RESEARCH PROTOCOL

Summary of Changes to the Protocol

Protocol History	
Version and Date of Protocol	**Comments**
Version 1, 29Mar2019	Original Version
Version 2, 21May2019	• Amended protocol to clarify that PK assessment is a secondary endpoint. • Updated exclusion criteria to include specific parameters for clinically significant liver and kidney dysfunction. • Added assessments of muscle strength to visit 1 (screening). • Clarified the maximum number of subjects that may be replaced. • Updated laboratory sites.
Version 3, 19Dec2019	• Clarified in inclusion criterion #6 that a Ricci score between 2 and 4 does not include subjects that use wheelchairs or walkers for any reason. • Removed the muscle biopsy during chronic treatment at Visit 8. All subjects will undergo muscle biopsies pre-treatment at Visit 4, and then earlier during treatment at Visit 5. • Amended the protocol to change Visit 5 from Week 12 ± 2 weeks to Week 14 ± 2 weeks to accommodate performance of either a 4-week or 8-week on-treatment muscle biopsy. Approximately half of the subjects will have biopsies at 4 weeks and half will have biopsies at 8 weeks • Added “Change from baseline in other disease transcripts by qPCR of skeletal muscle” as an Exploratory Objective • Added FSHD History and Genetic Confirmation of FSHD1 to Schedule of Assessments as it was left out of the previous version. • Added flexibility to the required number of subjects needed to complete the first interim analysis. • Modified the timing of the second IA to occur around the time of analysis of the ongoing Phase 2b ReDUX4 study. • Amended language to clarify that glucose testing is performed at Visit 1/Screening and at subsequent visits where serum chemistries are collected. • Updated laboratory vendors. • Changed ECG process so that the assessment is no longer performed in triplicate. • Clarified that the functional workspace is a component of the RWS • Clarified that subjects are not given a diary to record drug dosing but instead, subjects will enter dosing in a web-based diary. • Clarified that subjects will start using the patient wearables for Outpatient Mobility Assessments at Visit 2. • Clarified that all study drug will be dispensed from the clinic.

Version 4	Withdrawn
Version 5, 13Nov2020	• Added an open-label extension to the protocol. Added specific objectives and endpoints for the extension part of the study. • Added Table 3 to describe Schedule of Assessments for the extension • Added language throughout to differentiate the main part of the study from the extension. • Clarified drug accountability: subjects will record drug dosing in an online diary, not paper for the main part of the study. For the extension, subjects will be required to bring drug to each scheduled visit. Accountability will be performed by the site at each scheduled visit. • Updated study enrollment numbers. • Clarified that losmapimod concentrations in muscle will be evaluated as secondary endpoint. • Removed assessment of PD/Target engagement (Muscle) at Visit 8 as it was incorrectly checked.
Version 6, 16Aug2022	• Reduced frequency of clinic visits to every 24 weeks, with a safety call 12 weeks between in-person clinic visits during the extension. • Removed study assessments for extension: MRI, discovery biomarkers, RWS, TUG, muscle ultrasound, MMT, MFM, FSHD-RODS, FSHD-HI, PGIC, 6-MWT, and spirometry. • Updated study objectives and endpoints for the extension to reflect removed study assessments. • Removed language specifying that the 15-mg dose of study drug is administered as two 7.5-mg tablets. • Changed name of metabolite from GSK198602 to FTX-5508. • Extended study duration for extension.

6-MWT=6-minute walking test; DUX4=double homeobox 4; ECG=electrocardiogram; FSHD=facioscapulohumeral muscular dystrophy; FSHD-HI=FSHD Health Index questionnaire; FSHD-RODS=FSHD Rasch-built Overall Disability Scale; MFM=Motor Function Measure; MMT=Manual Muscle Testing; MRI=magnetic resonance imaging; PD=pharmacodynamic; PGIC=Patients' Global Impression of Change; PK=pharmacokinetic; qPCR=quantitative polymerase chain reaction; RWS=Reachable Workspace; TUG=Timed Up and Go

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

Change and Rationale	**Affected Sections**
Reduced frequency of in-person clinic visits to every 24 weeks, with a safety call 12 weeks between clinic visits during the extension to reduce participant and site burden given study duration.	SUMMARY, Section 3.1, Schedule of Assessments – Extension (Table 3)
Updated study objectives and endpoints for the extension.	SUMMARY, Section 2.2
Clarified that extension will continue until 90 days after commercial drug is available post regulatory approval.	SUMMARY, Section 3.1, Section 5.1, Section 6.1
Changed name of metabolite from GSK198602 to FTX-5508 to align with current Investigator's Brochure.	Section 1.2.2, Section 1.3.2, Section 13.1
Removed study assessments for extension to reduce site burden: MRI, discovery biomarkers, RWS, TUG, muscle ultrasound, MMT, MFM, FSHD-RODS, FSHD-HI, PGIC, 6-MWT, and spirometry.	Section 8.2, Schedule of Assessments – Extension (Table 3)
Added home pregnancy tests every 12 weeks between in-person visits for women of childbearing potential.	Clinical Laboratory Tests (Table 1), Schedule of Assessments – Extension (Table 3)
Extended study duration for the extension.	Schedule of Assessments – Extension (Table 3)
Removed language specifying that the 15-mg dose of study drug is administered as two 7.5-mg tablets to account for a manufacturing change.	SUMMARY, Section 5.1, Section 6.1, Section 6.6
Added language for justification for dosing change from two 7.5-mg tablets to one 15-mg tablet.	Section 6.5
Typographical and administrative changes were also made to improve the clarity of the document.	Throughout

6-MWT=6-minute walking test; FSHD=facioscapulohumeral muscular dystrophy; FSHD-HI=FSHD Health Index questionnaire; FSHD-RODS=FSHD Rasch-built Overall Disability Scale; MFM=Motor Function Measure; MMT=Manual Muscle Testing; MRI=magnetic resonance imaging; PGIC=Patients' Global Impression of Change; RWS=Reachable Workspace; TUG=Timed Up and Go

PROTOCOL TITLE An Open-Label Pilot Study of Losmapimod to Evaluate the Safety, Tolerability, and Changes in Biomarker and Clinical Outcome Assessments in Subjects With Facioscapulohumeral Muscular Dystrophy 1 (FSHD1)

Protocol ID	FIS-001-2019
Short title	Evaluation of the Safety, Tolerability, and Changes in Biomarker and Clinical Outcome Assessments of Losmapimod for FSHD1 with Extension
EudraCT number	2019-001006-20
Version	6.0
Date	16 August 2022
Coordinating investigator/ project leader	[redacted], PharmD Telephone: [redacted] Email: [redacted]
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	[redacted] Email: [redacted]
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Subsidising party	Fulcrum Therapeutics
Independent expert (s)	Not applicable for this study
Laboratory sites	[redacted]

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PROTOCOL SIGNATURE SHEET

Protocol Approval – Sponsor Signatory

Study Title An Open-Label Pilot Study of Losmapimod to Evaluate the Safety, Tolerability, and Changes in Biomarker and Clinical Outcome Assessments in Subjects With Facioscapulohumeral Muscular Dystrophy 1 (FSHD1)

Protocol Number FIS-001-2019, Version 6.0

Protocol Date 16 August 2022

Protocol accepted and approved by:

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

3D	3-dimensional
6-MWT	6-minute walking test
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from 0 to infinity
BID	twice per day
CES-1	carboxylesterase-1
CI	confidence interval
C_{max}	maximum observed plasma concentration
COPD	chronic obstructive pulmonary disease
CSR	clinical study report
CYP	cytochrome P450
DUX4	double homeobox 4
ECG	electrocardiogram
FSHD	facioscapulohumeral muscular dystrophy
FSHD-HI	FSHD-Health Index
FSHD-RODS	FSHD Rasch-built Overall Disability Scale
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
METC	medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MFM	Motor Function Measure
MMT	Manual Muscle Testing
MRI	magnetic resonance imaging
NHP	nonhuman primate

PD	pharmacodynamic(s)
PGIC	Patients' Global Impression of Change
pHSP27	Phosphorylated HSP27
PK	pharmacokinetic(s)
PO	oral(ly)
PRO	patient-reported outcome
PT	Preferred Term
qPCR	quantitative polymerase chain reaction
QTcF	QT interval by Fredericia
RWS	Reachable Workspace
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Half-life
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum observed plasma concentration
TUG	Timed Up and Go
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Facioscapulohumeral muscular dystrophy (FSHD; also known as Landouzy-Dejerine's disease) is a genetic muscular disorder that affects 1 in 12,000 to 20,000 people. FSHD has an autosomal dominant inheritance pattern with reduced penetrance. About two-thirds of cases are familial-inherited in an autosomal dominant fashion and one-third are sporadic. FSHD is characterised by descending progressive skeletal muscle weakness affecting the face, shoulders, arms, and trunk, followed by weakness of the distal lower extremities and pelvic girdle. Symptoms typically first appear later in the second decade of life but can begin at any age (Tawil et al., 2015). FSHD causes significant physical disability. Treatment is limited to symptomatic therapies such as reaching devices, canes, and wheelchairs. There are no disease modifying or curative treatments available for FSHD; therefore, there is a high need for treatments for FSHD.

Aberrant expression of the double homeobox 4 (DUX4) program drives FSHD pathology and is due to either genetic deletion of the D4Z4 repeat on chromosome 4q35 in the case of FSHD1, or to pathogenic mutations in the chromatin modifier SMCHD1 in the case of FSHD2. DUX4 is a homeobox transcription factor that plays a key role early in embryonic development. The end result of DUX4 activity is myofibre death with replacement of skeletal muscle by fat, resulting in a clinical manifestation of progressive loss of strength and accumulation of physical disability. Therefore, compounds that reduce or prevent aberrant expression of DUX4 and its transcriptional program should provide a robust disease-modifying therapeutic approach for treatment of FSHD at its root cause.

Fulcrum has identified losmapimod as a potential disease-modifying treatment for FSHD. Losmapimod is a p38α/β MAP kinase inhibitor that has been shown to reduce DUX4 activity and expression of the DUX4 gene transcript pathway in preclinical studies. Losmapimod was widely tested by GlaxoSmithKline (GSK) across many adult indications, but its clinical development was discontinued due to lack of efficacy, despite satisfactory safety and tolerability. Extensive safety data from previous clinical studies by GSK in over 3,500 human subject exposures with losmapimod tablets provide robust evidence supporting losmapimod safety and tolerability, including during chronic dosing at the proposed dose of 15 mg orally (PO) twice per day (BID). The therapeutic hypothesis for Fulcrum Therapeutic's clinical development program is that treatment of FSHD with losmapimod will slow or arrest disease progression by reducing aberrant DUX4 expression via inhibition of p38α/β MAP kinase. This open-label pilot study will investigate the safety, tolerability, pharmacokinetics (PK) and target engagement during long-term dosing with losmapimod tablets in adult subjects with FSHD1. Furthermore, it will provide an initial look into the changes that may take place in DUX4 activity in muscle biopsies, muscle damage by magnetic resonance imaging (MRI) and ultrasound, neurological function using various clinical outcome assessments, and subject reports of disease impact during long-term treatment with losmapimod compared to a pre-

treatment period. The extension of this study will enable continued investigation the safety and tolerability during long-term dosing with losmapimod tablets in adult subjects with FSHD1.

Main Study Objectives:

Primary Objective

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

Secondary Objectives

1. To assess target engagement of losmapimod tablets in blood and skeletal muscle over long-term dosing
2. To evaluate repeated dose PK of losmapimod tablets in subjects with FSHD1 over long-term dosing

Exploratory Objectives

1. To evaluate on-treatment change in target engagement and DUX4 activity and other disease transcripts in skeletal muscle needle biopsy
2. To evaluate on-treatment change in skeletal muscle by [redacted]
3. To evaluate on-treatment change in skeletal muscle function by clinical outcome assessments
4. To evaluate on-treatment change in upper and lower limb mobility in the outpatient setting
5. To evaluate on-treatment change in lung ventilatory function
6. To evaluate on-treatment change in circulating proteins associated with DUX4 expression or muscle injury or repair

Extension Objectives:

Primary Objective

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

Study Design: This is a single-centre, open-label pilot study that will investigate the safety, tolerability, PK, and target engagement during long-term dosing with losmapimod tablets in adult subjects with FSHD1. Subjects will be evaluated during an 8-week pre-treatment period (Visits 1 through 3) to establish pre-treatment baseline assessments. Subjects will then be treated with losmapimod for approximately 1 year (Visits 4 through 9) and assessed at relatively regular intervals for change from pre-treatment assessments. All subjects will undergo 2 muscle biopsies; one at baseline, pre-treatment (Visit 4, Week 8 ± 1 week) and the second on-treatment muscle biopsy approximately 4 or 8 weeks later (Visit 5, Week 14 ± 2 weeks). Up to 8 subjects will have an on-treatment biopsy at 4 weeks and up to 8 subjects will have the on-treatment biopsy at 8 weeks. There are 2 interim analyses (IA) planned: the first interim analysis will occur after approximately 6 to 8 subjects have completed the Visit 5 biopsy, and the second IA will occur around the time of analysis for the Phase2b ReDUX4

study. The IAs are designed to get an initial look at the early changes from baseline that may occur upon treatment with losmapimod for the DUX4 [redacted] in muscle biopsies from affected muscles (first IA), and on all or a top-line subset of the imaging, clinical outcome assessments, and patient reported outcomes (second IA).

During the extension, subjects will attend clinic visits approximately every 24 weeks and have a safety phone call 12 weeks between in-person clinic visits until 90 days after commercial drug is available post regulatory approval or until study termination. The extension of this study will enable continued investigation of the safety and tolerability during long-term dosing with losmapimod tablets in adult subjects with FSHD1.

Study Population: This study will enroll approximately 16 subjects with genetically confirmed FSHD1. Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study.

Enrollment has completed with 14 subjects with genetically confirmed FSHD1 included in the study.

Intervention: Subjects will be dosed open-label with 15 mg losmapimod PO BID with meals for up to approximately 52 weeks. Subjects will have the option of participating in the extension portion of the study to continue receiving 15 mg losmapimod BID until 90 days after commercial drug is available post regulatory approval or study termination.

Main Study Parameters/Endpoints:

Primary Endpoint

Assessment of safety and tolerability based on adverse events (AEs), serious adverse events (SAEs), clinically significant laboratory test results, electrocardiograms (ECGs), and vital signs (safety endpoint)

Secondary Endpoints

1. Changes from baseline during treatment in phosphorylated HSP27 (pHSP27) and ratio of pHSP27/total HSP27 as measured by sorbitol stimulated peripheral whole blood (pharmacodynamic [PD] endpoint)
2. Changes from baseline in the ratio of pHSP27/total HSP27 in muscle during the dosing period (PD endpoint)
3. Plasma and muscle concentrations of losmapimod (PK endpoint)

Exploratory Endpoints

Changes from baseline during the dosing period in the following:

1. DUX4 activity by quantitative polymerase chain reaction (qPCR) of skeletal muscle using a subset of DUX4-regulated and other disease specific gene transcripts
2. Skeletal muscle lean tissue volume by whole-body MRI
3. Skeletal muscle tissue replacement by fat using whole-body MRI
4. Skeletal muscle echogenicity by ultrasound (selected muscles)
5. Reachable Workspace (RWS) with and without weights
6. Ambulatory function by classic and FSHD-optimised Timed Up and Go (TUG)
7. Physical function by Motor Function Measure (MFM) domain 1
8. Muscle strength by quantitative manual dynamometry
9. Disease impact by subject report using FSHD-Rasch-built Overall Disability Scale (FSHD-RODS)
10. Disease impact by subject report using FSHD-Health Index (FSHD-HI)
11. Disease impact by subject report using Patients' Global Impression of Change (PGIC)
12. Upper and lower limb mobility in the outpatient setting using wearables
13. Change in ambulation as measured by the 6-minute walking test (6-MWT)
14. Change in lung ventilatory function as measured by Spirometry

Extension Endpoints:

Primary Endpoint

1. Safety and tolerability based on AEs, clinical laboratory test results, ECGs, and vital signs

Nature and Extent of the Burden and Risks Associated with Participation, Benefit and Group Relatedness: Participation in this study does not mean that the clinical symptoms, progression of disease, or underlying cause of FSHD1 will be improved or cured. While losmapimod is a potential disease-modifying treatment of FSHD based on its strong preclinical efficacy at inhibiting DUX4 expression and reducing DUX4-regulated gene transcripts and apoptosis across multiple FSHD1 and FSHD2 cell lines without impacting myotube differentiation, benefits of the treatment are not certain. FSHD1 clinical symptoms and/or progression may worsen at any time during this study.

Subjects may experience side effects or complications from the study treatment, as well as AEs and discomforts from the study assessments. Side effects of the investigational product include headache, fatigue, nasopharyngitis, dizziness, and back pain. Side effects of the study assessments include pain or bruising from blood draws; pain, bruising, swelling, redness, or bleeding from muscle biopsy; claustrophobia from MRI; and skin irritation from ECG electrode stickers. All potential side effects will be listed in the subject informed consent form.

Subjects will be asked to follow strict study procedures and respond to questionnaires. There

may also be incidental findings about the subject's health during the study. The subject and his/her primary care physician will be notified if findings are pertinent to his/her health so that appropriate follow-up can be arranged.

There are currently no expected safety risks of the study drug. However, there are some potential safety signals that continue to be investigated. These are summarised in the Investigator's Brochure (IB).

1. INTRODUCTION AND RATIONALE

1.1 Benefit/Risk Assessment

Facioscapulohumeral muscular dystrophy (FSHD) is a rare disabling disease with an estimated worldwide population prevalence of between 1:15,000 and 1:20,000 (Statland and Tawil, 2014a), or approximately 16,000 to 21,000 affected individuals in the United States and about 2,000 patients in the Netherlands (Deenen et al., 2014). About two-thirds of cases are familial-inherited in an autosomal dominant fashion and one-third are sporadic. FSHD is characterised by descending progressive skeletal muscle weakness affecting the face, shoulders, arms, and trunk, followed by weakness of the distal lower extremities and pelvic girdle. Symptoms typically first appear later in the second decade of life but can begin at any age (Tawil et al., 2015).

Progression of FSHD is slow but steady; muscle strength, measured by quantitative muscle testing decreases at an average rate of approximately 1% to 4% per year (Statland and Tawil, 2014a). The most frequent newly developed functional motor limitations include difficulty getting up from lying down in bed and difficulty using arms for activities of daily living (Statland and Tawil, 2014b). The 6-year risk of wheelchair use is 24% (Statland et al., 2015). Muscle biopsies show myopathic or dystrophic changes including variability in fibre size, rounded fibres, central nuclei, necrotic or regenerating fibres, increased connective tissue, and fatty deposition. Up to one-third of muscle biopsies show a lymphocyte-predominant perivascular inflammatory infiltrate (Statland et al., 2015). FSHD causes significant physical disability, including progressive loss of function in the face, arms, trunk, and legs. The majority of cases present initially with shoulder girdle weakness, which is eventually found in nearly all subjects (Padberg, 1982). All quality of life domains on the 36-Item Short Form Health Survey are significantly impaired, and over half of subjects with FSHD report at least mild to moderate pain (Moris et al., 2018; Padua et al., 2009). 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, 2014a). Cardiac and respiratory muscles are spared.

FSHD is caused by aberrant expression of the double homeobox 4 (DUX4) gene, a homeobox transcription factor. DUX4 is located within D4Z4 macrosatellite repeats on chromosome 4q35 and is not normally expressed in adult skeletal muscle when the number of repeat units is >10 (Lemmers et al., 2010). In the majority of subjects with FSHD (FSHD1), the D4Z4 repeat array is contracted to 1 to 9 units on 1 allele. Subjects with FSHD carrying a smaller number of repeat units (1 to 3 units) are on average more severely affected (Tawil et al., 1996). Loss of these repetitive elements (referred to as contraction) leads to de-repression of the D4Z4 locus and DUX4 expression (de Greef et al., 2008; Statland and Tawil, 2014a).

DUX4 is a transcription factor that plays an important role as a master regulator of a transcriptional program required early during embryogenesis (Hendrickson et al., 2017) but has no function postnatally, except perhaps in spermatogenesis (Geng et al., 2012). DUX4 pathological expression in skeletal muscle as a result of the D4Z4 repeat contraction (in FSHD1) or SMCHD1 mutations (in FSHD2) leads to a large transcriptional deregulation cascade that causes FSHD (Bosnakovski et al., 2014; Homma et al., 2015; Jagannathan et al., 2016; Shadle et al., 2017; Yao et al., 2014). The end result of aberrant DUX4 expression is myofibre death with the replacement of skeletal muscle by fat resulting in a clinical manifestation of progressive loss of strength and accumulation of physical disability. Therefore, compounds that reduce or prevent aberrant expression of DUX4 and its transcriptional program should provide a robust disease-modifying therapeutic approach for treatment of FSHD at its root cause.

There are currently no approved disease-modifying treatments for FSHD. Controlled trials of albuterol, corticosteroids, and a myostatin inhibitor all failed to show benefit (Tawil et al., 2015). Low-intensity aerobic exercise that is tailored to the subject's distribution of weakness may provide some limited beneficial effect (Janssen et al., 2016). Limited range of motion in the shoulder girdle can stem from periscapular muscle weakness, and in such cases surgical scapular fixation (scapulodesis) can result in some functional improvement for select subjects (Tawil et al., 2015). Very few compounds are currently in clinical development for FSHD, and none target the disease at its root cause. No therapy has been proven to reduce disease severity or delay the progression of the disease; therefore, there is a high unmet need for an effective therapy for FSHD.

Fulcrum is developing losmapimod, a selective p38α and β kinase small molecule inhibitor that specifically reduces or inhibits DUX4 activity in FSHD myotubes for treatment of FSHD at its root cause. The original developer widely tested losmapimod in various subject populations across at least 10 adult indications, including coronary artery disease, rheumatoid arthritis, and chronic obstructive pulmonary disease (COPD). There is subject exposure data from 19 publicly available clinical studies. In aggregate, over 3,500 subjects have been dosed with losmapimod, as documented in the published literature, and summarised in the IB. Of these, 149 and 151 COPD subjects were treated for at least 24 weeks at 7.5 mg and 15 mg BID, respectively (Watz et al., 2014). In another variable duration study in 90 COPD subjects that was terminated early due to futility, the mean treatment exposure to losmapimod was 7.0 months with 10 subjects dosed for a full year at 15mg PO BID (Pascoe et al., 2017). A significant number of female adults have been treated with losmapimod (about 30% across the major studies for doses up to 15 mg BID) (Newby et al., 2014; O'Donoghue et al., 2016; Pascoe et al., 2017; Watz et al., 2014). This extensive safety data from previous clinical studies with losmapimod provide robust evidence supporting losmapimod safety and tolerability, including during chronic dosing at the proposed dose of 15 mg PO BID.

Losmapimod is a potential disease-modifying treatment for FSHD based on its strong preclinical efficacy at inhibiting DUX4 expression and reducing DUX4-regulated gene transcripts and apoptosis across multiple FSHD1 and FSHD2 cell lines without impacting myotube differentiation. Fulcrum has demonstrated that losmapimod rapidly distributes to the target tissue in rat skeletal muscle, engages the drug target (p38α also known as MAPK14), and results in muscle:plasma drug exposure ratios ≥0.6 following oral administration of dose levels predicted to result in clinically relevant plasma concentrations in the clinic. Based on clinical pharmacokinetic (PK)/pharmacodynamic (PD) studies performed with losmapimod in humans by GlaxoSmithKline (GSK) (Barbour et al., 2013), it is predicted that the proposed human dose of losmapimod at 15 mg PO BID would provide drug concentrations in skeletal muscle sufficient to reduce p38α activity and DUX4 expression in FSHD patients. The therapeutic hypothesis is that treatment with losmapimod will slow or arrest disease progression in subjects with FSHD1 by reducing aberrant DUX4 expression. In addition to slowing or preventing progression, it is possible that improvement may also occur if symptoms such as pain and fatigue are reduced and/or if muscle regeneration repairs damaged muscle. This pilot study will focus on evaluating the safety, tolerability, PK, and target engagement during long-term dosing with losmapimod tablets in adult subjects with FSHD1 and explore for the first time potential changes from pre-treatment in [redacted] and clinical outcome assessments during the treatment period.

1.2 Nonclinical Information

1.2.1 Nonclinical Pharmacology

Extensive nonclinical data indicates that losmapimod is a selective p38α/β MAPK inhibitor with appropriate pharmacology, target engagement, and safety to support dosing in subjects with FSHD1. In vitro absorption, distribution, metabolism, and excretion (ADME) and safety assessments indicate that losmapimod has limited risk of significant interaction with other kinases, transporters, or cytochrome P450 (CYP) enzymes at pharmacologically relevant concentrations. Further in vitro characterisation of the effects of losmapimod in FSHD patient-derived immortalised myotubes showed potent and selective inhibition of the p38α pathway, reduction of DUX4 protein and of the DUX4-regulated gene expression program, inhibition of apoptosis and prevention of death of the FSHD myotubes. Additionally, Fulcrum's pre-clinical data was consistent with target engagement observed in previous preclinical studies, as there was a dose-dependent reduction of phosphorylated HSP27 (pHSP27). These data are consistent with the previous sponsor’s data demonstrating that as losmapimod concentrations change, the resulting change in pharmacology at the site of action occurs at the same time (See the IB for details).

In vivo muscle PK/PD studies in non-fasted mice and rats demonstrated that a single dose of losmapimod (0.3 mg/kg, PO) resulted in clinically relevant plasma exposure, significant

skeletal muscle exposure, and significant p38α/β MAPK pathway inhibition in skeletal muscles. The muscle exposures achieved are predicted to result in 50% or higher reduction in DUX4-dependent targets in FSHD subject's skeletal muscle biopsies based upon the in vitro efficacy data in FSHD myotubes. The PK/PD analysis additionally indicated that significant p38α/β MAPK pathway inhibition would be expected in muscle with clinical doses of 15 mg PO BID (Barbour et al., 2013).

The data generated by Fulcrum Therapeutics supports the conclusion that losmapimod potently and selectively reduces the DUX4 transcriptional program in FSHD patient-derived myotubes and leads to target engagement in rodent skeletal muscles that support testing of the therapeutic hypothesis in the clinic. Furthermore, the data predict that dose levels used extensively in losmapimod clinical trials previously executed by the original developer and selected by Fulcrum Therapeutics for dosing with losmapimod in this trial should provide sufficient target inhibition to reduce or prevent the aberrant expression of the DUX4 transcriptional program in subjects with FSHD1.

1.2.2 Nonclinical PKs and Metabolism

Losmapimod displayed reasonable oral bioavailability (>30%) in mouse, rat, dog, and cynomolgus monkey and low clearance (<30% hepatic blood blow) in every species tested except for the dog, results which were supported by in vitro microsomal stability experiments. The half-life ($T_{1/2}$) following oral administration ranged from 1 to 3.2 hours depending on the route, dose, and species. 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. Metabolism occurs primarily via hydrolysis of the cyclopropylamide group by carboxylesterase-1 (CES-1) to form a pharmacologically inactive primary metabolite, FTX-5508. The ratio of metabolite to parent is approximately 0.03 to 0.25 in nonclinical species and higher in humans. Losmapimod is considered unlikely to have a clinically relevant drug-drug interaction with substrates or inhibitors of CYP, P-glycoprotein, human organic anion transporter (OAT) polypeptide 1B1 or 1B3, human OATs, or human renal cation transporter 2. Likewise, the major inactive metabolite, FTX-5508, is unlikely to interact with substrates or inhibitors of CYP, P- glycoprotein, human OATP1B1, OATP1B3, or human OATs. While interactions of losmapimod and/or FTX-5508 with other transporters such as BCRP, MATE1, and MATE2-K have been suggested by in vitro studies, there is a low risk of clinically relevant interactions based on the wealth of clinical study data reported to date. One area of precaution is for BCRP substrates having a narrow therapeutic index – see the Investigator's Brochure [IB] Drug-Drug interaction section. The totality of the ADME data support continued clinical development of losmapimod, including treatment of FSHD.

1.2.3 Nonclinical Toxicology and Safety Pharmacology

The nonclinical and clinical safety of losmapimod has been extensively characterised in

studies completed by the previous sponsor that satisfy International Council for Harmonisation (ICH) M3(R2) guidelines for the conduct of nonclinical safety studies to support chronic dosing in humans up to and including levels proposed in this FSHD1 study by the sponsor with losmapimod, including repeat dose toxicity studies in 2 species for up to 26 weeks (rat) and 52 weeks (cynomolgus monkey). In addition, rodent carcinogenicity studies have been completed. These studies in rodents and cynomolgus monkeys provided exposure to the major inactive human metabolite. The ICH guidance-appropriate series of in vivo safety and toxicology studies included in vitro safety assessment, rat and nonhuman primate (NHP) toxicology studies, safety pharmacology including NHP cardiovascular and rat respiratory and central nervous system safety assessment, and rat and rabbit reproductive toxicology studies. Losmapimod produced no concerning effects on cardiovascular function in vivo (rats and monkeys), electrophysiology in vivo (monkey), or in vitro (hERG) at exposure multiples and concentrations well-above the clinical exposure levels. Data from genotoxicity assessments indicate that losmapimod does not present a genotoxic hazard to humans. Embryo-foetal developmental effects were observed and appropriate measures should be taken to protect women of childbearing potential. The totality of the nonclinical package indicated that there were no findings in chronic toxicology (rodent and nonrodent), safety pharmacology, carcinogenicity or genetic toxicity studies that would preclude the oral administration of losmapimod to humans.

1.3 Clinical Pharmacology

1.3.1 Clinical Pharmacology

The original developer of losmapimod (GSK) performed extensive testing across at least 10 adult indications but never in FSHD or other muscle disorders in the clinic. Although not effective in any of the indications tested and never filed for approval, losmapimod demonstrated a favourable PK, target engagement, safety, and tolerability profile during extensive clinical testing, including during chronic dosing. More than 3,500 adult study subjects have been treated with losmapimod.

Single oral doses of losmapimod as high as 60 mg and repeated oral doses as high as 15 mg BID for 24 weeks were well tolerated across multiple studies (15 randomised, placebo-controlled trials, 2 open-label studies, and 1 meta-analysis of 6 individual studies), which included healthy volunteers or subjects with atherosclerosis, hypercholesterolaemia, coronary artery disease, myocardial infarction, rheumatoid arthritis, COPD, major depressive disorder, neuropathic pain, or focal segmental glomerulosclerosis. One study in COPD reported dosing at 15 mg BID for up to a year (Pascoe et al., 2017).

1.3.2 Clinical PKs and Metabolism

A 2-compartment model with first-order elimination and time-dependent first-order absorption

was found to best fit the concentration-time profiles of losmapimod following oral administration. There was no apparent difference in the structure of the PK model among healthy subjects with rheumatoid arthritis and COPD. Sex, bodyweight, and age factors did not result in the need for dose adjustments (Yang et al., 2013). No apparent differences in PK were observed in subjects with different ethnic backgrounds (Ino et al., 2015).

The principle route of metabolism is hydrolysis of the cyclopropylamide group by CES-1 to form a pharmacologically inactive metabolite, FTX-5508. The PK of this primary but inactive metabolite has been evaluated. The time to reach maximum observed plasma concentration (T_{max}) for FTX-5508 was similar after oral administration to losmapimod, but the $T_{1/2}$ was slightly longer. Exposure, as measured by plasma area under the plasma concentration-time curve (AUC), was typically twice as high as losmapimod (Barbour et al., 2015; Barbour et al., 2013; Ino et al., 2015).

Losmapimod has moderate binding to human serum albumin (94.9%) (Aston et al., 2009). A low level of brain exposure was seen in rat studies (brain:plasma ratio 0.1) (Aston et al., 2009).

A human radiolabeled study of losmapimod showed that the elimination of losmapimod was almost exclusively by metabolism, with only 2% of the administered dose recovered as unchanged drug in the urine and faeces. The majority of the dose was eliminated by metabolism via CES-1 to form the inactive metabolite FTX-5508. This major metabolite is mainly eliminated by the kidney (Yang et al., 2013).

Although sex, bodyweight, and age were factors influencing some PK parameters of losmapimod, the relatively small magnitude and lack of clinical significance of the effect did not result in concerns for dose adjustment (Yang et al., 2013). No apparent differences in PK were observed in subjects with different ethnic backgrounds including Japanese (Ino et al., 2015). No apparent differences in PK were observed across multiple adult indications (Yang et al., 2013).

Food was found to increase the oral absorption of losmapimod for both milled and micronised formulations of the drug but mainly at higher doses. The analysis of AUC from zero to infinity ($AUC_{0\text{-}inf}$) and maximum observed plasma concentration (C_{max}) showed statistically higher systemic exposure in the fed state compared to the fasted state with both formulations. There was some evidence of an interaction between food status and drug formulation in $AUC_{0\text{-}inf}$. The average increase in systemic exposure was 31% with the micronised formulation and 60% with the milled formulation when using the highest dose tested by GSK, 60-mg tablets. The food effects on AUC and C_{max} were lower with the 15 mg tablet. A high fat meal increased the AUC (approximately 10%) and C_{max} (approximately 40%) of losmapimod (wet granulation formulation) compared to the fasted state. This increase in exposure was not considered

clinically significant. However, all the previous efficacy clinical trials of losmapimod across multiple indications used the fed state for dosing to reduce PK variability and a similar approach will be followed in this study in FSHD.

Approximate dose-proportional increases in exposure in terms of AUC_{0-inf} of losmapimod were observed after single-dose administration of losmapimod 2.5, 7.5, and 20 mg to healthy subjects (slope by power model, 0.91 [90% confidence interval (CI), 0.870 to 0.953]). For C_{max}, the increase in exposure was lower than that of dose increase (slope by power model, 0.75 [90% CI, 0.690 to 0.806]) (Ino et al., 2015).

1.3.3 Clinical Toxicology and Safety Pharmacology

The safety and tolerability of losmapimod has been demonstrated by GSK and academic investigators in over 3,500 study subjects in over 20 studies over the last decade as summarised in the IB. The results of these studies show that losmapimod demonstrated excellent safety and tolerability for both acute and chronic administration in healthy adults as well as in adults across all disease indications tested at single doses as high as 60 mg and at repeated doses as high as 15 mg BID for up to a year. These doses are equal to or exceed the doses proposed for this FSHD study.

There are currently no expected safety risks of losmapimod that could prevent further clinical development in FSHD or any other indication. Most AEs observed were related to exacerbation of disease; others were typically reported by a similar proportion of subjects on losmapimod and placebo. Losmapimod did not consistently result in more study drug-related SAEs or deaths than placebo. There was no clinically relevant difference in laboratory measures, ECGs, or vital signs with losmapimod versus placebo. Details about the safety of losmapimod in all previous clinical trials are summarised in the IB.

1.3.4 Medical and Regulatory Background

This study will evaluate the safety, tolerability, PK, and target engagement during long-term dosing with losmapimod in adult subjects with FSHD1. It will also provide an initial evaluation of the potential changes that may take place in DUX4 activity in muscle biopsies, muscle damage by MRI and ultrasound, neurological function using various clinical outcome assessments, and subject reports of disease impact during long-term treatment with losmapimod compared to a pre-treatment period. The results of this open-label pilot study will be used to guide further development of losmapimod for the indication of FSHD. The losmapimod tablets used for this study will be the same tablets manufactured by GSK and used in previous clinical trials. The safety of losmapimod with single doses up to 60 mg and repeated doses up to 15 mg PO BID for up to 52 weeks has been confirmed; thus, the 52 weeks of exposure to 15 mg losmapimod PO BID in this FSHD study is expected to be well within the established safety profile for losmapimod in the previous indications tested by GSK.

2. OBJECTIVES

2.1 Main Study Objectives

2.1.1 Primary Objectives

1. To evaluate the safety and tolerability of long-term dosing of losmapimod tablets in subjects with FSHD1

2.1.2 Secondary Objectives

1. To assess target engagement of losmapimod tablets in blood and skeletal muscle over long-term dosing
2. To evaluate repeated dose PK of losmapimod tablets in subjects with FSHD1 over long-term dosing

2.1.3 Exploratory Objectives

1. To evaluate on-treatment change in target engagement and DUX4 activity and other disease transcripts in skeletal muscle needle biopsy
2. To evaluate on-treatment change in skeletal muscle by [redacted]
3. To evaluate on-treatment change in skeletal muscle function by clinical outcome assessments
4. To evaluate on-treatment change in upper and lower limb mobility in the outpatient setting
5. To evaluate on-treatment change in lung ventilatory function
6. To evaluate on-treatment change in circulating proteins associated with DUX4 expression or muscle injury or repair

2.2 Extension Objectives

2.2.1 Primary Objectives

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

2.3 Hypothesis Testing

There is no hypothesis testing for this protocol.

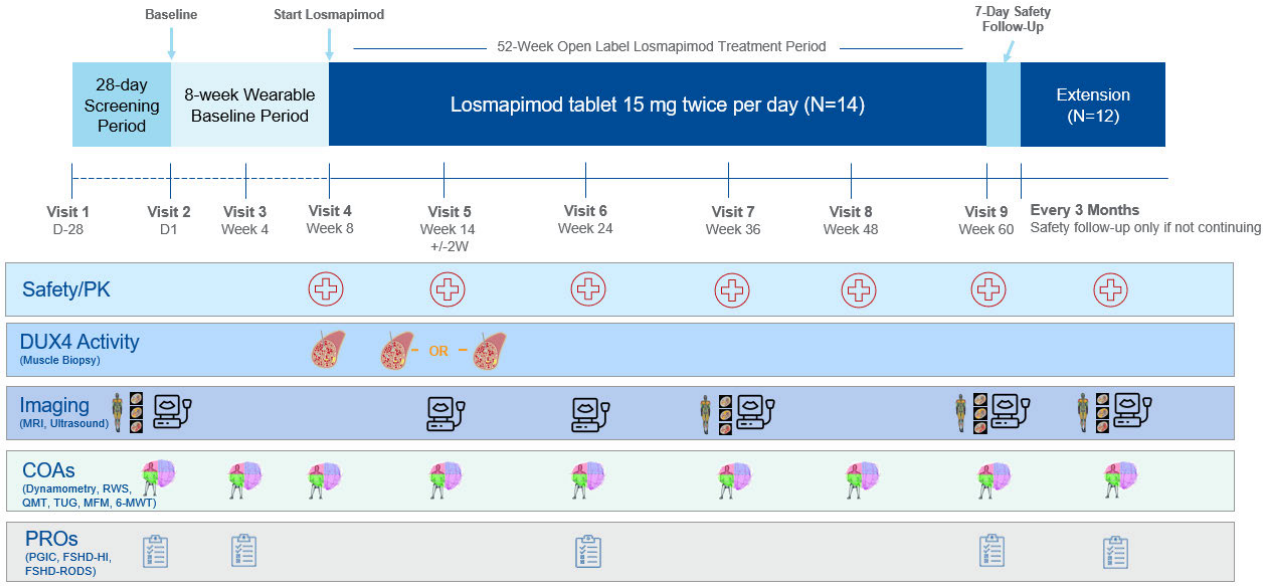
3. STUDY DESIGN

3.1 Study Design and Plan

This is a single-centre, open-label pilot study that will investigate the safety, tolerability, PK, and target engagement during long-term dosing with losmapimod tablets in adult subjects with FSHD1. Subjects will be evaluated during an 8-week pre-treatment period (Visits 1 through 3) to establish pre-treatment baseline assessments. Subjects will then be treated with losmapimod for approximately 1 year (Visits 4 through 9) and assessed at relatively regular intervals for change from pre-treatment assessments. All subjects will undergo 2 muscle biopsies; one at baseline, pre-treatment (Visit 4, Week 8 ± 1 week) and the second on-treatment muscle biopsy approximately 4 or 8 weeks later (Visit 5, Week 14 ± 2 weeks). Up to 8 subjects will have an on-treatment biopsy at 4 weeks and up to 8 subjects will have the on-treatment biopsy at 8 weeks. There are 2 interim analyses (IA) planned: the first interim analysis will occur after approximately 6 to 8 subjects have completed the Visit 5 biopsy, and the second IA will occur around the time of analysis for the Phase 2b ReDUX4 study. The IAs are designed to get an initial look at the early changes from baseline that may occur upon treatment with losmapimod for the DUX4 [redacted] in muscle biopsies (first IA), and on all or a top-line subset of the imaging, clinical outcome assessments, and patient reported outcomes (second IA).

During the extension, subjects will attend clinic visits approximately every 24 weeks and have a safety phone call 12 weeks between in-person clinic visits until 90 days after commercial drug is available post regulatory approval or until study termination. The extension of this study will enable continued investigation of the safety and tolerability during long-term dosing with losmapimod tablets in adult subjects with FSHD1.

3.1.1 Study Design Schema



Abbreviations: 6-MWT=6-minute walking test; D=day; COAs=clinical outcome assessments; DUX4=double homeobox 4; FSHD-HI=facioscapulohumeral muscular dystrophy-Health Index; FSHD-RODS=FSHD-Rasch-built Overall Disability Scale; MFM=Motor Function Measure; MRI=magnetic resonance imaging; PGIC=Patients' Global Impression of Change; PK=pharmacokinetics; PRO=patient-reported outcome; QMT=quantitative myometry; RWS=Reachable Workspace; TUG=Timed Up and Go; W=week.
Only subjects terminating the study after Week 60 will have the Visit 10 End of Study visit. Subjects proceeding to the extension will continue to Week 72 visit.
Note: All visits during the extension will have a ± 4-week window; early termination visits can occur at any time.

3.1.2 Screening

The Screening period will only be started after full written, verbal, and signed informed consent has been obtained, according to the study site standard operating procedures. The entire Screening period may take place up to 28 days prior to inclusion in the study. All screening procedures are listed in the Schedule of Assessments (Table 2). The entire screening process will last approximately 4 hours.

Study eligibility must be met per inclusion/exclusion criteria prior to enrolment. Subjects who do not meet the eligibility criteria may be re-screened once at the discretion of the principal investigator depending on the reason for initial screen failure. No repeat of tests is necessary for screening assessments that meet the eligibility criteria that are still within the window.

3.1.3 Treatment and Observation Period

In the pre-treatment period, subjects will visit the study site 3 times, at Baseline (Visit 2, Day 1), Visit 3 (Week 4 ± 1 week), and Visit 4 (Week 8 ± 1 week). In the on-treatment period, the

second muscle biopsy will occur at Visit 5 (Week 14 ± 2 weeks); then subjects will visit the study site every 12 weeks from Visit 5 (Week 14 ± 2 weeks) until Visit 10 (Week 64 ± 2 weeks [end of study]). Assessments are described in Table 2.

3.1.4 Extension

Subjects will have the option to roll over to the extension study after they complete their Week 60 visit. In the extension study, all subjects will receive 15 mg losmapimod PO BID. Subjects who wish to roll over into the extension must complete all procedures from the Week 60 end of treatment period/start of extension visit (Table 2).

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

During the extension, subjects will attend clinic visits approximately every 24 weeks (Table 3). Losmapimod will be administered BID and should be taken with food.

3.1.5 Treatment Duration

The total duration for this study will be approximately 68 weeks, and the total treatment duration will be approximately 52 weeks in the main portion of the study. Subjects will have the option of participating in the extension portion of the study until 90 days after commercial drug is available post regulatory approval or study termination.

4. STUDY POPULATION

4.1 Population (Base)

This study will enroll approximately 16 subjects with genetically confirmed FSHD1. Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

Subjects who meet all of the inclusion criteria in Section 4.2 and none of the exclusion criteria in Section 4.3 will be eligible for the study.

Enrollment has completed with 14 subjects with genetically confirmed FSHD1 included in the study.

4.2 Inclusion Criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. FSHD1 subjects age 18-65 years.
2. Subject will sign and date an informed consent form (ICF).
3. Subjects will have a confirmed diagnosis of FSHD1 with 1 to 9 repeats via assessment of the size of the D4Z4 array on chromosome 4 using the calculator provided by the sponsor. Genetic confirmation must be obtained prior to the screening MRI and baseline muscle biopsy; genetic confirmation can come from previous testing if verified with appropriate documentation. Due to stable transmission of repeat sizes within families, subjects with a clinical diagnosis of FSHD who have a first degree relative with a genetically confirmed diagnosis of FSHD1 may be entered into the study for screening and MRI. During screening, a confirmatory genetic diagnosis is conducted. If genetic testing during screening is necessary, the 4-week screening window will not start until the results are obtained and verified by the principal investigator.
4. Subject will be willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, scheduled needle muscle biopsies, and other study procedures.
5. Male or female subjects:
    a. A female subject is eligible to participate if she is of non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhoea or if of childbearing potential is using a highly effective method for avoidance of pregnancy (refer to Section 5.5) for the duration of the clinical trial and until 90 days following the last dose. The decision to include or exclude women of childbearing potential may be made at the discretion of the investigator and in accordance with local practice in relation to adequate contraception.
    b. Male subjects must agree to use one of the contraception methods listed in Section 5.5. This criterion must be followed from the time of the first dose of study medication until 90 days after the last study drug dose.
6. Subject has a Clinical Severity Score between 2 and 4 on Ricci's scale (scale range is from 0 to 5). Subjects that use a wheelchair or walker for any activity are not permitted

to enroll in the study.
7. Subject commitment to complete the 2 visits for skeletal muscle needle biopsy and all visits for whole-body MRI.
8. Subject is able to complete the RWS, Timed Up and Go (TUG), and FSHD patient-reported outcomes (PROs) (FSHD-RODS and FSHD-HI) at the screening visit.
9. Subject has an MRI-eligible muscle for biopsy as determined by the central reader.
10. Subject must complete the main study through the Week 60 visit in order to participate in the extension.

4.3 Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Subject has a history of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject. This may include, but is not limited to, 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; and history of cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years).
2. Subject has a known or clinically suspected infection with human immunodeficiency virus or hepatitis B or C viruses.
3. Subject has current clinically significant liver (alanine aminotransferase > 2X upper limit of normal or total bilirubin >1.5 X upper limit of normal) or kidney (GFR < 30 mL/min/1.73m^2) dysfunction.
4. Subject screens positive for hepatitis B surface antigen, hepatitis C virus (HCV) antibody, or antibodies against human immunodeficiency viruses 1 and 2 (HIV 1/HIV 2 antibodies).
5. Subject has any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy, or other gastrointestinal tract surgery, except appendectomy).
6. Subject has a standard 12-lead ECG demonstrating QT interval by Fredericia (QTcF) >450 msec for male subjects and QTcF >470 msec for female subjects at Screening. If QTcF exceeds 450 msec for males or 470 msec for females, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the subject's eligibility.
7. Subject has a history of cardiac dysrhythmias requiring anti-arrhythmia treatment(s); or history or evidence of abnormal ECGs that, in the opinion of the investigator or Medical Monitor, would preclude the subject's participation in the study.
8. Male subject has a female partner who is planning to become pregnant during the study or within 90 days after the last study drug dose.
9. Subject has donated blood (of approximately 1 pint [500 mL] or more) or has had any significant loss of blood within 90 days before the first study drug dose, as determined by the investigator.
10. Vaccination with a live attenuated vaccine within 6 weeks of randomisation.
11. Subject has a history of alcohol, analgesic/opioid, and/or illicit drug abuse as defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, in the last 6 months before screening, or a positive test for drugs of abuse at screening.
12. Subject has participated in a clinical trial in which they have received an investigational

product within the following time period prior to enrolment in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever was longer).

13. For subjects that are on drug(s) or supplements that may affect muscle function as determined by the treating physician or included in the list of drugs presented in Section 15: subjects must be on a stable dose of that drug(s) or supplement for at least 3 months prior to enrolment in the study and remain on that stable dose for the duration of the study (list of drugs presented in Section 15). 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.
14. Subject has a history of sensitivity to any of the study medications or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicated their participation.
15. Female subject is pregnant as determined by positive urine human Chorionic Gonadotropin test at Screening or prior to dosing.
16. Female subject is lactating.
17. Subject is unwilling or unable to follow the procedures outlined in the protocol.
18. Subject has any contraindication for MRI (including severe claustrophobia and any shrapnel or metal implants in the body that are not MRI compatible).
19. Subject was mentally or legally incapacitated up to 2 years prior to enrolment.
20. Subject has abnormal laboratory results indicative of any significant medical disease that, in the opinion of the investigator or the medical monitor, would preclude the subject's participation in the study.
21. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.
22. Subject has taken any anticoagulants for at least 1 month and anti-platelet agents for at least 1 week before each muscle biopsy. Such agents are prohibited, as they increase the risk of hematomas following skeletal muscle needle biopsy.

4.4 Sample Size Calculation

Sixteen subjects are planned to be treated with losmapimod. While this sample size is not based on statistical considerations, a sample size of 16 subjects receiving losmapimod is considered sufficient to obtain estimates of the safety, tolerability, PK, and target engagement properties of losmapimod tablets over long-term dosing and to inform initial and ongoing evaluations of assumptions on the potential impact of treatment on [redacted] and clinical outcome assessments compared to the pre-treatment period.

Enrollment has completed with 14 subjects with genetically confirmed FSHD1 included in the study.

5. TREATMENT OF SUBJECTS

5.1 Investigational Product/Treatment

During the treatment period, subjects will be dosed open-label with 15 mg losmapimod PO BID with meals for up to approximately 52 weeks. During the extension subjects will continue to receive 15 mg losmapimod BID until 90 days after commercial drug is available post regulatory approval or study termination.

5.2 Concomitant Medications

All medications (prescription and over-the-counter) taken within 30 days of study screening will be recorded with indication, route of administration, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit and any changes recorded.

Concomitant medications are allowed for subjects with FSHD1 if there is no interference with the study endpoints (safety or efficacy). The rationale will be clearly documented by the investigator.

5.3 Escape Medication

Not applicable for this study, as there are no available treatments for FSHD.

5.4 Lifestyle Restrictions

1. As the study medication needs to be taken BID with meals, the approximate meal times will be relative to the need of taking the study medication BID. On clinic visit days, the medication needs to be taken in the clinic at a time determined by the study coordinator or staff at the site.
2. Any nutrients known to modulate CYP enzymes activity (eg, grapefruit or Seville orange containing products or quinine containing drinks (tonic water or bitter lemon) should be avoided.
3. The use of (illicit) drugs can influence the measurements. Therefore, using 'drugs' is not permitted for the duration of the study. Since poppy seeds can cause a positive 'drugs' result, these should be avoided. If a positive result occurs without an explanation, the subject cannot participate in the study. However, positive urine drug screen for prescribed medication is allowed at the discretion of the Principal Investigator.
4. Alcohol should be avoided from at least 48 hours before screening, and each scheduled visit. At other times throughout the study, subjects should avoid consuming more than 3 units of alcohol daily on average (1 unit is equivalent to a 285 mL glass of full-strength beer or 425 mL schooner of light beer or 1 [30 mL] measure of spirits or 1 glass [100 mL] of wine). Subjects may undergo an alcohol breath test at the discretion of the investigator.
5. Subjects should avoid excessive caffeine consumption, defined as >800 mg per on days of study visits. Caffeine quantities defined as: 1 cup of coffee contains 100 mg of caffeine; 1 cup of tea, or 1 glass of cola, or portion of chocolate (dark: 100 g; milk: 200 g) contains approximately 40 mg of caffeine; 1 bottle of Red Bull contains

approximately 80 mg of caffeine. At other times during the study, subjects should maintain their normal habits of caffeine consumption.

6. Subjects should avoid using tobacco- or nicotine-containing products (including e-cigarettes and patches) on days of study visits. At other times during the study, subjects should maintain their normal habits of tobacco or nicotine use.
7. Strenuous physical activity (eg, heavy lifting, weight, or fitness training) is not allowed from 48 hours prior to each 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. Restriction of strenuous physical activity is especially important on the day of the muscle biopsies and the 2 days before it as it may affect results of the testing.

5.5 Contraception Requirements

Teratogenicity and effects on embryo-foetal survival were noted in rat and rabbit reproductive toxicology studies with losmapimod. Therefore, losmapimod should not be taken by women of childbearing potential who are not utilising adequate contraceptive methods.

All women of childbearing potential and all males must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.

Women of childbearing potential are defined as all women physiologically capable of becoming pregnant, unless they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhoea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follow:

- Females: Using 1 or more of the following acceptable methods of contraception: surgical sterilisation (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap).
- Males: Effective male contraception includes the use of condoms until 90 days after last dosing. Subjects with a vasectomy with negative semen analysis at end of study will use condoms until 7 days after last dosing.

Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, and post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

6. INVESTIGATIONAL PRODUCT

6.1 Name and Description of Investigational Product

Subjects will be dosed open-label with 15 mg losmapimod PO BID with meals for up to approximately 52 weeks. Subjects in the extension portion of the study will continue to receive losmapimod 15 mg BID until 90 days after commercial drug is available post regulatory approval or study termination.

Study drug administration will be with food followed by 240 mL of still water.

6.2 Summary of Findings from Non-Clinical Studies

See the IB and Section 1.2.

6.3 Summary of Findings from Clinical Studies

See the IB and Section 1.3.

6.4 Summary of Known and Potential Risks and Benefits

6.4.1 Known and Potential Risks

There are no known contraindications to the administration of losmapimod.

Losmapimod should not be administered to subjects who are hypersensitive to losmapimod or the excipients used in the losmapimod tablets.

Losmapimod should not be administered to pregnant women or women at risk of becoming pregnant because it was associated with embryo-foetal malformations in rats and rabbits.

Abnormal elevation of transaminases with or without increased bilirubin has been observed with other p38α inhibitors. Although there is little evidence that this occurs with losmapimod based on the experience from previous clinical trials in over 3,500 subjects, monitoring for potential liver enzyme abnormalities is specified in the protocol as part of safety monitoring.

Clinical studies to date have not shown any consistent increase in the incidence, severity, or type of infections in subjects who received losmapimod compared to placebo. However, because of a potential modest impact of losmapimod on immune function due to inhibition of p38α pharmacology, there could be circumstances when the theoretical risk of losmapimod administration may outweigh its potential benefits to subjects with FSHD1 (eg, concurrent administration with cytotoxic chemotherapy for cancer). Whether losmapimod could decrease the efficacy of immunisations has not been formally studied.

There has been no increase in renal insufficiency or renal adverse events with losmapimod

compared to placebo in previous clinical trials. However, a small increase in serum creatinine (ratio: 1.07; 95% CI, 1.02 to 1.11) was noted in 1 study, and similar trends were observed in other studies. This increase appears to attenuate with continued treatment and is reversible upon discontinuation. Losmapimod is an inhibitor of MATE1 renal transporter, which may explain this finding.

There has been no increase in cardiac arrythmias or ECG abnormalities with losmapimod compared to placebo in the clinical trials.

Although no studies have been conducted to evaluate the potential of losmapimod for abuse and dependence, there is no reason to suspect that this will be the case based on its mechanism of action.

There are currently no identified adverse drug reactions and no expected safety risks of losmapimod that would prevent further clinical development in FSHD1 or any other indication.

See the IB for details.

6.4.2 Known and Potential Benefits

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 FSHD1.

The therapeutic hypothesis is that treatment with losmapimod will slow or arrest disease progression in subjects with FSHD1 by reducing aberrant DUX4 expression. In addition to slowing or preventing progression, it is possible that improvement may also occur if symptoms such as pain and fatigue are reduced and/or if muscle regeneration repairs damaged muscle. This pilot study will focus on evaluating the safety, tolerability, PK, and target engagement during long-term dosing with losmapimod tablets in adult subjects with FSHD1 and explore for the first time potential changes from pre-treatment in [redacted] and clinical outcome assessments during the treatment period. There may be no benefit for the subjects in this study.

6.5 Description and Justification of Route of Administration and Dosage

Losmapimod has been investigated in several adult indications by the original developer (GSK) and by academic investigators. Losmapimod is well tolerated and generally safe, but without any evidence of efficacy in the indications previously studied. Completed clinical trials with losmapimod include more than 3,500 subjects dosed with single doses as high as 60 mg, repeated doses as high as 15 mg PO BID, and treatment duration as long as 52 weeks. The greatest experience has been with the 7.5 mg PO BID dose. Losmapimod has also been extensively studied in adults with the 15 mg PO BID doses, with an initial dosing period of 7.5 mg PO BID for 2 or 4 weeks. No clear safety signal has been identified and tolerability has

been satisfactory (see the IB for details).

Most of the studies previously completed were conducted using losmapimod oral tablets given with food. All subjects in these previous studies were adult males or females and included healthy volunteers or subjects with atherosclerosis, hypercholesterolaemia, coronary artery disease, myocardial infarction, rheumatoid arthritis, COPD, major depressive disorder, neuropathic pain, or focal segmental glomerulosclerosis. Single oral doses as high as 60 mg and repeated oral doses as high as 15 mg BID for up to 24 weeks were well-tolerated. One study in COPD reported dosing at 15 mg BID for up to a year (Pascoe et al., 2017). Most AEs observed were related to exacerbation of disease; others were typically reported by a similar proportion of subjects on losmapimod and placebo. Losmapimod did not consistently result in more study drug related SAEs or deaths than placebo. There was no clinically relevant difference in laboratory measures, ECGs, or vital signs with losmapimod versus placebo. No adverse events that can definitely be attributed to losmapimod have been identified.

In addition to evidence of safety and tolerability, the selection of 15 mg BID dosing in FSHD is further supported by in vitro efficacy studies demonstrating the reduction of DUX4 activity during treatment of FSHD myotubes treated with various concentrations of losmapimod compared to vehicle control. Heat shock protein 27 (HSP27) is a phosphorylated substrate of p38α/β 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. Pharmacokinetic/PD analyses indicate that the 15 mg PO BID dose results in 40 to 70% pHSP27 reduction (Barbour et al., 2013 and Cheriyan et al., 2011, and summarised in the investigator's brochure). Losmapimod PK in humans has been well characterised including at the planned dose of 15 mg BID for this study. Pharmacokinetic/PD analyses demonstrated that the inhibition of pHSP27 is directly related to the plasma concentration of losmapimod and as the losmapimod concentration changes with time, the resulting change in pHSP27 occurs almost instantaneously (Barbour et al., 2013). Pre-clinical data from Fulcrum shows that this change in pHSP27 correlates with a significant reduction in DUX4 levels and transcriptional activity.

Preclinical in vivo PK/PD studies in non-fasted mice and rats demonstrated that the dose levels of losmapimod that achieved clinically relevant plasma exposures also produced significant skeletal muscle exposure and p38α/β MAPK pathway inhibition (further details provided in the IB). The muscle exposures achieved in rodents that are similar to the human 15 mg BID exposures in blood resulted in robust muscle target engagement in vivo, and such concentrations resulted in 50% or higher reduction in DUX4-dependent targets in FSHD myotubes.

Although dosing with 7.5 mg losmapimod BID also results in target engagement, it may not be sufficient especially at C_{min}. In COPD subjects dosed for 12 weeks, the target engagement

inhibition at C_{min} was 21% while the post-dose (C_{max}) target engagement inhibition was 39% to 44% (GSK study MKI102428); the trough losmapimod plasma concentrations maintained in this study were generally <20 ng/mL. Importantly, the previous sponsor demonstrated that target engagement in blood is maintained over 12 weeks of dosing (GSK study MKI102428).

Pharmacokinetic/PD analyses of rodent (Studies FULTX-00002, FULTX-00004, FULTX 00005, and FULTX-00006) and human (Barbour et al., 2013) data performed by Fulcrum indicated that robust and sustained target engagement in muscle should be achieved when plasma losmapimod concentrations are >30 ng/mL, and therefore robust p38α/β MAPK inhibition would be expected in skeletal muscle with the 15 mg PO BID planned dose for FSHD. Although increasing concentrations resulted in increases in target engagement in vitro (Study FULTX- 00008), there is no evidence that increasing the dose above 15 mg PO BID will result in greater exposures (due to saturation of absorption) and additional target engagement. Therefore, clinical dosing beyond 15 mg BID with the current formulation is not warranted (further details are provided in the investigator's brochure), and dosing at less than 15 mg PO BID is likely not as effective.

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

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

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

6.6 Dosages, Dosage Modifications, and Method of Administration

Losmapimod will be dosed 15 mg PO BID with meals.

6.7 Preparation and Labelling of Investigational Medicinal Product

Study drug will be supplied by the sponsor to the local pharmacy. The sponsor will hire a qualified vendor to supply the study drug to the site. The dispensing of the study drug will be performed by the pharmacy in person during clinical visits. Study drug will be dispensed for all subjects starting at Visit 4.

Losmapimod storage should not exceed 30ºC in the containers provided. All drug supplies must be stored in a secure, temperature-controlled area with limited access. For batch-specific storage instructions, see the packaging.

6.8 Drug Accountability

Drug accountability will be maintained by the sponsor and assessed by maintaining adequate study drug dispensing records.

The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator. Subjects will self-administer the study drug by mouth BID with food (preferably meals). During the main study period, subjects will record the study drug administration in an online drug administration diary via their computer, smart phone, or other electronic device. This data will then be transferred to the study database. For the extension period of the study, subjects will return their bottles for accountability at each scheduled clinic visit.

If a subject misses a dose, they will skip that dose and take the next scheduled dose.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable for this study.

8. METHODS

8.1 Study Parameters/Endpoints

8.1.1 Main Study Endpoints

Primary endpoint:

The primary endpoint is the assessment of safety and tolerability based on AEs, SAEs, clinically significant laboratory test results, ECGs, and vital signs (safety endpoint).

The secondary endpoints are as follows:

1. Changes from baseline during treatment in pHSP27 and the ratio of pHSP27/total HSP27 as measured by sorbitol stimulated peripheral whole blood (PD endpoint)
2. Changes from baseline in the ratio of pHSP27/total HSP27 in muscle during the dosing period (PD endpoint)
3. Plasma and muscle concentrations of losmapimod (pharmacokinetic [PK] endpoint)

Exploratory endpoints include changes from baseline during the dosing period in the following:

1. DUX4 activity by quantitative polymerase chain reaction (qPCR) of skeletal muscle using a subset of DUX4-regulated gene transcripts
2. Other disease transcripts by qPCR of skeletal muscle
3. Skeletal muscle lean tissue volume by whole-body MRI
4. Skeletal muscle tissue replacement by fat using whole-body MRI
5. Skeletal muscle echogenicity by ultrasound (selected muscles)
6. RWS with and without weights
7. Ambulatory function by classic and FSHD-optimised TUG
8. Physical function by MFM domain 1
9. Muscle strength by quantitative manual dynamometry
10. Disease impact by subject report using FSHD-RODS
11. Disease impact by subject report using FSHD-HI
12. Disease impact by subject report using PGIC
13. Upper and lower limb mobility in the outpatient setting using wearables
14. Change in ambulation as measured by the 6-minute walking test
15. Change in lung ventilatory function as measured by Spirometry See Table 2 for the timepoints of the assessments.

8.1.2 Extension Endpoints

Primary endpoint:

Safety and tolerability based on AEs, clinical laboratory test results, ECGs, and vital signs.

8.2 Study Assessments

Vital Signs

Evaluations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature will be performed throughout the study at the timepoints specified in the Schedule of Assessment table (Table 2 and Table 3). Pulse and blood pressure will be taken after approximately 5 minutes in the supine position. Automated oscillometric blood pressures and pulse rate will be measured using electronic devices. Temperature will be measured tympanically with digital clinical thermometers. For each vital sign measure, change from baseline values will be calculated at each post-treatment timepoint.

ECGs

Standard 12-lead ECGs will be performed after the subject has been supine for at least 5 minutes. ECGs will be collected at screening, before dosing only at Visit 4, and at approximately 3 hours (± 90 minutes) after morning dosing at all on-treatment visits as specified in the Schedule of Assessments (Table 2 and Table 3).

The investigator will assess the ECG recording as 'normal', 'abnormal - not clinically significant', or 'abnormal - clinically significant' and include a description of the abnormality as required. The ECG parameters to be assessed will include heart rate, pulse rate, QRS, QT, and QTcB and QTcF (calculated using Bazett’s and Fridericia's method, respectively). For each ECG parameter, change from baseline values will be calculated at each post-treatment timepoint. Any abnormal ECGs will be submitted for secondary review by central reader.

Clinical Laboratory Tests

Blood and other biological samples will be collected for the clinical laboratory tests specified in Table 1.

Table 1 Clinical Laboratory Tests

Haematology	Haemoglobin (including MCV, MCH, MCHC), haematocrit, RBC, total WBC, and platelet count. Differential blood count, including basophils, eosinophils, neutrophils, lymphocytes, and monocytes.	3 mL of venous blood in a BD Vacutainer® K2EDTA tube. Samples will be analysed at [redacted].

Coagulation	International normalised ratio, prothrombin time, activated partial thromboplastin time, and fibrinogen.	2.7 mL of venous blood in a BD Vacutainer® Sodium Citrate (99NC BD) tube. Samples will be analysed at [redacted].
Clinical Chemistry	Glucose, sodium, potassium, calcium, inorganic phosphate, total protein, albumin, BUN, creatinine, uric acid, total bilirubin[a], alkaline phosphatase, AST, ALT gamma-GT, LDH and CPK.	5 mL of venous blood in a BD Vacutainer® SST Gel and Clot Activator tube. Samples will be analysed at [redacted].
Serology	HIV-1 and HIV-2 antigen and antibodies, HBsAg, HCV antibodies	8.5 mL of venous blood in a BD Vacutainer® SST Gel and Clot Activator tube. Samples will be analysed at the [redacted].
Pregnancy[b]	Urine hCG, Serum hCG	3.5 mL of venous blood in a BD Vacutainer® SST Gel and Clot Activator tube for serum hCG and a urine specimen for urine hCG. Both samples will be analysed at [redacted].
Urine drug screen	Cocaine, amphetamines, opiates (morphine), benzodiazepines, and cannabinoids	The urine specimen will be analysed at [redacted].

a Conjugated bilirubin will be reported only when total bilirubin is outside the reference range.
b Pregnancy test for women of childbearing potential will be performed at Screening (in serum) and at each in-person study visit (in urine) and confirmed negative prior to medication supply at clinic visits during the on-treatment period. Home pregnancy tests (in urine) for women of childbearing potential will be performed every 12 weeks between in-person study visits during the extension.

ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; CPK=creatine phosphokinase; gamma-GT=gamma-glutamyltransferase; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; LDH=lactate dehydrogenase; MCH=mean corpuscular haemoglobin; MCHC=mean corpuscular haemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell count; SST=serum separator tube; WBC=white blood cell count.

AEs

The definitions, reporting, and follow-up of AEs, SAEs, and potential pregnancies are described in Section 9.

Phosphorylated HSP27 (PD endpoint)

Phosphorylated HSP27 (pHSP27) and total HSP27 in sorbitol stimulated peripheral whole

blood and in skeletal muscle will be measured at the timepoints specified in the Schedule of Assessments (Table 2). The Visit 4 (pre-treatment) value will be defined as the baseline value for change from baseline calculations. pHSP27 and total HSP27 values will be transformed using the natural log function. The change from baseline in pHSP27/total HSP27 in sorbitol stimulated whole blood and change from baseline in pHSP27/total HSP27 in muscle natural log values will be calculated at each post-treatment timepoint. Post-treatment will be obtained at the estimated C_{max} time (eg, 4h ± 1h).

Plasma and Muscle PK parameters of Losmapimod (PK endpoint)

There will be no PK parameters calculated. Plasma and muscle concentrations of losmapimod will be summarised by timepoint. PK samples will be collected at the timepoints specified in the Schedule of Assessments (Table 2) Details about sample collection, handling, and processing will be described in the study reference manual.

MRI

Whole-body Dixon MRI for lean muscle tissue and muscle replacement by fat (fat fraction) will be measured at the timepoints specified in the Schedule of Assessments (Table 2) to evaluate the change from the pre-treatment period in skeletal muscle lean tissue volume, and tissue replacement by fat. The change from baseline in fat fraction will be calculated at each post-treatment timepoint.

Standardised MRI protocols for imaging in neuromuscular disorders, including the measurement of skeletal muscle tissue replacement by fat using the Dixon technique (Dixon, 1984), have been recommended as a result of 2 consortia organised by the Treat NeuroMuscular Disease network (Hollingsworth et al., 2012). The MRI technique to be used in this study is a standardised, objective, quantitative technique with automatic skeletal muscle segmentation and fat fraction analyses via robust algorithms using Dixon imaging to measure the extent of skeletal muscle tissue replacement by fat in subjects with FSHD1.

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

Ultrasound

Ultrasound for skeletal muscle echogenicity will be measured at the timepoints specified in the Schedule of Assessments (Table 2) to evaluate the change from the pre-treatment period in skeletal muscle echogenicity. Details about the muscles to be assessed and the quantification of changes in echogenicity will be described in the study reference manual.

Skeletal Muscle Needle Biopsy and Blood Products

Needle biopsies of skeletal muscle tissue will be collected at Visit 4 (pre-treatment) and at Visit 5 (on-treatment) as specified in the Schedule of Assessments (Table 2).

DUX4 activity and other disease related gene transcripts in skeletal muscle will be measured at the timepoints specified in the Schedule of Assessments (Table 2) by RNA sequencing and by qPCR in a panel of DUX4-regulated gene transcripts. Details on the derivation of the DUX4 activity exploratory efficacy endpoint will be provided in the Statistical Analysis Plan (SAP). Discovery for biomarkers of DUX4 activity and biomarkers of FSHD muscle injury or repair will be done in plasma and serum samples drawn at timepoints specified in the Schedule of Assessments using protein assays on a panel of proteins hypothesised to be dysregulated in disease. Whole-venous blood will be purified to plasma and serum to support these measurements.

Physicians experienced in skeletal muscle needle biopsy will perform the muscle biopsies. These needle muscle biopsies in general, take only a short time and are well-tolerated, including when done repeatedly. In 1 large series, no complications were reported in 400 consecutive skeletal muscle needle biopsies (Edwards et al., 1983). Rarely (<1%), there can be superficial infection or haematomas (Edwards et al., 1983). Several muscles from the legs are safely accessible by needle for biopsy.

The choice of the muscle(s) to be biopsied in this study will be informed by skeletal muscle MRI during the screening visit. Muscles in the thigh and the calf on either side will be evaluated for eligibility by MRI using a central reader. This information will be communicated to the study site. Based on the information provided by the central reader and their own experience with muscle biopsy, the site will select the muscle or muscles for biopsy. The muscle(s) approved for biopsy will be those demonstrating a STIR-positive signal with some but not excessive fatty infiltration on the screening MRI, as determined by the central reader. The same muscle will be biopsied twice when possible.

The muscle tissue collected at each biopsy will be analysed by central laboratories for DUX4 activity using RNA sequencing and a molecular panel of DUX4-regulated gene transcripts using qPCR, drug concentration, and target engagement.

The specific details of the biopsy procedures, materials to be provided, materials to be resourced locally, personnel qualification, vendors, and methods for tissue collection, processing and analysis will be specified in the study reference manual. The study reference manual will be version controlled and may be updated as needed if the ongoing quality review of the tissue samples warrants changes. The informed consent will describe the muscle biopsy procedure for the subjects, as well as the risks and mitigations related to the procedure.

RWS

RWS with and without weights will be measured at Baseline and at the timepoints specified in the Schedule of Assessments. (Table 2). The functional workspace is a component of the RWS

The RWS uses a 3-dimensional (3D) vision-based sensor system (using a single system depth-ranging sensor) that can unobtrusively detect an individual's range of motion that reflects individual shoulder and proximal arm upper extremity function.

During the evaluation, subjects are seated in front of the Microsoft Kinect sensor and a large TV screen for demonstration and undergo a standardised upper extremity movement protocol under the supervision of a study clinical evaluator. The Microsoft Kinect sensor-tracks the 3D hand trajectory and transforms the movements into a body-centric coordinate system. Each individual's RWS envelope is reconstructed in a graphical output. Each side's RWS envelope is divided into 4 quadrants (2 upper quadrants and 2 lower quadrants, 2 ipsilateral and 2 contralateral quadrants) with the shoulder joint serving as the origin. The absolute total RWS surface envelope area (in m^2) as well as areas for each of the quadrants will be calculated by a central reader after quality assessment of the raw data. Scaling of the data by each person's arm length will allow normalisation for comparison between subjects. (Han et al., 2015). The change from baseline in RWS measures will be calculated at each on-treatment visit. Further details about the RWS are provided in the study reference manual.

TUG

TUG will be measured at the timepoints specified in the Schedule of Assessments (Table 2).

The classic TUG test is a simple test used to assess a person's mobility and requires both static and dynamic balance and muscle strength. It measures the time that a person takes to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down.

The FSHD-optimised TUG test is the usual classic TUG but adds the component for getting up from a laying position on a low-lying mat at the start of the test and laying back down on the back at the end of the test. The change from baseline in both classic TUG and FSHD-optimised TUG measures will be calculated at each post-dose timepoint.

Muscle Strength

Muscle strength will be measured by quantitative dynamometry with hand-held devices (manual) and with bed frame equipment, and with Manual Muscle Testing (MMT) at the timepoints specified in the Schedule of Assessments (Table 2). Dynamometry is used to objectively assess the strength of multiple muscles or muscle groups. Manual Muscle

Testing is one of the most commonly used forms of muscle testing. With MMT, the subject is instructed to hold the corresponding limb or appropriate body part to be tested at the end of its available range while the evaluator provides opposing manual resistance. Manual Muscle Testing will be assessed in the extension period of the study. The procedure for dynamometry assessments and MMT for specific muscles to be measured will be described in a separate study reference manual. The change from baseline in muscle strength measures will be calculated at each post-dose assessment.

MFM Domain 1

The MFM domain 1 will be measured by a physical therapist at the timepoints specified in the Schedule of Assessments (Table 2).

The MFM scale assesses the severity of the motor deficit in the main neuromuscular diseases as determined by a physical therapist and has good psychometric properties. The score is reproducible, the coefficients of the interrater reliability are good or excellent. The total score provides a good measure of the overall functional severity across various domains. This trial will only use Domain 1. Domain 1 focuses on ambulation and transfers ability. The change from baseline in MFM domain 1 scores will be calculated at each post-dose timepoint. Details will be described in the study reference manual.

FSHD PROs

FSHD-HI

The FSHD-HI will be measured at the timepoints specified in the Schedule of Assessments (Table 2).

The FSHD-HI is a 15-domain questionnaire designed and based on subject interviews to measure total FSHD health-related quality-of-life, including both motor impairment and the social and emotional impact of FSHD. A total of 116 questions are combined into a total score and domain scores, the scores are transformed onto a percentage scale, with 100 representing maximal disability, and lower scores representing decreasing disability. The scoring is done centrally by the vendor who developed the tool.

The change from baseline in FSHD-HI total score will be calculated at each post-dose timepoint.

FSHD-RODS

The FSHD-RODS will be measured at the timepoints specified in the Schedule of Assessments (Table 2).

The FSHD-RODS is a patient-reported, linearly weighted scale that precisely measures ADLs and participation in subjects with FSHD using 50 items based on the Rasch model. Details will be described in the study reference manual.

The change from baseline in FSHD-RODS score will be calculated at each post-dose timepoint.

Real-world Mobility Assessments

Each subject's activity will be monitored in the outpatient setting intermittently from Visit 2 to the end of the study. Wearable activity monitoring devices will be provided to each subject. The training for the devices will be done at the clinical site before they are handed the wearable devices. The subjects will be able to place their devices on their body by themselves. One device is placed on 1 arm, and 1 device goes on 1 leg.

The exact time of wearing the devices will be variable for each subject, but the duration of wearing the device will be similar. It is expected that the subject will wear the devices as soon as they wake up in the morning and are able to put on the device. Subjects may be asked to perform some standardised physical activity after putting on and before removing the devices.

Subjects who do not put on the device during the study period may be contacted to remind them to put on the device or to offer assistance.

Detailed instructions and details on wearables will be provided to the study site and subjects in a separate study reference manual.

Subjects will be asked to record the use of ankle-foot-orthotics or other assistive devices on a paper calendar during the time they are wearing the wearables, if applicable.

Real world mobility will be assessed only in the main part of the study. Real world mobility will not be assessed in the extension part of the study.

PGIC

The PGIC will be measured at the timepoints specified in the Schedule of Assessments (Table 2).

The self-report measure PGIC reflects a subject's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a subject's rating of overall improvement. Subjects rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

6-MWT

A 6-MWT will be performed at the timepoints specified in the Schedule of Assessments (Table 2) to evaluate the change from the pre-treatment period in the distance the subject is able to walk over a total of 6 minutes. Details about the 6-MWT will be described in the study reference manual.

Spirometry

Spirometry will be measured at the timepoints specified in the Schedule of Assessments (Table 2) to evaluate the change from the pre-treatment period in lung ventilatory function. Details about the spirometry assessment will be described in the study reference manual.

8.3 Treatment Allocation

All subjects will have biopsy at Visit 4. For the second biopsy, subjects will be assigned to either the Visit 5 or Visit 8 for their first on-treatment muscle biopsy. The first 8 subjects enrolled will be assigned to the Visit 5 biopsy, and the second 8 subjects enrolled will be assigned to the Visit 8 biopsy.

8.4 Study Procedures

The Schedule of Assessments for the main portion of the study is described in Table 2. The Schedule of Assessments for the extension is described in Table 3.

Table 2 Schedule of Assessments – Main Study

Assessment	Pre-Treatment Period				Treatment Period						Follow-up Period
	Study Visit[a]										
	Visit 1 (Screening [Day -28 to -1])[b]	Visit 2 (Baseline [Day 1])	Visit 3 (Week 4 [±1 wk])	Visit 4 (Week 8[c] [±1 wk])	Visit 5 (Week 14 [±2 wks])	Visit 6 (Week 24 [±2 wks])	Visit 7 (Week 36 [(±2 wks])	Visit 8 (Week 48 [±2 wks])	ET Visit	Visit 9[d] (Week 60/ [±4 wks] EOT or Rollover to Extension)	Visit 10 (Week 64/ [±2 wks] EOS)
Informed consent	X										
Eligibility	X										
Reconfirm eligibility				X							
Demographics	X										
Medical history	X										
FSHD History[e]	X										
Outpatient visits	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[f]	X								X		X
Physical examination[g]	X										
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X
ECG[i]	X			X	X	X	X	X	X	X	X
Genetic Confirmation of FSHD1[j]	X										
Blood sample for serology testing[k]	X										
Urine drug screen	X										
Serum hCG test[l]	X										
Urine hCG test[l]				X	X	X	X	X	X	X	

Assessment	Pre-Treatment Period				Treatment Period						Follow-up Period
	Study Visit[a]										
	Visit 1 (Screening [Day -28 to -1])[b]	Visit 2 (Baseline [Day 1])	Visit 3 (Week 4 [±1 wk])	Visit 4 (Week 8[c] [±1 wk])	Visit 5 (Week 14 [±2 wks])	Visit 6 (Week 24 [±2 wks])	Visit 7 (Week 36 [(±2 wks])	Visit 8 (Week 48 [±2 wks])	ET Visit	Visit 9[d] (Week 60/ [±4 wks] EOT or Rollover to Extension)	Visit 10 (Week 64/ [±2 wks] EOS)
Serum FSH (postmenopausal females only)	X										
Serum chemistry	X			X	X	X	X	X	X	X	X
Haematology	X			X	X	X	X	X	X	X	X
Coagulation studies	X										
PK (blood)[m]				X	X	X	X	X	X	X	
PD (blood)[n]				X	X	X	X	X	X	X	
MRI[o]	X						X		X	X	
Muscle US		X			X	X	X		X	X	
Skeletal muscle needle biopsy				X[p]	X[p]						
Discovery biomarkers (serum)				X	X			X			
PD/Target engagement (Muscle)				X	X					X	
Losmapimod concentration (muscle)				X	X					X	
[redacted]											
RWS	X		X	X	X	X	X	X	X	X	
TUG[r]	X		X	X	X	X	X	X	X	X	

Assessment	Pre-Treatment Period				Treatment Period						Follow-up Period
	Study Visit[a]										
	Visit 1 (Screening [Day -28 to -1])[b]	Visit 2 (Baseline [Day 1])	Visit 3 (Week 4 [±1 wk])	Visit 4 (Week 8[c] [±1 wk])	Visit 5 (Week 14 [±2 wks])	Visit 6 (Week 24 [±2 wks])	Visit 7 (Week 36 [(±2 wks])	Visit 8 (Week 48 [±2 wks])	ET Visit	Visit 9[d] (Week 60/ [±4 wks] EOT or Rollover to Extension)	Visit 10 (Week 64/ [±2 wks] EOS)
Muscle strength by quantitative dynamometry with hand-held device	X		X		X	X		X	X	X	
Muscle strength by quantitative dynamometry with bed frame equipment	X		X							X	
MFM domain 1	X			X		X		X	X	X	
FSHD-RODS	X		X			X			X	X	
FSHD-HI	X		X			X			X	X	
PGIC					X	X	X	X	X	X	
6-MWT	X		X	X	X	X	X	X	X	X	
Spirometry		X				X		X	X	X	
Losmapimod dispensing				Study Drug will be dispensed starting at Visit 4. Resupply will be provided as needed throughout the study, until EOT							
Outpatient Mobility Assessment		Intermittently from Visit 2 to End of Study									
AE Monitoring		Continuous from signing of ICF to End of Study									
Medications review		Continuous from signing of ICF to End of Study									

a. Unscheduled visits can be scheduled at the discretion of the principal investigator to perform any assessments related to any AEs/SAEs that arise.
b. Subjects are required to fast for at least 4 hours prior to the screening visit.
c Visit 4 is the end of the pre-treatment period and the beginning of the treatment period. Dosing will begin at Visit 4.
d Any visit can be split into 2 days with overnight hotel stay as needed to accommodate performance of MRI and US, or to accommodate busy site schedules.

e Specific questions about FSHD history will be included in the baseline medical history exam.
f Height will be measured at screening only
g A full physical examination, including a neurological examination, will be performed at Screening. Symptom-directed physical examinations and laboratory assessments can be performed at any time at the discretion of the investigator.
h. Vital sign measurements will be performed after subjects have rested for at least 5 minutes.
i. Standard 12-lead ECGs will be performed after the subject has been supine for at least 5 minutes. ECGs will be collected at screening, before dosing only at Visit 4, and at approximately 3 hours (± 90 minutes) after dosing for all other on-treatment visits.
j. Genetic confirmation must be obtained before the screening MRI and baseline muscle biopsy are performed; genetic confirmation can come from previous testing, if verified with appropriate documentation. Due to the stable transmission of repeat sizes within families, subjects with a clinical diagnosis of FSHD who have a first-degree relative with a genetically confirmed diagnosis of FSHD1 may be entered into the study for screening and MRI. During screening, a confirmatory genetic diagnosis will be conducted. If genetic testing is necessary, the 4-week screening window and activities will not start until the results are obtained and verified by the principal investigator.
k. Subjects will be screened for HBsAg, HCV antibody, or antibodies against HIV 1/HIV 2.
l. Pregnancy test for women of childbearing potential will be performed at Screening (in serum) and at each study visit (in urine) and confirmed negative prior to medication supply during clinical visits on the on-treatment period.
m. Collect a predose PK sample and then a postdose PK sample shortly (within 15 minutes) after the ECG that is scheduled for 1.5 to 4.5 hours postdose.
n. Blood samples for PD will be taken predose and 3.5 hours postdose (+/- 30 minutes) at Visits 4, 5, 6, 7, 8, 9, and ET visit.
o. Subjects will fill out a safety questionnaire to be sure it is safe to perform an MRI.
p. All subjects will undergo muscle biopsy at Visit 4 (pre-treatment) and Visit 5 (on-treatment at 4-or 8-weeks).
[redacted]
r. Both the classic and FSHD- TUG tests will be performed at each timepoint.

6-MWT=6-minute walking test; AE=adverse event;. C_{max}=maximum observed plasma concentration; DUX4=double homeobox 4; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; FSHD=facioscapulohumeral muscular dystrophy; FSHD-HI=FSHD Health Index questionnaire; FSHD-RODS=FSHD Rasch-built Overall Disability Scale; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV 1=human immunodeficiency virus 1; HIV 2=human immunodeficiency virus 2; ICF=informed consent form; MFM=Motor Function Measure; MRI=magnetic resonance imaging; PD=pharmacodynamics; PGIC=Patients' Global Impression of Change; PK=pharmacokinetic; RWS=Reachable Workspace; SAE=serious adverse event; TUG=Timed Up and Go; US=ultrasound; wk(s)=week(s).

Table 3 Schedule of Assessments – Extension

Assessment	Week 72 Week 120 Week 168 etc.	Week 84 Week 132 Week 180 etc.	Week 96 Week 144 Week 192 etc.	Week 108 Week 156 Week 204 etc.	ET Visit[a]	End of Study Follow-Up
Visit Window (weeks)[b]	±4	±4	±4	±4		
Outpatient visits		X		X	X	X
Safety phone visit	X		X			
Weight/Height				X		X
[redacted]						
Physical examination[d]				X		
Vital signs[e]		X		X	X	X
ECG[f]		X		X	X	X
Urine hCG test[g]	X[h]	X	X[h]	X	X	
Serum chemistry		X		X	X	X
Haematology		X		X	X	X
Losmapimod dispensing		X		X		
AE Monitoring	Continuous from signing the ICF through the safety follow-up visit					
Concomitant medications	Continuous from signing the ICF through the safety follow-up visit					
Concomitant treatments and procedures	Continuous from signing the ICF through the safety follow-up visit					

a. If a subject prematurely discontinues study treatment during the extension, they will be encouraged to remain in the study and continue with all other aspects of the study. If a subject decides to prematurely discontinue study treatment during the Extension and not continue with all other aspects of the study, they will be considered to have withdrawn from the study. If a subject withdraws from the study during the extension, they will be asked to complete the ET visit as soon as possible after the decision to terminate study participation and to complete the safety follow-up visit 7 (±3) days after their last dose of study drug. If the ET visit will be scheduled more than 7 days after the last dose of study drug, the safety follow-up and ET visits may be combined, with no duplication of assessments required.
b. Any visit can be split into 2 days with overnight hotel stay as needed to accommodate busy site schedules.
[redacted]
d. A full physical examination, including a neurological examination, will be performed annually. Symptom-directed physical examinations and laboratory assessments can be performed at any time at the discretion of the investigator.
e. Vital sign measurements will be performed after subjects have rested for at least 5 minutes.
f. Standard 12-lead ECGs will be performed after the subject has been supine for at least 5 minutes. ECGs are not mandatory assessments and will be carried out at the discretion of the investigator.
g. Pregnancy test for women of childbearing potential will be performed at each in-person study visit (in urine) and confirmed negative prior to medication supply during clinical visits on the on-treatment period.
h. Home pregnancy tests for women of childbearing potential will be performed every 12 weeks between in-person clinic visits.

AE=adverse event; hCG= human chorionic gonadotropin; ECG=electrocardiogram; ET=early termination; FSHD=facioscapulohumeral muscular dystrophy; ICF=informed consent form.

8.5 Withdrawal of Individual Subjects

8.5.1 Study Drug Interruption or Discontinuation

Before trial medication is administered, changes in the subject's health status since the previous visit must be checked, including laboratory results if applicable. The investigator must temporally interrupt or permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the subject. The interruption, lowering (to mg PO BID), or premature discontinuation of the study drug might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (eg, ECG or laboratory abnormalities), or, for administrative reasons, the withdrawal of the subject's consent. The reason for study drug interruption, dose lowering either transiently or permanently, or premature discontinuation must be clearly documented and approved by the sponsor.

8.5.2 Subject Withdrawal

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Subjects who permanently discontinue treatment may choose to continue on the study at the discretion of the sponsor.

8.6 Replacement of Individual Subjects After Withdrawal

Subjects withdrawing for reasons other than AEs or any other tolerability issues with the treatment may be replaced according to sponsor discretion. Replacement subjects will help ensure that a sufficient number of subjects achieve the Week 60 and Week 64 visits; no more than 8 subjects (ie, 50% of the total sample size) will be replaced.

8.7 Follow-up of Subjects Withdrawn from Treatment

Should a subject decide to withdraw from the study, all efforts should be made to complete and report the observations, particularly the end of study visit examinations, as thoroughly as possible, and any safety events should be clearly assessed and followed up until full resolution or persistence are documented.

8.8 Premature Termination of the Study

At any time, the sponsor, the investigators, or the institutional review boards/independent ethics committees may terminate this study for reasonable cause. Conditions that may lead to reasonable cause and warrant termination include, but are not limited to the following:

- Subject or investigator noncompliance
- Unsatisfactory subject enrolment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data

- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the regulatory authority
- Written notification that includes the reason for the clinical study termination is required.

9. SAFETY REPORTING

9.1 Temporary Halt for Reasons of Subject Safety

In accordance with section 10, subsection 4 of the Medical Research Involving Human Subjects Act (WMO), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited medical research ethics committee (METC) without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs, and Suspected Unexpected Serious Adverse Reactions (SUSARs)

9.2.1 AEs

AEs are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All AEs reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 SAEs

An SAE is any untoward medical occurrence or effect that

- Results in death;
- Is life threatening (at the time of the event);
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect; or
- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as an SAE.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor or authorised representative will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the SAEs.

9.2.3 SUSARs

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following 3 conditions are met:

1. The event must be serious (see Section 9.2.2);
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - IB for an unauthorised medicinal product.

The sponsor will expedite report of the following SUSARs to the METC through the web portal *ToetsingOnline*:

- SUSARs that have arisen in the clinical trial that was assessed by the METC; or
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study drug, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or *ToetsingOnline* is sufficient as notification to the competent authority.

The sponsor will expedite report of all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be a maximum of 7 days for a preliminary report with another 8 days for completion of the report.

Since this is an open-label pilot study, there is no code to break for SUSAR reporting.

9.3 Annual Safety Report

In addition to the expedited reporting of SUSARs, the sponsor will submit a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States once a year throughout the clinical trial.

This safety report consists of the following:

- A list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study; and
- A report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of AEs

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported until the end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board/Safety Committee

Not applicable for this study. The investigators at the site, the sponsor, and the vendor hired for pharmacovigilance will actively monitor the study for AE/SAEs from first signing of ICF to last subject last visit.

10. STATISTICAL ANALYSIS

10.1 Statistical Analysis Plan

A SAP will be generated and approved prior to the first interim analysis. The SAP will detail the implementation of all planned statistical analyses and the calculation of all derived endpoints. The SAP can be updated at any time during the study. Any updates to the SAP and any deviations from the planned analyses will be described and justified in the final clinical study report (CSR). The study is not blinded. The study subjects, personnel at the site, sponsor employees, and vendors are all fully aware that all subjects are taking active investigational product starting at Visit 4.

10.1.1 Analysis Methods

In general, all study endpoints will be summarised using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, median, minimum, and maximum. Plasma concentrations of losmapimod will be summarised by timepoint. Summaries of change from baseline variables will include only subjects who have both a baseline value and corresponding value at the timepoint of interest. Baseline is defined as the pre-treatment period and all values prior to losmapimod treatment. Descriptive statistics for categorical data will include frequency and percentage. Where appropriate, descriptive statistics may be presented with 95% CIs.

Listings will be provided for all collected study data.

10.2 Primary Study Parameter(s)

10.2.1 Demographics and Baseline Variables

Demographic and other baseline characteristics will be summarised using descriptive statistics.

10.2.2 Feasibility

Feasibility of outpatient evaluation of mobility (eg, wearable technology) will be assessed on an ongoing basis. This measurement will be discontinued if it is found to be not feasible in the pre-treatment period.

10.2.3 Safety and Tolerability Endpoints

The safety data analysis set will be used to perform all safety analyses. Subjects who take at least 1 dose of study medication will be included in the safety analysis.

Baseline is defined as the pre-treatment period and all values prior to losmapimod treatment. Change from baseline will be calculated for all continuous safety parameters.

Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The overall incidence of AEs will be summarised by MedDRA primary System Organ Class (SOC) and Preferred Term (PT).

All AEs will be displayed in listings or graphs when appropriate. In addition, SAEs and treatment-emergent AEs (TEAEs) leading to discontinuation of study drug will be listed.

A TEAE is defined as an AE observed after starting administration of the specific treatment. If a subject does experience an event both prior to and after starting administration of a treatment, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (ie, it is reported with a new start date) after starting administration of the specific treatment and prior to the start of another treatment.

The number of TEAEs and the number of subjects with at least 1 TEAE will be summarised for the following:

- SOC and PT;
- SOC, PT, and maximum severity;
- SOC, PT, and maximum drug relatedness.

Clinical Laboratory Tests

Reported values and change from baseline values of clinical laboratory variables will be summarised using descriptive statistics by timepoint. The number of available observations and out-of-range values (absolute and in percentage) will also be presented. Clinical laboratory values will be listed.

ECGs

Reported values and change from baseline values of ECG variables will be summarised using descriptive statistics and timepoint. The number of available observations and out-of-range values (absolute and in percentage) will also be presented. ECG values will be listed.

Vital Signs

Reported values and change from baseline values of supine blood pressure, pulse rate, respiratory rate, and temperature will be summarised using descriptive statistics by timepoint. The number of available observations and out-of-range values (absolute and in percentage) will be presented. Vital sign variables will be listed. Values outside the reference range will be flagged in the listing.

10.3 Secondary Study Parameter(s)

10.3.1 PD Endpoints

PD parameters include target engagement in pHSP27 as measured in peripheral whole blood after sorbitol stimulation ex vivo and in skeletal muscle needle biopsies without ex vivo stimulation.

PD endpoints will be summarised by timepoint. Natural log (ln) transformed values of pHSP27 will be analysed using paired t-test or similar methods. The difference between the post dose log transformed pHSP27 value and the baseline log transformed value will be tested versus zero.

Point estimates for the difference will be presented along with 95% CIs. Estimates will be back transformed using the exponential function to estimate the ratio of post dose pHSP27 value to baseline value. Further details of the PK/PD analysis of pHSP27 will be specified in the SAP.

10.3.2 PK Endpoints

Plasma and muscle concentrations of losmapimod will be summarised by timepoint. Individual concentrations will be plotted versus time using both linear and log scales for the y-axis. Additionally, concentration versus time curves will be plotted as a spaghetti plot with the group median added. Individual subject listings will also be provided.

10.4 Exploratory Study Parameter(s)

The following exploratory PD parameters will be summarised by timepoint: MRI-based muscle volume and fat fraction, pHSP27/total HSP27 in muscle and blood, change in DUX4 activity and change in other disease related gene transcripts in muscle biopsies, change in potential [redacted] of DUX4 activity and/or muscle injury or repair if discovered, mobility assessments, RWS with and without weights, classic TUG, FSHD-optimised TUG, muscle strength, MFM domain 1, FSHD PRO, PGIC, FSHD-HI, 6-MWT, and spirometry. Individual subject listings for each parameter will also be provided. The analyses for these parameters will be performed as change from pre-treatment period over the duration of treatment, within each subject and for the group as a whole.

All exploratory endpoints will be detailed in the SAP.

Deviations from the original statistical plan will be documented in the CSR.

10.5 Other Study Parameters

There are no other study parameters.

10.6 Interim Analysis

There are 2 interim analyses planned in this study: the first interim analysis will occur after approximately 6 to 8 subjects have completed the Visit 5 (Week 14 ± 2 weeks) on-treatment muscle biopsy, and the second interim analysis will occur around the time of analysis for the Phase2b ReDUX4 study. The interim analyses will evaluate for initial changes from pre-treatment in efficacy, clinical outcome assessments, and molecular and [redacted] with treatment of losmapimod. The 2 separate interim analyses are designed to get an initial look at the change from baseline for the DUX4 [redacted] in muscle biopsies at the first interim analysis, and for the [redacted] and ultrasound endpoints at the second interim analysis. No formal statistical hypothesis testing will be performed.

11. ETHICAL CONSIDERATIONS

11.1 Regulation Statement

The investigator will ensure that this study is conducted in full compliance with the protocol, the principles of the Declaration of Helsinki (www.wma.net), ICH Good Clinical Practice (GCP) guidelines (http://www.ich.org/products/guidelines.html), with the laws and regulations of the country in which the clinical research is conducted, and in accordance with the WMO.

11.2 Recruitment and Consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The investigator must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

The Informed Consent and Subject Information will be provided in Dutch.

11.3 Objection by Minors or Incapacitated Subjects

Not applicable for this study.

11.4 Benefits and Risks Assessment, Group Relatedness

FSHD is a rare disabling disease in which there are currently no approved disease-modifying treatments. Very few compounds are currently in clinical development for FSHD, and none target the disease at its root cause. No therapy has been proven to reduce disease severity or delay the progression of the disease; therefore, there is a high unmet need for an effective therapy for

FSHD. Fulcrum is developing losmapimod, a selective p38α and β kinase small molecule inhibitor that specifically reduces or inhibits DUX4 activity in FSHD myotubes for treatment of FSHD at its root cause. The original developer widely tested losmapimod in various subject populations across at least 10 adult indications, including rheumatoid arthritis and COPD, and there is subject exposure data from 19 publicly available clinical studies. In aggregate, over 3,500 subjects have been dosed with losmapimod, as documented in the published literature, and summarised in the IB.

Losmapimod is a potential disease-modifying treatment for FSHD based on its strong preclinical efficacy at inhibiting DUX4 expression and reducing DUX4-regulated gene transcripts and apoptosis across multiple FSHD1 and FSHD2 cell lines without impacting myotube differentiation. The expectation is that sufficient target engagement with losmapimod at the proposed dose of 15 mg PO BID will slow down or arrest disease progression in subjects with FSHD by reducing aberrant DUX4 expression in skeletal muscle and other affected organs. As FSHD is a slowly progressive disease, this pilot study was designed for long-term treatment (52

weeks).

Based on the observed efficacy for inhibiting or reducing aberrant DUX4 expression and therefore activity in FSHD cells, the PD and safety data from nonclinical studies, and the extensive clinical safety data available in the public domain from over 3,500 dosed subjects, the benefit/risk balance supports clinical development with losmapimod in FSHD.

Participation in this study does not mean that the clinical symptoms, progression of disease, or underlying cause of FSHD1 will be improved or cured. While losmapimod is a potential disease-modifying treatment of FSHD based on its strong preclinical efficacy at inhibiting DUX4 expression and reducing DUX4-regulated gene transcripts and apoptosis across multiple FSHD1 and FSHD2 cell lines without impacting myotube differentiation, benefits of the treatment are not certain. FSHD1 clinical symptoms and/or progression may worsen at any time during this study.

Subjects may experience side effects or complications from the study treatment, as well as AEs and discomforts from the study assessments. Side effects of the investigational product include headache, fatigue, nasopharyngitis, dizziness, and back pain. Side effects of the study assessments include pain or bruising from blood draws; pain, bruising, swelling, redness, or bleeding from muscle biopsy; claustrophobia from MRI; and skin irritation from ECG electrode stickers. All potential side effects will be listed in the subject informed consent form.

Subjects will be asked to follow strict study procedures and respond to questionnaires. There may also be incidental findings about the subject's health during the study. The subject and his/her primary care physician will be notified if findings are pertinent to his/her health so that appropriate follow-up can be arranged.

Further details on benefits and risks are provided in Section 1.1 and the IB.

11.5 Compensation for Injury

11.5.1 Insurance

The sponsor/investigator has a liability insurance, which is in accordance with Article 7 of the WMO.

The sponsor (also) has an insurance, which is in accordance with the legal requirements in the Netherlands (Article 7 of the WMO). This insurance provides coverage for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Subjects will be appropriately compensated for their time and any travel expenses.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and Storage of Data and Documents

12.1.1 Data Collection

Data will be recorded on electronic data collection forms for subsequent statistical analysis. The data will be handled confidentially. A Subject Screening and Enrolment Log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

12.1.2 Database Management and Quality Control

A quality control check will be done by the sponsor staff on all data entered in the database using data entry progress checks and database listings (blind data review). Errors with obvious corrections will be corrected before database lock.

Results of clinical laboratory and PK analyses will be sent electronically to the sponsor and loaded into the database.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the investigator, sponsor, and the statistician.

12.2 Monitoring and Quality Assurance

This study will be conducted according to applicable Standard Operating Procedures. Quality assurance will be performed under the responsibility of the sponsor's Quality Assurance Manager.

In accordance with applicable regulations and GCP, sponsor's monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GCP requirements. There will be a formal site initiation meeting, either in person or remotely, with an overview of the study protocol, personnel qualification, data capture, GCP requirements, and review of ethics committee and site contract documentation. This initiation visit will be performed before the first subject is included.

Monitoring visits and contacts will occur at regular intervals thereafter, according to a frequency defined in the study-specific monitoring plan. A close-out visit will be performed after study closure.

The sponsor will monitor the study consistent with the demands of the study and site and vendor activity to verify that:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected

- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements
- The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

12.3 Amendments

Any change to a protocol has to be considered as an amendment.

12.3.1 Substantial Amendment

A 'substantial amendment' is defined as an amendment to the terms of the METC application or to the protocol or any other supporting documentation that is likely to affect to a significant degree the following:

- The safety or physical or mental integrity of the subjects of the trial;
- The scientific value of the trial;
- The conduct or management of the trial; or
- The quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

12.3.2 Non-Substantial Amendment

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual Progress Report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, SAEs/serious adverse reactions, other problems, and amendments.

12.5 Temporary Halt and (Prematurely) End of Study Report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last subject's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within 1 year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the competent authority.

12.6 Public Disclosure and Publication Policy

The results of the study will be made public consistent with the Central Committee on Research Involving Human Subjects (CCMO) publication policy. The authorship guidelines of the Vancouver Protocol will be followed regarding co-authorship.

The principal investigator will have the opportunity to review the analysis of the data and to discuss with the sponsor the interpretation of the study results prior to publication.

The list of authors of any formal publication or presentation of study results may include, as appropriate, 1 or more representatives of the sponsor and will be determined by mutual agreement and only if they qualify for authorship per the Vancouver Protocol.

13. STRUCTURED RISK ANALYSIS

13.1 Potential Issues of Concern

a. Level of knowledge about mechanism of action

There is sufficient evidence to support that aberrant expression of the DUX4 program is the root cause of FSHD. The end result of DUX4 activity is myofibre death with replacement of skeletal muscle by fat, resulting in a clinical manifestation of progressive loss of strength and accumulation of physical disability. Therefore, compounds that reduce or prevent aberrant expression of DUX4 and its transcriptional program should provide a robust disease-modifying therapeutic approach for treatment of FSHD at its root cause. See the IB for details.

Fulcrum is developing losmapimod, a selective p38α and β kinase small molecule inhibitor that specifically reduces DUX4 activity in FSHD myotubes, for treatment of FSHD at its root cause. Losmapimod is a potential disease-modifying treatment for FSHD based on its strong preclinical efficacy at inhibiting DUX4 expression and reducing DUX4-regulated gene transcripts and apoptosis across multiple FSHD1 and FSHD2 cell lines without impacting myotube differentiation. The expectation is that sufficient target engagement with losmapimod at the proposed dose of 15 mg PO BID will slow down or arrest disease progression in subjects with FSHD by reducing aberrant DUX4 expression in skeletal muscle and other affected organs. See the IB for details.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Losmapimod has been widely tested in various subject populations across at least 10 adult indications, including coronary artery disease, rheumatoid arthritis, and COPD, and there is subject exposure data from 19 publicly available clinical studies from the original developer (GSK) and additional studies summarised in the IB. In aggregate, over 3,500 subjects have been dosed with losmapimod, as documented in the published literature. Losmapimod was not previously evaluated for treatment of neuromuscular diseases or FSHD. See the IB for details.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex vivo* human cell material?

Yes, this has been done by the sponsor and is described in detail in the IB. Nonclinical studies indicate that losmapimod is likely to reduce or prevent DUX4 activity in human FSHD cells, and to engage the drug target in skeletal muscle in humans following oral administration at the planned dose of 15 mg BID. In rodent skeletal muscle, losmapimod rapidly distributes to skeletal muscle and engages the drug target (p38α/β). For all single-dose studies, the muscle to plasma drug exposure ratios are ≥0.6 following oral administration using doses predicted to result in clinically relevant plasma concentrations in the clinic. Based on clinical blood PK/PD studies previously performed with losmapimod by GSK (Barbour et al., 2013) and the sponsor's nonclinical studies, it is predicted that the proposed human doses of 15 mg BID of losmapimod will provide drug concentrations in FSHD1 skeletal muscle sufficient to reduce p38α activity and

DUX4 activity in this study. See the IB for details.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Losmapimod is a selective p38α/β MAPK inhibitor with appropriate pharmacology, target engagement, and safety to support dosing in subjects with FSHD1. In vitro ADME and safety assessments indicate that losmapimod has limited risk of significant interaction with other kinases, transporters, or CYP enzymes at pharmacologically relevant concentrations. Further in vitro characterisation of the effects of losmapimod in FSHD1 patient-derived immortalised myotubes showed potent and selective inhibition of the p38α pathway, reduction of DUX4 protein and of the DUX4-regulated gene expression program, and inhibition of apoptosis and prevention of death of the FSHD1 myotubes. Additionally, Fulcrum's pre-clinical data was consistent with target engagement observed in previous preclinical studies; as there was a dose- dependent reduction of pHSP27. These data are consistent with the previous sponsor's data demonstrating that as losmapimod concentrations change, the resulting change in pharmacology at the site of action occurs at the same time (see the IB for details).

In vivo muscle PK/PD studies in non-fasted mice and rats demonstrated that dose levels of losmapimod, which achieved clinically relevant plasma exposures, also produced significant skeletal muscle exposure and p38α/β MAPK pathway inhibition in rodent skeletal muscles (see the IB for details). The muscle exposures achieved are predicted to result in 50% or higher reduction in DUX4-dependent targets in FSHD subject's skeletal muscle biopsies based upon the in vitro efficacy data in FSHD myotubes. The PK/PD analysis additionally indicated that maximal target engagement in muscle was achieved when plasma losmapimod concentrations were >30 ng/mL, and that significant p38α/β pathway inhibition would be expected in muscle with clinical doses of 15 mg BID (Barbour et al., 2013).

See the IB for details.

e. Analysis of potential effect

Based on clinical PK/PD studies in humans with losmapimod (Barbour et al., 2013), it is predicted that the proposed human dose of losmapimod at 15 mg PO BID would provide drug concentrations in skeletal muscle sufficient to significantly reduce p38α activity and DUX4 expression and therefore activity in FSHD1. The expectation is that sufficient target engagement with losmapimod at this planned dose will slow down or arrest disease progression in subjects with FSHD by reducing aberrant DUX4 expression in skeletal muscle and other affected organs.

A review of all existing clinical safety data as presented in the IB indicates that there are currently no identified adverse drug reactions and no expected safety risks of losmapimod that would prevent further clinical development in FSHD1 or any other indication. Adverse events of special interest that were investigated over many years by the previous developer are listed in the IB and are being monitored as part of the proposed Schedule of Assessments.

f. PK considerations

The principal route of metabolism is hydrolysis of the cyclopropylamide group by CES-1 to form a pharmacologically inactive metabolite, FTX-5508. The PK of the primary but inactive metabolite has been evaluated. The T_{max} for FTX-5508 was similar to the parent drug after oral administration of losmapimod, but the $T_{1/2}$ was slightly longer. Exposure, as measured by plasma AUC, was typically twice as high as losmapimod (Barbour et al., 2013; Barbour et al., 2015; Ino et al., 2015).

g. Study population

This study is evaluating subjects with FSHD1, a rare disabling disease characterised by descending progressive skeletal muscle weakness affecting the face, shoulders, arms, and trunk, followed by weakness of the distal lower extremities and pelvic girdle. Progression of FSHD1 is slow but steady; muscle strength, measured by quantitative muscle testing decreases at an average rate of approximately 1% to 4% per year (Statland and Tawil, 2014a).

Losmapimod should not be administered to pregnant women or women at risk of becoming pregnant because it was associated with embryo-foetal malformations in rats and rabbits. Women who are pregnant or with childbearing potential are not included in this study. Male subjects with a female partner who is planning to become pregnant during the study or within 90 days after the last study drug dose are also not included in this study.

Due to a theoretical, potential modest impact of losmapimod on immune function due to inhibition of p38α pharmacology, there could be circumstances when the theoretical risk of losmapimod administration may outweigh its potential benefits to subjects with FSHD1

(ie, concurrent administration of cytotoxic chemotherapy for cancer). Whether losmapimod could decrease the efficacy of immunisations has not been studied.

A review of all existing clinical safety data as presented in the IB indicates that there are currently no identified adverse drug reactions and no expected safety risks of losmapimod that could prevent further clinical development in FSHD1 or any other indication. Adverse events of special interest that were investigated over many years by the previous developer are listed in the IB.

h. Interaction with other products

Based on in vitro data, losmapimod and its major metabolite, FTX-5508, are unlikely to interact with substrates or inhibitors of CYP, P-glycoprotein, human OATP1B1 and OATP1B3, or human OATs. However, both losmapimod and FTX-5508 are inhibitors of BCRP in vitro with IC50 values of 1.3 and 42 µM, respectively. Following oral dosing, local concentrations of losmapimod are likely to exceed the in vitro IC50, leading to the possibility that losmapimod may inhibit the efflux of BCRP substrates, resulting in increased systemic exposure to such compounds. See the IB for details.

i. Predictability of effect

Fulcrum is developing losmapimod, a selective p38α/β mitogen activated protein kinase (MAPK) inhibitor that specifically reduces DUX4 protein activity in FSHD myotubes, for treatment of FSHD at its root cause. FSHD is caused by aberrant expression of the DUX4 gene, a homeobox transcription factor that plays an important role as a master regulator of a transcriptional program required early during embryogenesis. Evidence of DUX4 expression is the major molecular signature that distinguishes FSHD from healthy muscle. The end result of DUX4 activity is myofibre death with the replacement of skeletal muscle by fat resulting in a clinical manifestation of progressive loss of strength and accumulation of physical disability. Therefore, compounds that reduce DUX4 or prevent aberrant expression of DUX4 and its transcriptional program should provide a robust disease-modifying therapeutic approach for treatment of FSHD.

This study will enroll only those subjects with genetically confirmed FSHD1. FSHD1 encompasses the majority of the FSHD population, as well as those subjects who will meet inclusion criteria for this study. Focusing on FSHD1 will decrease heterogeneity of disease phenotypes, as this is a pilot study with a relatively small sample size. Controlling for this variability may enable a more accurate initial assessment of the potential efficacy of losmapimod as a potential disease modifying therapy for FSHD.

This open-label pilot study will include PK/PD assessments as well as an exploratory assessment of DUX4 activity in skeletal muscle as measured by RNA sequencing and by quantitative reverse transcription PCR in a panel of DUX4-regulated gene transcripts. The study will assess inhibition of p38α/β-related substrates as the target engagement PD marker in skeletal muscle.

Based on pre-clinical assessments, it is anticipated that treatment with losmapimod at the proposed dose will result in 50% or higher decrease in DUX4 activity. However, the true effect size is not known, and this pilot study will provide initial valuable information to inform ongoing and planned studies.

j. Can effects be managed?

There are currently no identified adverse drug reactions and no expected safety risks of losmapimod that would prevent further clinical development in FSHD or any other indication. There is potential for harm if human embryos or foetuses are exposed to losmapimod, therefore, strict contraception is required for female of childbearing potential to participate in the study.

13.2 Synthesis

Most of the studies previously completed were conducted using losmapimod oral tablets given with food. All subjects in these previous studies were adult males or females and included healthy volunteers or subjects with atherosclerosis, hypercholesterolemia, coronary artery disease, myocardial infarction, rheumatoid arthritis, COPD, major depressive disorder, neuropathic pain, or focal segmental glomerulosclerosis. Single oral doses as high as 60 mg and

repeated oral doses as high as 15 mg BID for up to 24 weeks were well-tolerated. One study in COPD reported dosing at 15 mg BID for up to a year (Pascoe et al., 2017). Most AEs observed were related to exacerbation of disease; others were typically reported by a similar proportion of subjects on losmapimod and placebo. Losmapimod did not consistently result in more study drug-related SAEs or deaths than placebo. There was no clinically relevant difference in laboratory measures, ECGs, or vital signs with losmapimod versus placebo. No adverse events that can definitely be attributed to losmapimod have been identified.

Based on the observed efficacy for inhibiting or reducing aberrant DUX4 expression and therefore activity in FSHD cells, the PD and safety data from nonclinical studies, and the extensive clinical safety data available in the public domain from over 3,500 dosed subjects, the benefit/risk balance supports clinical development with losmapimod in FSHD.

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15. APPENDIX: DRUGS POTENTIALLY AFFECTING MUSCLE FUNCTION

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

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