singer, and Investigators Losmapimod Study. 2012. 'An oral inhibitor of p38 MAP kinase reduces plasma fibrinogen in patients with chronic obstructive pulmonary disease', *J Clin Pharmacol*, 52: 416-24.

Mellion, M. L., L. Ronco, C. L. Berends, L. Pagan, S. Brooks, M. J. van Esdonk, E. M. J. van Brummelen, A. Odueyungbo, L. A. Thompson, M. Hage, U. A. Badrising, S. Raines, W. G. Tracewell, B. van Engelen, D. Cadavid, and G. J. Groeneveld. 2021. 'Phase 1 clinical trial of losmapimod in facioscapulohumeral dystrophy: Safety, tolerability, pharmacokinetics, and target engagement', *Br J Clin Pharmacol*, 87: 4658-69.

Moris, G., L. Wood, R. FernaNdez-Torron, J. A. Gonzalez Coraspe, C. Turner, D. Hilton-Jones, F. Norwood, T. Willis, M. Parton, M. Rogers, S. Hammans, M. Roberts, E. Househam, M. Williams, H. Lochmuller, and T. Evangelista. 2018. 'Chronic pain has a strong impact on quality of life in facioscapulohumeral muscular dystrophy', *Muscle Nerve*, 57: 380-87.

Oliva, J., S. Galasinski, A. Richey, A. E. Campbell, M. J. Meyers, N. Modi, J. W. Zhong, R. Tawil, S. J. Tapscott, and F. M. Sverdrup. 2019. 'Clinically advanced p38 inhibitors suppress DUX4 expression in cellular and animal models of facioscapulohumeral muscular dystrophy', *J Pharmacol Exp Ther*, 370: 219-30.

Padua, L., I. Aprile, R. Frusciante, E. Iannaccone, M. Rossi, R. Renna, S. Messina, G. Frasca, and E. Ricci. 2009. 'Quality of life and pain in patients with facioscapulohumeral muscular dystrophy', *Muscle Nerve*, 40: 200-5.

Pascoe, S., M. Costa, J. Marks-Konczalik, E. McKie, S. Yang, and P. S. Scherbovsky. 2017. 'Biological effects of p38 MAPK inhibitor losmapimod does not translate to clinical benefits in COPD', *Respir Med*, 130: 20-26.

Preston, M. K., R. Tawil, and L. H. Wang. 2020. 'Facioscapulohumeral Muscular Dystrophy.' in M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. W. Gripp, G. M. Mirzaa and A. Amemiya (eds.), *GeneReviews(®)* (University of Washington, Seattle (Original work published 1993)

Copyright © 1993-2022, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.: Seattle (WA)).

Ricci, E., G. Galluzzi, G. Deidda, S. Cacurri, L. Colantoni, B. Merico, N. Piazzo, S. Servidei, E. Vigneti, V. Pasceri, G. Silvestri, M. Mirabella, F. Mangiola, P. Tonali, and L. Felicetti. 1999. 'Progress in the molecular diagnosis of facioscapulohumeral muscular dystrophy and correlation between the number of KpnI repeats at the 4q35 locus and clinical phenotype', *Ann Neurol*, 45: 751-57.

Rojas, L. A., E. Valentine, A. Accorsi, J. Maglio, N. Shen, A. Robertson, S. Kazmirski, P. Rahl, R. Tawil, D. Cadavid, L. A. Thompson, L. Ronco, A. N. Chang, A. M. Cacace, and O. Wallace. 2020. 'p38alpha Regulates Expression of DUX4 in a Model of Facioscapulohumeral Muscular Dystrophy', *J Pharmacol Exp Ther*, 374: 489-98.

Rubin, Donald B. 1976. 'Inference and missing data', *Biometrika*, 63: 581-92.

Statland, J. M., K. J. Odrzywolski, B. Shah, D. Henderson, A. F. Fricke, S. M. van der Maarel, S. J. Tapscott, and R. Tawil. 2015. 'Immunohistochemical Characterization of Facioscapulohumeral Muscular Dystrophy Muscle Biopsies', *J Neuromuscul Dis*, 2: 291-99.

Statland, J. M., B. Shah, D. Henderson, S. Van Der Maarel, S. J. Tapscott, and R. Tawil. 2015. 'Muscle pathology grade for facioscapulohumeral muscular dystrophy biopsies', *Muscle Nerve*, 52: 521-6.

Statland, J. M., and R. Tawil. 2014. 'Risk of functional impairment in Facioscapulohumeral muscular dystrophy', *Muscle Nerve*, 49: 520-7.

Stübgen, J. P., and A. Stipp. 2010. 'Facioscapulohumeral muscular dystrophy: a prospective study of weakness and functional impairment', *J Neurol*, 257: 1457-64.

Tawil, R., J. T. Kissel, C. Heatwole, S. Pandya, G. Gronseth, and M. Benatar. 2015. 'Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine', *Neurology*, 85: 357-64.

Tawil, R., K. Wagner, J. Statland, L. Wang, A. Genge, Sacconi S., H. Lochmülller, D.R. Leiva, J. Diaz-Manera, J. Alonso-Perez, N. Muelas, J.J. Vilchez, A. Pestronik, S. Gibson, N. Goyal, J. Hamel, L. Hayward, N. Johnson, S. LoRusso, M. Freimer, P. Shieh, S.

Subramony, D. G. Leung, B. van Engelen, J. Kools, O. Dahlqvist, P. Widholm, J. Jiang, A. Odueyungbo, W. Tracewell, A. Rahilly, L. A. Rojas, A. Accorsi, S. Mennen, L. Ronco, D. Cadavid, C. Moxham, C. Morabito, R. Gould, and M. Mellion. 2021. "Whole Body MRI Quantitative Muscle Analysis to Evaluate Efficacy of Losmapimod in a Phase 2 Placebo-Controlled Study in Subjects withFSHD (ReDUX4): ReDUX4 (NCT04003974)." In *World Muscle Society Annual Conference*. Virtual.

Wang, L. H., S. D. Friedman, D. Shaw, L. Snider, C. J. Wong, C. B. Budech, S. L. Poliachik, N. E. Gove, L. M. Lewis, A. E. Campbell, R. J. F.L Lemmers, S. M. Maarel, S. J. Tapscott, and R. N. Tawil. 2019. 'MRI-informed muscle biopsies correlate MRI with pathology and DUX4 target gene expression in FSHD', *Hum Mol Genet*, 28: 476-86.

Watz, H., H. Barnacle, B. F. Hartley, and R. Chan. 2014. 'Efficacy and safety of the p38 MAPK inhibitor losmapimod for patients with chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial', *Lancet Respir Med*, 2: 63-72.

West, J., T. Romu, S. Thorell, H. Lindblom, E. Berin, A. S. Holm, L. L. Åstrand, A. Karlsson, M. Borga, M. Hammar, and O. D. Leinhard. 2018. 'Precision of MRI-based body composition measurements of postmenopausal women', *PLoS One*, 13: e0192495.

Williamson, A., and B. Hoggart. 2005. 'Pain: a review of three commonly used pain rating scales', *J Clin Nurs*, 14: 798-804.

Wong, Chao-Jen, Leo H Wang, Seth D Friedman, Dennis Shaw, Amy E Campbell, Chris B Budech, Leann M Lewis, Richard J F L Lemmers, Jeffrey M Statland, Silvère M van der Maarel, Rabi N Tawil, and Stephen J Tapscott. 2020. 'Longitudinal measures of RNA expression and disease activity in FSHD muscle biopsies', *Human Molecular Genetics*, 29: 1030-43.

Yao, Z., L. Snider, J. Balog, R. J. Lemmers, S. M. Van Der Maarel, R. Tawil, and S. J. Tapscott. 2014. 'DUX4-induced gene expression is the major molecular signature in FSHD skeletal muscle', *Hum Mol Genet*, 23: 5342-52.

Yonezawa, A., and K. Inui. 2011. 'Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics', *Br J Pharmacol*, 164: 1817-25.

APPENDIX 1. SCHEDULES OF ASSESSMENTS

Table 7: Part A: Placebo-Controlled Treatment Period Schedule of Assessments

Event/Assessment	Screening	Baseline	Week 4	Week 12	Week 24	Week 36	Week 48	ET Visit[a]	Safety F/U [redacted] after last dose of study drug[b]	Safety F/U Phone Screen [redacted] after last dose of study drug[b]
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**-**	***Variable[c]***	***Variable[c]***
Study Day	[redacted]	**1**	**28**	**84**	**168**	**252**	**336**	**-**	**343**	**373**
Visit Window (days)[d]	**N/A**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±3**	**±5**
Clinic visit	X	X	X	X	X	X	X	X	X	
ICF	X									
Inclusion/ exclusion	X	X								
Demographics	X									
Medical history	X									
Weight[e]	X	X			X		X	X	X	
Height[e] and BMI	X									
Genetic confirmation of FSHD[f]	X									
Randomization		X								
[redacted]	[redacted]									
Urine drug screen[h]	X									
Vital signs[i]	X	X	X	X	X	X	X	X	X	
Standard 12-lead ECG[j]	X	X	X	X	X	X	X	X	X	
Physical examination[k]	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	
Serum FSH[l]	X									
Serum pregnancy test[m]	X									

Event/Assessment	**Screening**	**Baseline**	**Week 4**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**ET Visit[a]**	**Safety F/U [redacted] after last dose of study drug[b]**	**Safety F/U Phone Screen [redacted] after last dose of study drug[b]**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**-**	***Variable[c]***	***Variable[c]***
Study Day	[redacted]	**1**	**28**	**84**	**168**	**252**	**336**	**-**	**343**	**373**
Visit Window (days)[d]	**N/A**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±3**	**±5**
Urine pregnancy test[n]		X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	
Serum chemistry[o]	X	X	X	X	X	X	X	X	X	
Serology (HBsAg, HCV, and HIV 1/HIV 2)[p]	X									
PK[q]			X				X	X[r]		
[redacted]		[redacted]	[redacted]				[redacted]	[redacted]		
RWS	X	X	X	X	X	X	X	X[r]		
Hand-Held Dynamometry		X	X	X	X	X	X	X[r]		
Neuro-QoL UE Function	X	X	X	X	X	X	X	X[r]		
MSK MRI	X				X		X	X[r]		
PGIC			X	X	X	X	X	X[r]		
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]		
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]		
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]		
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Study drug dispensation		X	X	X	X	X				

Event/Assessment	**Screening**	**Baseline**	**Week 4**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**ET Visit[a]**	**Safety F/U [redacted] after last dose of study drug[b]**	**Safety F/U Phone Screen [redacted] after last dose of study drug[b]**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**-**	***Variable[c]***	***Variable[c]***
Study Day	[redacted]	**1**	**28**	**84**	**168**	**252**	**336**	**-**	**343**	**373**
Visit Window (days)[d]	**N/A**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±3**	**±5**
Study drug count			X	X	X	X	X	X		
Qualitative exit interview							X			
Medications review	*Continuous from signing ICF through [redacted] safety follow-up visit*									
Concomitant treatments and procedures										
Adverse events										

Abbreviations: BMI = body mass index; ECG = electrocardiogram; [redacted] ET = early termination; FSH = follicle stimulating hormone; FSHD = facioscapulohumeral muscular dystrophy; F/U = follow-up; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; MRI = magnetic resonance imaging; MSK = musculoskeletal; Neuro-QoL = Quality of Life in Neurological Disorders; [redacted]; PGIC = Patient Global Impression of Change; [redacted]; PK = pharmacokinetics; PRO = patient-reported outcome; RWS = reachable workspace; UE = upper extremity.

[a] If a patient prematurely discontinues study treatment, they will be encouraged to remain in the study and continue with all other aspects of the study. If a patient 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 patient withdraws from the study, 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 [redacted] days and a safety phone screen [redacted] days after their last dose of study drug. If the ET visit will be scheduled more than [redacted] after the last dose of study drug, the safety follow-up and ET visits may be combined, with no duplication of assessments required.

[b] The [redacted] and [redacted] safety follow-up visits will be required for all patients who discontinue study treatment early or do not to rollover into Part B. The [redacted] safety follow-up visit may be performed as a phone screen, unless ongoing clinical laboratory findings or AEs require additional follow-up.

[c] Patients who do not rollover into Part B only.

[d] Scheduled visits may be split over 2 days, if required, and must be completed within the protocol-defined visit windows. Unscheduled visits may be performed if clinically indicated.

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

[f] Genetic confirmation must be obtained before the patient is randomized. Genetic confirmation can come from previous testing, if verified with appropriate documentation from an accredited laboratory. If genetic testing is necessary, the [redacted] screening window and activities will not start until the results are obtained and verified by the Principal Investigator.

[g] Patients must have a Ricci score of 2 to 4 to be eligible. The score will be assigned according to the worst clinical assessment on physical examination. Patients who are wheelchair-dependent or dependent on walker or wheelchair for activities are not permitted to enroll in the study.

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

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

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

[k] Physical examination at the screening visit and safety follow-up 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 musculoskeletal system.

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

[m] Serum pregnancy tests will be performed for all female patients of child-bearing potential at the screening visit.

[n] Urine pregnancy tests will be performed for all female patients of child-bearing potential before randomization and before dispensation of study drug at all other visits. If pregnancy is found, patients must be terminated from the study effective immediately. Home pregnancy tests will be performed for all female subjects of child-bearing potential if required per local regulations.

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

[p] Subjects with a known history of hepatitis infection must be tested to confirm active infection. All subjects will be tested for hepatitis B surface antigen and, if positive, will not be allowed to enroll in the study. All subjects will be tested for hepatitis C antibody and, if positive, should be tested for viral RNA. If the viral RNA test is negative indicating inactive/resolved hepatitis C infection, then the subject can enroll in the study as long as their liver panel is within range of the inclusion and exclusion criteria (Section 4.1). If the viral RNA test is positive, indicating active viral hepatitis C, the subject will not be allowed to enroll in the study. ***For Italy only:*** Tuberculosis will also be tested at Screening (Appendix 2).

[q] Patients will be required to take their study drug dose in-clinic and blood collection for PK will occur immediately predose and 4 hours (±30 minutes) after administration of the study dose.

[r] If the ET visit occurs ≥12 weeks after the last visit, noted assessments should be performed. If the ET visit occurs ≥24 weeks after the last visit, MRI should be performed.

Table 8: Part B: Open-Label Extension Schedule of Assessments

Event/Assessment	Year 1				Year 2		Safety F/U [redacted] after last dose	Safety F/U Phone Screen [redacted] after last dose of study drug[b]
	Baseline[a] Week 48	Week [redacted]	Weeks [redacted]	Week [redacted]	Weeks [redacted]	Weeks [redacted]		
Visit number [c]	**1**	**2**	**3, 4, 5**	**6**	**7+**	**8+**	***Variable***	***Variable***
Visit window (days)	**+7**	**+7**	**±14**	**±14**	**±14**	**±14**	**±3**	**±5**
Clinic visit	**X**		**X**	**X**		**X**	**X**	
Phone call		**X**			**X**			**X**
ICF	X							
Inclusion/exclusion	X							
Weight[d]	X		X	X		X	X	
Height[d] and BMI	X							
Vital signs[e]	X		X	X		X	X	
Standard 12-lead ECG[f]	X			X		X[g]	X	
Physical examination[h]	X		X	X		X	X	
Urinalysis	X		X	X		X	X	
Urine pregnancy test[i]	X		X	X		X	X	
Hematology	X		X	X		X	X	
Serum chemistry[j]	X		X	X		X	X	
[redacted]								
Study drug	X		X	X		X		

Event/Assessment	Year 1				Year 2		Safety F/U [redacted] after last dose	Safety F/U Phone Screen [redacted] after last dose of study drug[b]
	Baseline[a] Week 48	Week [redacted]	Weeks [redacted]	Week [redacted]	Weeks [redacted]	Weeks [redacted]		
Visit number [c]	**1**	**2**	**3, 4, 5**	**6**	**7+**	**8+**	***Variable***	***Variable***
Visit window (days)	**+7**	**+7**	**±14**	**±14**	**±14**	**±14**	**±3**	**±5**
Clinic visit	**X**		**X**	**X**		**X**	**X**	
Phone call		**X**			**X**			**X**
dispensation								
Study drug count			X	X		X		
Concomitant meds & procedures	*Continuous from signing ICF through [redacted] safety follow-up visit*							
Adverse events								

Abbreviations: BMI = body mass index; ECG = electrocardiogram; [redacted]; FSHD = facioscapulohumeral muscular dystrophy; F/U = follow-up; ICF = informed consent form; PRO = patient-reported outcome; RWS = reachable workspace.

[a] In most cases, the baseline visit of Part B will occur on the same day as Week 48 visit of Part A, and patients should complete all Part A Week 48 assessments before signing the informed consent for Part B. Informed consent for Part B will be signed before any Part B specific assessments are performed. In the event that a patient has their baseline visit of Part B after the Part A Week 48 visit (but within the [redacted] window), they will NOT have to repeat any Part B assessments that were specified to be performed at the Week 48 visit of Part A.

[b] The [redacted] safety follow-up will be required for all patients who discontinue study treatment early. This assessment may be performed as a phone call, unless ongoing clinical laboratory findings or adverse events require additional follow-up.

[c] Unscheduled visits may be performed if clinically indicated.

[d] Weight and height will be measured with shoes off and preferably with the same balance at each visit.

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

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

[g] Twelve-lead ECGs will be performed annually after [redacted] (ie, only at [redacted])

[h] Physical examinations 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 musculoskeletal system.

[i] Urine pregnancy tests will be performed for all female patients of childbearing potential before dispensation of study drug at all other visits. If pregnancy is found, patients must be terminated from the study effective immediately. Home pregnancy tests will be performed for all female subjects of child-bearing potential if required per local regulations.

[j] For baseline visit, patients will be required to fast for at least 4 hours prior to laboratory blood samples being taken.

APPENDIX 2. COUNTRY/REGION-SPECIFIC DIFFERENCES

The full history of this protocol is detailed below, including all past and current global and country-specific amendments:

Protocol History	
Version and Date of Protocol	***Comments***
Version 1.0, 17 February 2022	**Original version**
Version 2.0, 03 March 2022	**Global Amendment 1**
Version 2.1, 27 July 2022	UK-specific amendment
Version 2.2, 21 September 2022	Germany-specific amendment
Version 2.3, 11 October 2022	Germany-specific amendment
Version 3.0, 08 August 2022	**Global Amendment 2**
Version 3.1, 12 October 2022	UK-specific amendment
Version 3.2, 17 November 2022	Germany-specific amendment
Version 3.3, 22 November 2022	Italy-specific amendment
Version 4.0, 01 March 2023	**Global Amendment 3**
Version 4.1, 22 March 2023	UK-specific amendment
Version 4.2, 22 March 2023	Italy-specific amendment
Version 5.1, 21 December 2023	**Global Amendment 4 (current version)**

Italy-specific differences:

Change and Rationale	**Affected Sections**
Added exclusion of vaccination with a live attenuated vaccine within 6 weeks prior to randomization until the safety follow-up visit	Section 4.1.1.2
Added tuberculosis to the serology testing at screening	Section 6.1.5, Table 7

APPENDIX 3. DRUGS POTENTIALLY AFFECTING MUSCLE FUNCTION

Potential list of drugs or supplements that 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

For patients who are on drug(s) or supplements that may affect muscle function, patients 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.

Treatment with a statin can be initiated during the study if it is medically required. In this case, preference should be given to hydrophilic statins (e.g., pravastatin, rosuvastatin, fluvastatin) over lipophilic statins (e.g., simvastatin, atorvastatin, lovastatin.) Particular attention should be paid to creatine phosphokinase (already part of the laboratory safety monitoring) in patients who start treatment with a statin during the study.

APPENDIX 4. LIST OF OAT1/OAT3 SUBSTRATES WITH A NARROW THERAPEUTIC INDEX

Potential lists of drugs that are substrates of OAT1/OAT3 and have a narrow therapeutic index (NTI) are included below.

OAT1/OAT3 Substrates with NTI
valproic acid
clofarabine
methotrexate
mercaptopurine
baricitinib
pemetrexed

Source: https://go.drugbank.com/categories/DBCAT003983