16.1.9 Documentation of Statistical Methods

This section contains the following document:

Final Statistical Analysis Plan version 1.0 dated 28 May 2020

Fulcrum Therapeutics

FIS-002-2019

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

28May2020

Final Statistical Analysis Plan
(Placebo-Controlled Treatment Period)

Version *1.0*

Prepared by:

Issued by: [redacted] _____ Date: ___/___/___

Lead Biostatistician, Biostatistics

Reviewed by: ____ _____ Date: ___/___/___

Senior Reviewer, AD, Biostatistics

Upon review of this document, the undersigned approves the statistical analysis plan. The analysis methods is acceptable and the table, listing, and figure production can begin.

Approved by: _____ Date: ___/___/___

Director, Biometrics
Fulcrum Therapeutics

DOCUMENT REVISION HISTORY

Version	Date	Details
0.5	06Dec2019	Stable Draft Version
0.6	07Jan2020	1) Update derivation of DUX4-related endpoints in 15.1, 15.2, and 15.3. 2) Removed section on inclusion and exclusion (Section 6.4) since no details are collected from screen failures. 3) Removed 16.2.3.2 in Section 15.6. 4) Updated number of 16.2.3.1 to 16.2.3 in Section 15.6.
0.7	05Feb2020	1) Updated section 8.1. Composite DUX4 score will now be provided by Q2 Lab Solutions. 2) Updated Appendices 15.1-15.5 to now contain assay validation, gene subset selection criteria/process, and derivation of DUX4 Score.
0.8	05May2020	1) Added details on the analysis for neurological examination results in Section 9.4 Physical Examination. 2) Added presentation of FSHD specific history in Section 6.2. 3) Updated Section 4.7 on sample size computation based on Version 3.0 of the protocol. 4) Added details about inclusion of open-label extension phase but a separate SAP will be created for this. 5) Updated SAP according to protocol Version 4.0 (COVID-19 Pandemic Emergency Amendment) a. Extended randomized placebo-controlled period from 24 to 48 weeks in Section 3.1, 3.2, 4.4, 4.8, 7.2.1, 8, 9, and 11. b. Added Open-label Losmapimod (Pre-COVID-19) Analysis Set in Section 4.9.6 and 8.Muscle biopsy to support the primary endpoint is updated to be performed on Week 16 or 36 for those subjects unable to have the biopsy at Week 16 due to the COVID-19 pandemic.

		c. Added interim analysis to be performed after a minimum of 22 paired muscle biopsies have been collected. d. Added hypothesis testing on primary and select secondary and exploratory endpoints in Section 8.1. e. Removed measurement of the metabolite GSK198602 in Section 2, 3.2 and 10. f. Updated Appendix 15.6 to include the latest schedule of events. g. Updated Appendices 15.7-15-9 to include the additional outputs and additional column to identify the outputs needed for topline and IA deliveries.
1.0	28May2020	Approved version

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CRF	case report form
DUX4	double homeobox 4
ECG	electrocardiogram
FAS	full analysis set
FSHD	facioscapulohumeral muscular dystrophy
FSHD-HI	FSHD Health Index
IRT	Interactive Response Technology
LMV	lean muscle volume
LOCF	Last Observation Carried Forward
LS	least-squares
MedDRA	Medical Dictionary for Regulatory Activities
MFF	muscle fat fraction
MFI	muscle fat infiltration
MFM	Motor Function Measure
MRI	Magnetic Resonance Imaging
MMRM	Mixed Effect Model for Repeated Measures
MSK	musculoskeletal
OL	open-label
OLE	open-label extension
PGIC	Patient's Global Impression of Change
PO	orally
PPS	per protocol set
PT	preferred term
RWS	Reachable Workspace
RSA	relative surface area
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SD	standard deviation
SE	standard error
SOC	system organ class
SRC	Safety Review Committee
TEAE	treatment-emergent adverse events
TUG	Timed Up and Go
WHODD	World Health Organization drug dictionary

1. Introduction

This study is being conducted under the sponsorship of Fulcrum Therapeutics (Fulcrum) in accordance with applicable standard operating procedures. Statistical analyses are being conducted under contract with [redacted] Inc., in collaboration with Fulcrum.

The Clinical, Data Management, and Biostatistics departments at [redacted] will work diligently and collaboratively with Fulcrum to ensure that the data collected and analyzed for this study are of the highest quality possible. This will be accomplished in part by having thorough edit checks written, programmed, and updated as needed.

This Statistical Analysis Plan (SAP) is based on the protocol version 4.0 (COVID-19 Pandemic Emergency Amendment), dated 10Apr2020. This SAP is for the randomized, placebo-controlled treatment period. A separate SAP will be written for the open-label extension (OLE).

Facioscapulohumeral muscular dystrophy (FSHD) is a rare disabling disease with an estimated worldwide population prevalence of between 1:15,000 and 1:20,000 (Statland and Tawil, 2014), or approximately 16,000 to 21,000 affected individuals in the United States. FSHD is characterized by descending progressive skeletal muscle weakness affecting the face, shoulders, arms, and trunk, followed by weakness of the distal lower extremities and pelvic girdle. FSHD is caused by aberrant overexpression of the double homeobox 4 (DUX4) gene, a homeobox transcription factor. DUX4 is located within D4Z4 macrosatellite repeats on chromosome 4q35 and is not normally expressed in adult skeletal muscle when the number of repeats is >10. Approximately 95% of patients with FSHD have type 1 (FSHD1), in which the D4Z4 repeat array is contracted to 1 to 10 units on one allele (Lemmers et al, 2010; Statland and Tawil, 2014). FSHD patients carrying a smaller number of repeats (1 to 3 units) are, on average, more severely affected (Tawil et al, 1996).

There are currently no approved disease-modifying treatments for FSHD. Fulcrum is developing losmapimod, a selective p38α/β inhibitor, which is predicted to reduce DUX4 in affected skeletal muscle. It is anticipated that the proposed human dose of losmapimod for FSHD at 15 mg orally (PO) twice daily (BID) will provide drug concentrations in skeletal muscles sufficient to significantly inhibit p38α/β and reduce aberrant expression of DUX4.

The term study drug that is being used throughout this document refers to losmapimod and/or placebo.

2. Objectives

2.1. Primary Objectives

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

2.2. Secondary Objectives

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

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

2.3. Exploratory Objectives

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

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

3. Investigational Plan

3.1. Overall Study Design and Plan

This study will be conducted in 2 parts: a randomized, double-blind placebo-controlled treatment period for 48 weeks, followed by a losmapimod open-label treatment period with a study population of males and females between 18 and 65 years of age at enrollment, inclusive, who have confirmed diagnosis of FSHD1 with 1 to 9 repeats via assessment of the size of the D4Z4 array on chromosome 4; a clinical severity score of 2 to 4 (RICCI score; range 0-5), inclusive, at screening; and a MRI eligible muscle for biopsy, as determined by a central reader.

During the placebo-controlled treatment period, approximately 76 subjects with FSHD1 will be randomized 1:1 to receive 15 mg PO of losmapimod (n=38) or placebo (n=38) tablets BID for 48 weeks. At the time of the latest protocol amendment (Version 4.0; 10Apr2020), enrollment was completed, a total of 80 subjects have been enrolled.

Once subjects reach Week 48, they will have the option to roll over into the open-label extension, with all subjects receiving 15 mg losmapimod PO BID. Subjects who wish to roll over into the

open-label extension must complete all procedures from the Week 48 end of placebo-controlled treatment period/start of open-label extension visit. Prior to the COVID-19 pandemic, subjects who reached the Week 24 visit had the option to roll over into the OLE. Subjects who have already rolled over to the OLE prior to the COVID-19 pandemic (n=12) will remain on open label treatment. Their next clinic visits will follow the assessments for the Week 36 and Week 48 visits in the placebo-controlled portion of the study in the COVID-19 Pandemic Emergency protocol version 4.0. These subjects will not undergo the Week 36 biopsy. Subjects who did not roll over prior to the COVID-19 pandemic, and thus are still on the randomized treatment, will continue on the randomized treatment and roll over into the OLE at the Week 48 visit. Please see the COVID-19 Pandemic Emergency protocol version 4.0 for further details.

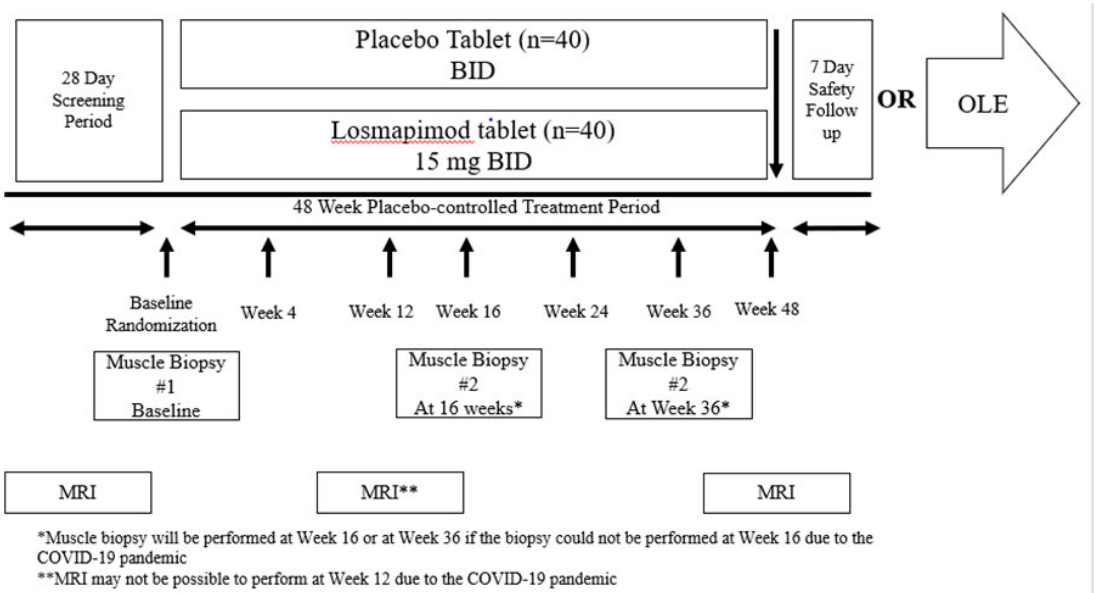
The placebo-controlled treatment period will include a 4-week screening period and a 24 or 48-week placebo-controlled treatment period. Subjects who rolled over to the OLE portion of the study prior to the COVID-19 pandemic (under protocol version 3.0) have completed a 4-week screening period followed by a 24-week placebo-controlled treatment period.

Blood samples for pharmacokinetics (losmapimod concentrations) endpoints will be collected at Day 1, Week 4, Week 16, and Week 36 at the following timepoints: immediately pre-dose and 4 hours (±30 minutes) after administration of the study drug. Blood samples for target engagement will be collected at Day 1 and Week 16 or Week 36 at the following timepoints: immediately pre-dose and 4 hours (±30 minutes) after administration of the study drug. Musculoskeletal MRIs will be performed at screening, Week 12, Week 24, and Week 48. Muscle biopsies will be taken at Day 1 and Week 16, or at Day 1 and Week 36 if the muscle biopsy could not be performed at Week 16 due to the COVID-19 pandemic.

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

A schematic of the study design of the placebo-controlled treatment period is presented in Figure 3-1.

Figure 3-1: Schematic of Study Design



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

During the open-label extension, subjects will be asked to attend clinic visits approximately every 12 weeks, and MRI will take place every 24 weeks. Study drug (open-label losmapimod) will be administered BID and should be taken with food. Subjects will remain in the open-label extension until study drug approval or until the study is discontinued by the Sponsor. All subjects who complete or discontinue from treatment will be asked to complete a 7-day safety follow-up period.

3.2. Study Endpoints

3.2.1. Primary Endpoint

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

3.2.2. Secondary Endpoints

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

- Safety and tolerability of losmapimod as defined by the following:
  - Type, frequency, severity, seriousness, and relationship of AEs to losmapimod;
  - Incidence of AESI;
  - Number of subjects who prematurely discontinue study drug due to an AE; and
  - Frequency of clinically significant changes in laboratory test, ECG, vital sign, and physical examination results

- Change from baseline in MFF, LMV, and MFI at Week 12, Week 24 (if applicable) and Week 48;
- Plasma concentrations of losmapimod at Week 4, Week 12, Week 16, Week 24, Week 36, and Week 48;
- Concentrations of losmapimod in skeletal muscle biopsy at steady state at Week 16 or Week 36;
- Target engagement parameters in blood, and skeletal muscle biopsy at Week 16 or Week 36.

3.2.3. Exploratory Endpoints

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

- Change from baseline in COAs, including
    - RWS with and without weights at Week 4, Week 12, Week 24, Week 36, and Week 48
    - Classic and FSHD TUG at Week 4, Week 12, Week 24, Week 36, and Week 48
    - Muscle strength by hand-held dynamometry at Week 4, Week 12, Week 24, Week 36, and Week 48
    - MFM Domain 1 at Week 12, Week 24, Week 36, and Week 48
    - FSHD-HI at Week 4, Week 12, Week 24, Week 36, and Week 48
    - PGIC at Week 4, Week 12, Week 16, Week 24, Week 36, and Week 48
- Change from baseline in inflammatory, immune, apoptotic, and muscle disease transcripts may be conducted in muscle biopsy at Week 16 or Week 36 and in circulating proteins in plasma and serum at Week 4, Week 12, Week 16, Week 24, Week 36, and Week 48.

3.3. Treatments

Study drug tablets in the placebo-controlled treatment period (losmapimod or placebo) and the open-label extension (losmapimod) will be dispensed to subjects at the visits detailed in Table 13-1 and Table 13-2 of the protocol, respectively.

During the placebo-controlled treatment period, subjects will receive either 15 mg losmapimod BID or placebo BID. In the open-label extension, all subjects will receive 15 mg losmapimod BID. As 7.5 mg losmapimod tablets will be used in this study, subjects will be taking 2 tablets, PO BID. The study drug should be taken with food, with the date and time of each dose taken recorded in the subject's diary.

4. General Statistical Considerations

4.1. Reporting Conventions

All data summaries, unless otherwise noted, will be presented by treatment group:

- Losmapimod 15 mg BID
- Placebo BID

The following conventions will be used for all the data presentations and analyses unless otherwise specified.

Appropriate descriptive statistics will be computed and displayed for both continuous and categorical variables. For continuous and quantitative variables, summaries will include n (number of subjects with non-missing data), mean, standard deviation (SD), Q1 (first quartile), Q3 (third quartile), median, minimum and maximum. Reporting conventions for descriptive statistics will follow the [redacted] Standard TLF Guidelines. For categorical variables, summaries will include the number and percentage of subjects who are in a particular category. Percentages will be computed based on the number of non-missing data points for patients in the applicable analysis set. Reporting of percentages will follow the [redacted] tandard TLF Guidelines.

A total column will be presented for all demographic, baseline characteristic, baseline disease characteristic, protocol deviation, and prior and concomitant medication summaries.

All data will be listed by treatment group, FSHD repeat number category, subject ID, Ricci score, sex and visit date, if available. Any repeat assessments or additional assessments, along with any unscheduled visits, will be presented in the listings. Sort order of data listings will be treatment group, FSHD repeat number category, subject ID, and visit date, if available.

Statistical tests will be 2-sided and will be conducted at the significance level provided in Table 12-1), unless otherwise specified. P-values will be reported to 4 decimal places, with p-values less than 0.0001 reported as "<0.0001".

All analyses will be performed using Statistical Analysis Software (SAS®, release 9.4 or higher). A separate document as an appendix to this SAP will contain the tables, listings, and figure (shells).

4.2. Handling of Missing Data

Missing data for primary efficacy endpoint will be handled as specified in the sensitivity analyses Section 8.2.1.

All missing and partial dates for the prior/concomitant medications and adverse events will be handled as outlined in Sections 7.1 and 9.1, respectively.

In categorical summaries, a missing category will be included if and only if any data for the given endpoint is missing.

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

4.3. Baseline, Study Day, and Change from Baseline Definitions

Unless indicated otherwise, baseline will be defined as the last non-missing evaluation on or before the day of first dose of study drug. In the event that the last non-missing evaluation and the study drug administration happen on the same day, timing of the evaluation will be used to determine the pre- or post-dose. If timing is not available, the evaluation is considered pre- or post-dose based on the schedule of events for that assessment. For example, AEs and concomitant medication are considered post-baseline evaluations.

For muscle biopsies, any assessment taken on the first day of study drug exposure will be considered baseline, irrespective of timing to study drug.

Relative study days will be calculated as:

(assessment date – dose administration date) + 1

if the assessment date is on the same day or after the dosing date, otherwise:

(assessment date – dose administration date).

Study day will be presented on all listings where appropriate.

Change from baseline will be computed as (post-baseline assessment value - baseline assessment value).

4.4. Visit Windows

In general, data for assessments that are collected by scheduled visits will be mapped to visits that appear in the schedule of assessments per the protocol using the actual study day of assessment. Data mapped to scheduled visits will include all data collected up to the reporting cut-off date and may include withdrawal visits and unscheduled visits.

Visit windows will be continuous from the midpoint between two consecutive study visits and will be dependent on the schedule of assessments for each variable independently. The exception is the Week 16 analysis window, which has been extended to allow for potentially delayed visit due to COVID-19 pandemic. An example of the Vital Signs visit window is given in Table 4-1. Visit windows for each variable will be constructed in the same manner.

Table 4-1: Visit Windows

Study Visit	Scheduled Day	Analysis Window
Baseline	1	<=1
Week 4	28	>1 to <=56
Week 12	84	>56 to <=98
Week 16	112	>98 to <=154
Week 24	168	>154 to <=210
Week 36	252	>210 to <=294
Week 48	336	>294 to <=378

4.5. Multiple Values

For summaries displayed by visit, multiple values for a given assessment within a time window will be handled as follows:

- Efficacy: The nearest non-missing value to the nominal timepoint will be assigned to the visit. If two values are equidistant from the nominal timepoint then the latest value will be selected.
- Safety: The first non-missing value to the nominal timepoint will be assigned to the visit.

For the PK and biomarker data, if the assay is believed to have failed for an assessment due to technical reasons, the sample will be re-run and the last/latest assessment date/time that is available will be used for the data analysis.

4.6. Subgroup

A subgroup analysis will be performed for the following subsets at baseline:

1) Repeat category (1 to 3 repeats, 4 to 9 repeats)
2) Clinical severity score (RICCI score 2 to 3, 3.5 to 4)

3) Sex (Male, Female)
4) Fat Fraction at biopsy site. This is an average of results from 2 Readers.
    a. > 10 to <=20%
    b. >20 to <=40%
5) Mean DUX4 score (DUX4 Score 1) at baseline values partitioned by 3 thresholds:
    a. >=Q1 (first quartile of observed mean DUX4 score (DUX4 Score 1) at baseline)
    b. >=Q2 (median of observed mean DUX4 score (DXU4 Score 1) at baseline)
    c. >=Q3 (third quartile of observed mean DUX4 score (DXU4 Score 1) at baseline)
6) Subjects completing 'RWS protocol with above shoulder movements' at baseline
7) Subjects who completed 'RWS protocol with above shoulder movements' all through the study
8) Subjects completing the classical TUG, without an assisted device, at baseline
9) Subjects completing the FSHD TUG, without an assisted device, at baseline
10) MFF_{tot}, LMV_{tot} and MFI_{tot} with thresholds at the median of observed baseline data
11) Subjects with non-censored laboratory observations for DUX4 score at baseline.

Endpoints for which the subgroup analysis will be performed are indicated in subsequent sections.

4.7. Sample Size

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

4.8. Randomization, Stratification, and Blinding

Subjects will be randomly assigned at the baseline visit (Day 1) to receive losmapimod (active drug) or placebo using a 1:1 allocation ratio. Randomization will be stratified to ensure that the treatment allocation is balanced across FSHD repeat number categories (ie, 1 to 3 repeats versus 4 to 9 repeats). An Interactive Response Technology (IRT) system will be used to administer study drug according to the randomization schedule.

The placebo-controlled treatment period will be performed in a double-blind fashion. The investigator, study staff, subjects, sponsor, and monitor will remain blinded to the treatment until study closure. The sponsor and/or its designee will remain blinded to the subject-level treatment assignment until after all subjects have completed the Week 48 visit (or have discontinued) and the database from the placebo-controlled treatment period has been locked for statistical analyses, after which time they will unblinded. The study drug and its matching placebo are indistinguishable and will be packaged in the same way. There are no tolerability issues that are expected to potentially unblind the assigned study drug.

During the open-label extension, no blinding will be performed (subjects will receive open-label losmapimod); however, subjects will remain blinded to their original treatment assignment from the placebo-controlled treatment period for the duration of the study. The Sponsor and/or its designee may be unblinded after all subjects have completed the Week 48 visit (or have discontinued) and the database from the placebo-controlled treatment period has been locked for statistical analyses.

4.9. Analysis Set

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

4.9.1. Full Analysis Set (FAS)

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

4.9.2. Per Protocol Set (PPS)

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

4.9.3. Safety Analysis Set

The Safety Analysis Set will consist of all subjects who receive any study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received.

4.9.4. Pharmacokinetics Analysis Set

The PK Analysis Set will consist of all subjects who receive at least 1 dose of losmapimod and have evaluable PK data for losmapimod.

4.9.5. Pharmacodynamics Analysis Set

The PD Analysis Set will consist of all subjects who receive at least 1 dose of losmapimod and have evaluable PD data for losmapimod.

4.9.6. Open-label Losmapimod (Pre-COVID-19) Analysis Set

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

5. Subject Disposition

5.1. Disposition

Subject disposition will be summarized for the FAS. A disposition of subjects includes the number and percentage of subjects for the following categories:

- Subjects who were randomized
- Subjects who completed the treatment
- Subjects who discontinued the treatment
- Subjects who completed the study
- Subjects who discontinued from the study

The reason for study discontinuation will also be summarized.

A summary of the subjects included in each analysis set will be presented.

All percentages will be based on the number of subjects in the FAS.

Subject disposition data will also be presented in a listing.

5.2. Protocol Deviations

Significant protocol deviations will be summarized by deviation type for all FAS subjects. A listing of all protocol deviations will be provided as well. Prior to DBL, the listing for protocol deviations will be determined in a blinded manner.

6. Demographics and Baseline Characteristics

6.1. Demographics

A summary of demographics and baseline characteristics will be presented. The demographic characteristics will consist of age (years), sex, race, and ethnicity. The baseline characteristics will consist of baseline height (cm), baseline weight (kg), and baseline body mass index (BMI)

(kg/m^2). Body mass index is calculated as (body weight in kilograms) / (height in meters)^2. Age, baseline height, baseline weight, and baseline BMI will be summarized using descriptive statistics. The number and percentage of subjects by sex (Male, Female), race (White, African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino) will also be reported. Percentages will be based on the total number of subjects in the FAS. A separate presentation may be done for the Safety Analysis Set.

Subject demographic and baseline characteristics will also be presented in a listing.

6.2. Baseline Disease Characteristics

Baseline disease characteristics include the following parameters:

- FSHD repeat number (1, 2, 3, 4, 5, 6, 7, 8, and 9)
- FSHD repeat category (1 to 3 repeats, 4 to 9 repeats)
- Clinical severity score (RICCI score 2, 2.5, 3, 3.5, 4)
- FSHD history
    - Age of symptom (years)
    - First symptom
        - Weakness
        - Difficulty smiling
        - Reaching over head
        - Walking
        - Running
        - Keeping up with peers
        - Pain
        - Others
    - Age at diagnosis (years)
    - Pain related to FSHD

Percentages will be based on the total number of subjects in the FAS. Listings will be presented for the FAS. A separate presentation may be done for the Safety Analysis Set.

6.3. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or higher. The number and percentage of subjects with any medical history will be summarized by treatment group and overall and presented by system organ class (SOC) and preferred term (PT). Percentages will be calculated based on the number of subjects in the FAS.

Subject medical history data including specific details will also be presented in a listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

All medications used within 28 days prior to the date of screening through safety follow-up will be collected on the CRF (case report form). All medications will be coded according to the World Health Organization Drug Dictionary (WHODD Global B3 Mar 2019 or higher).

A prior medication is defined as any medication that is taken prior to the first dose of study drug and stopped before the date of study drug administration. A concomitant medication is defined as any medication that is taken on or after the date of study drug administration regardless when the medication is started up to 7 days after the last dose date.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK, UKN, and UNKN indicate unknown or missing day, month, and year, respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of administration of study drug, assume 01-MMM-YYYY. If the month and year are the same as the administration of study drug month and year and the end date (after any imputation) is on or after the administration of study drug, then assume the first day of the month of the administration of study drug. If the month and year are the same as month and year of the study drug administration and the end date (after any imputation) is prior to the study drug administration, then assume the first day of the month of the administration of the study drug for the start date;
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of the study drug administration, assume DD-JAN-YYYY/01-JAN-YYYY of the collected year. If the year is the same as study drug administration year and the end date (after any imputation) is on or after the study drug administration, then assume the date of the study drug administration. If the year is the same as the study drug administration and the end date (after any imputation) is prior to the first dose of study drug, then assume the first day of the month of the administration of the study drug for the start date.

Missing stop dates (where UK, UKN, and UNKN indicated unknown or missing day, month, and year, respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY: Assume DD-DEC-YYYY;
- UK-UKN-YYYY: Assume 31-DEC-YYYY.

If the start date is completely missing and end date is not prior to the study drug administration, then the medication will be classified as concomitant. If the start date is completely missing and the end date is within 30 days prior to the first dose of study drug, then the medication will be

classified as prior. If the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are missing will be classified as concomitant.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification level 4 and preferred drug name, respectively. When ATC classification level 4 is missing, the next available ATC level will be used as ATC level 4.

Summaries will be performed using the Safety Analysis Set.

Data on prior and concomitant medications will also be presented in a listing.

7.1.1. Prior Medications

The total number of prior medications and the number and percentage of subjects with at least one prior medication will be summarized by treatment group and overall. The number and percentage of all prior medications will be summarized by treatment group and overall and presented by Anatomical Therapeutic Chemical (ATC) level 4 and PT. All summaries will be performed using the FAS.

7.1.2. Concomitant Medications

The total number of concomitant medications and the number and percentage of subjects with at least one concomitant medication will be summarized by treatment group and overall. The number and percentage of all concomitant medications will be summarized by treatment group and overall and presented by Anatomical Therapeutic Chemical (ATC) level 4 and PT. All summaries will be performed using the Safety Analysis Set.

7.2. Study Treatments

7.2.1. Extent of Exposure

Duration of exposure is defined as the total number of days a subject is exposed to study drug and will be presented as the total number of days from the first dose date (Day 1) to the last dose date (ie, calculated as the date of last dose minus the date of first dose + 1). If the last dose date is missing, or if a subject is lost to follow-up, but the drug accountability log confirms that the subject has taken study drug, the visit date following the last completed drug accountability log will be used.

The exposure to study drug will also be characterized by cumulative dose, which is defined as the cumulative number of tablets taken.

The duration of exposure to study drug by treatment group will be summarized for all subjects in the Safety Analysis Set and will be presented in a table using summary statistics. The duration of exposure will then be classified into one of the following categories: < 8 weeks, >= 8 weeks, >=

16 weeks, >= 24 weeks, >=36 weeks and >=48 weeks and will be presented as the number and percentage of subjects in each duration category. Percentages will be computed from the number of subjects in the Safety Analysis Set.

The total cumulative dose in mg will be defined as the total number of tablets taken across all study days times 7.5 mg. Average daily dose will be defined as cumulative dose divided by total days on study drug. The average daily dose and cumulative dose will be summarized using summary statistics.

A summary of each subject's exposure will also be presented in a listing.

7.2.2. Treatment Compliance

Study drug compliance will be calculated for each subject by taking into account whether a subject takes all doses of study drug as instructed. The number of tablets taken will be calculated by subtracting the number of tablets returned from the number of tablets dispensed.

The study drug compliance (%) for each visit will be calculated by dividing the total number of tablets taken up to the next visit by the total number of tablets prescribed at each visit and then multiplying by 100. Compliance (%) = [(total number of tablets dispensed – total number of tablets returned) / (number of days in visit interval * number of tablets prescribed per day)] * 100. The overall study drug compliance (%) will be calculated by dividing the total number of tablets taken at all visits by the total number of tablets prescribed for all visits and then multiplying by 100.

The overall study drug compliance will be summarized by treatment group.

The number and percentage of subjects in different percentage compliance categories (<80%, >=80% to <120%, and >= 120% compliant) will be presented. Percentages will be calculated from the number of subjects in the Safety Analysis Set.

8. Efficacy Analysis

Efficacy endpoints will be analyzed using the FAS. The primary efficacy endpoint will also be performed on the PPS and will be considered supportive of the primary analyses on the FAS. As part of sensitivity analysis, a separate analysis will be done of efficacy endpoints using the Open-label Losmapimod (Pre-COVID-19) Analysis Set.

8.1. Hypothesis Testing Procedure for Key Study Endpoints

A fixed sequential testing procedure will be used to control for the experiment-wise Type I Error to test the following key study endpoints as ordered below:

- DUX4 change from baseline at Week 16 or Week 36 [DUX4 Score 1. See Section 8.2]
- LMV change from baseline at Week 48 [Total LMV, composite of assessments from multiple muscles. See Section 8.3]

- FSHD TUG change from baseline at Week 48 [average completion time of FSHD TUG. See Section 8.4.2]

At each step in this sequential ordering, statistical significance for the endpoint will be claimed only if the p-value for the test is less than the final alpha obtained from the O'Brien-Fleming Spending Function (Table 12-1) and the p-values for the tests for all previous endpoints in the list are also less than the final alpha provided.

The testing hierarchy will be as follows:

- If the p-value for the test of the comparison of DUX4 change from baseline between the two treatment groups is less than the final alpha, then the comparison of the LMV change from baseline will be conducted. If the p-value from this comparison is also less than the final alpha, then the comparison of the FSHD TUG change from baseline will be conducted.
- Once a p-value is greater than or equal to the final alpha for the current endpoint being evaluated, then only the tests for the preceding endpoints will be considered significant.
- The formal statistical tests for any of the endpoints will be considered statistically nonsignificant when the test has a p-value of greater than or equal to final alpha. However, nominal p-values will still be provided for these endpoints.

8.2. Change from Baseline in DUX4 Activity in Skeletal Muscle at Week 16 or Week 36

A subset of DUX4-gene transcripts will be measured in skeletal muscle biopsies, using a validated QRT-PCR assay, to assess the treatment effect of losmapimod over placebo on aberrant DUX4 activity. A mean DUX4 score (DUX4 Score 1) will be derived for each patient, at each time point based on normalized gene expression values for the panel of pre-selected genes.DUX4 Score 1 is a mean of normalized (delta-CT) for the pre-selected panel of 6 genes, by subject, for each timepoint.

The quantification of gene expression and normalization of qPCR are conducted at a central laboratory (Q2 Lab Solutions) in a blinded fashion, with no access to treatment assignment information. A total of six DUX4-regulated gene transcripts (CCNA1; KHDC1L; MBD3L2; PRAMEF6; SLC34A2; ZSCAN4) have been pre-selected for inclusion in the mean DUX4 score. DUX4 Score 1 will be used for the primary analysis. A second and third composite scores (DUX4 Score 2 and DUX4 Score 3, respectively) will be used for sensitivity analysis. For details on assay validation, gene subset selection criteria/process, and derivation of DUX4 Score, see Appendices 15.1 – 15.5.

DUX4 score 1 will be summarized as change from baseline to either Week 16 or Week 36. Study subjects can only have one post-baseline biopsy (either Week 16 or Week 36, but not both). If the pre-treatment or on-treatment DUX-4 results are unavailable, then the assessment is considered missing. See Section 8.2.1 for details of missing data handling for DUX4 Score.

For each treatment, descriptive statistics of aberrant DUX4 activity will be presented at Baseline and post-baseline (Week 16 or Week 36) as well as change from baseline. An ANCOVA model

will be used to analyze the change from baseline in DUX4 activity in affected skeletal muscle, which is the response variable, with repeat number category and treatment group as fixed effects and baseline DUX4 activity in affected skeletal muscle as a covariate. Within-group least-squares (LS) means, the associated standard errors (SEs) and 2-sided 95% CIs, treatment differences in LS means and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the model and presented in the table. If the model-based p-value of the treatment difference in the change from baseline is less than the final alpha provided in Table 12-1, the difference between two treatment groups will be determined to be statistically significant.

Similar methods will be used to analyze the change from baseline in DUX4 activity within subgroups identified in Section 4.6 to evaluate consistency of treatment effects across the subgroups. For the repeat category subgroup analysis, the repeat category will be excluded as fixed effect from the model.

The LS mean change from baseline by visit of the DUX4 activity will be graphically presented.

8.2.1. Sensitivity Analyses of Primary Endpoint

Missing Data: The following sensitivity analyses will be conducted on the primary efficacy endpoint to assess the impact of missing data on study conclusions:

- **Last Observation Carried Forward (LOCF):** Post-baseline missing DUX4 score will be imputed using baseline DUX4 score for each subject with missing data. Patients who are missing the baseline assessment will be excluded from the analysis.

- **Placebo Mean Imputation:** Post-baseline missing DUX4 score will be imputed using mean post-baseline score calculated from the placebo arm. Patients who are missing the baseline assessment will be excluded from the analysis.

- **Observed worst case imputation:** For subjects with missing baseline DUX4, imputation will be done using the smallest baseline DUX4 score among subjects with non-missing data. For subjects missing post-baseline DUX4, imputation will be done using the highest DUX4 score among subjects with non-missing data.

DUX4 by timepoint: The primary endpoint will be analyzed separately for Week 16 and Week 36 to assess the impact of biopsy timing on study conclusions.

COVID-19 related treatment disruptions: Subjects may be diagnosed with COVID-19 and proceed on a quarantine or have no access to study treatment for a prolonged duration. These subjects will be excluded from analysis of the primary endpoint, to assess the impact of COVID-19 related treatment disruptions on the study conclusions.

Excluding cross-over subjects: Subjects who already transitioned into open label losmapimod based on the prior protocol version will be excluded from the analysis.

DUX4 change excluding subjects with censored laboratory observations at baseline: Subjects with censored observations at baseline for any of the transcripts in the panel of 6 DUX4-regulated transcripts will be excluded from the analysis.

8.3. MSK MRI Muscle Fat Fraction, Lean Muscle Volume and Muscle Fat Infiltration

Measurement of the extent of skeletal muscle tissue replacement by fat in FSHD patients will be done through automatic skeletal muscle segmentation for the 3D muscle volumes and fat fraction analysis via robust algorithms using Dixon imaging. This will be assessed at Screening, Week 12, and Week 48.

A. **Composite measures:** Composite variables, incorporating pre-selected muscles, will be derived for longitudinal analysis of muscle fat fraction, lean muscle volume and muscle fat infiltration (MFF_{tot}, LMV_{tot}, and MFI_{tot} respectively), as described in Appendix 15.6. The scores will be derived by scientists at the MRI Service Provider (AMRA Medical Inc.) in a blinded fashion, with no access to treatment assignment information.

   For each treatment, descriptive statistics of MFF_{tot} , LMV_{tot}, and MFI_{tot} per visit as well as changes from baseline will be presented. A Mixed Effect Model for Repeated Measures (MMRM) model will be used to analyze the change from baseline in each composite MRI score, with repeat number category, treatment group, visit, and treatment-by-visit interactions as fixed effects and baseline value of the parameter as a covariate. Within-group LS mean changes from baseline, the associated SEs and 2-sided 95% CIs, treatment differences in LS mean changes from baseline at Weeks 12 and 48 and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model and will be provided in the summary table. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. If models using unstructured covariance do not converge, an AR(1) covariance structured will be used instead. **LMV_{tot} is the key endpoint for hypothesis testing.**

B. **Individual Muscles**: For each muscle location, a similar method will be used to analyze muscle fat fraction (%), lean muscle volume (L), and muscle fat infiltration (%) per visit as well as changes from baseline.

The LS mean change from baseline by visit of the MSK MRI muscle fat fraction, lean muscle volume, and muscle fat infiltration will be graphically presented.

The change from baseline in the composite parameters will also be summarized by subgroups identified in Section 4.6 to evaluate consistency of treatment effects across the subgroups.

8.4. Clinical Outcome Assessments

8.4.1. Reachable Work Space With and Without Weights

The reachable work space (RWS) is a 3-dimensional sensor-based system (using a single depth-ranging sensor) that can unobtrusively detect an individual's RWS and reflects an individual global upper extremity function, including shoulder and proximal arm. The evaluation will be performed with and without weights and on both the right and left arms at Baseline, Week 4, Week 12, Week 24, Week 36, Week 48 and Safety Follow-up.

The absolute total RWS surface envelope area (m^2) as well as areas for each of the quadrants will be calculated and provided by a vendor in a blinded fashion, with no access to treatment assignment information. The reachable workspace relative surface area (RSA) represents the portion of the unit hemisphere that is covered by an individual's hand movement.

For each treatment, descriptive statistics of RSA results per visit as well as the change from baseline will be presented by quadrant, for total upper quadrants (Q1+Q3) and total area (Q1+Q2+Q3+Q4) for the assessment with weights and without weights, and by dominant and non-dominant arm. An MMRM model will be used to analyze the change from baseline in total area with repeat number category, treatment group, visit, and treatment-by-visit interactions as fixed effects and baseline value of the total area as a covariate. A separate model will be run with and without weights and for the dominant and non-dominant hand. Within-group LS mean changes from baseline, the associated SEs and 2-sided 95% CIs, treatment differences in LS mean changes from baseline at post-baseline visits and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model and will be provided in the summary table. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. If models using unstructured covariance do not converge, an AR(1) covariance structured will be used instead. Similar methods will be used to analyze the change from baseline in RSA for each quadrant.

Summary tables will be generated, showing percentage of subjects with RWS decline of >=5%, >=2% at each post-baseline timepoint.

See Section 4.6, #6 and #7, for sub-group analyses to be conducted on this endpoint.

The functional work space (FWS) will also be summarized using number and percentages of subjects belonging to the categories of normal or low speed. The detected time within each target will be presented in a listing.

8.4.2. Classic and FSHD TUG

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

back down on his or her back at the end of the test. The FSHD TUG will capture total completion time and completion times for each segment (supine to sit, stand-walk-sit, and sit to supine). Each test will be done twice per visit and will be assessed at Baseline, Week 4, Week 12, Week 24, Week 36, Week 48, and Safety Follow-up. The average of Trial 1 and Trial 2 assessments at each visit will be derived for both the classic TUG completion time and each of the FSHD TUG completion times (ie, supine to sit, stand-walk-sit, sit to supine, and total) and will be used for the analysis.

For each treatment, descriptive statistics of classic TUG average completion time and FSHD TUG average completion times in seconds per visit as well as the change from baseline will be provided in tables. **The average completion time of the FSHD TUG is a key study endpoint, for hypothesis testing.** Descriptive statistics of FSHD TUG average completion times will be presented for each segment (supine to sit, stand-walk-sit, sit to supine, and total). An MMRM model will be used to analyze the change from baseline in classic TUG average completion time with repeat number category, treatment group, visit, and treatment-by-visit interactions as fixed effects and baseline value of classic TUG average completion time as a covariate. Within-group LS mean changes from baseline, the associated SEs and 2-sided 95% CIs, treatment differences in LS mean changes from baseline at post-baseline visits and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model and will be provided in the summary table. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. If models using unstructured covariance do not converge, an AR(1) covariance structured will be used instead. Similar methods will be used to analyze the change from baseline in FSHD TUG average completion times.

Similar analysis will also be conducted for each of the individual components of the FSHD TUG.

The change from baseline in the classic and FSHD TUG average completion times will also be summarized by subgroups #8 and #9, respectively, identified in Section 4.6 to evaluate consistency of treatment effects across the subgroups.

8.4.3. Manual Dynamometry

Qualitative isometric dynamometry (hand-held dynamometer) will be used to assess the skeletal muscle strength of study subjects in both the upper and lower limbs bilaterally. Shoulders, flexors and extensors in the elbow, knees, and ankles as well as the grip bilaterally will be measured at each applicable visit. Isometric dynamometry measures the static muscle strength without any movement. This will be assessed at Baseline, Week 4, Week 12, Week 24, Week 36, Week 48, and Safety Follow-up.

For each treatment, descriptive statistics of average and maximum weight in kilogram per visit as well as the change from baseline will be presented by overall and according to assessment (right shoulder abductors, left shoulder abductors, right elbow flexors, left elbow flexors, right elbow extensors, left elbow extensors, right knee extension, left knee extension, right knee flexion, left knee flexion, right ankle dorsiflexors, left ankle dorsiflexors, right hand grip, and left hand grip). An MMRM model will be used to analyze the change from baseline in average weight with repeat

number category, treatment group, visit, and treatment-by-visit interactions as fixed effects and baseline value of average weight as a covariate. Within-group LS mean changes from baseline, the associated SEs and 2-sided 95% CIs, treatment differences in LS mean changes from baseline at post-baseline visits and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model and will be provided in the summary table. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. If models using unstructured covariance do not converge, an AR(1) covariance structured will be used instead. Similar methods will be used to analyze the change from baseline in maximum weight.

Similar analysis will be done for total average manual dynamometry for: (a.) all muscles combined; (b.) upper extremity strength, in the shoulders and elbows combined; and (c.) lower extremity strength, which includes right knee extension, left knee extension, right knee flexion, left knee flexion, right ankle dorsiflexors, and left ankle dorsiflexors muscles combined.

8.4.4. MFM Domain 1

The MFM scale assesses the severity of the motor deficit. It provides a clinician's assessment of functionality impairment for standing and transfers. Domain 1 has 13 items in version 1 and 15 items in version 3 of the protocol with each item scored from 0 to 3. The MFM Domain 1 score corresponds to the sum of the item scores divided by the maximum score for this dimension and multiplied by 100 (ie, sum of scores/39*100 for 13 items questionnaire and sum of scores/45*100 for the 15 items questionnaire). This will be assessed at Baseline, Week 12, Week 24, Week 36, and Week 48.

For each treatment, descriptive statistics of the MFM Domain 1 scores (individual item scores and Domain 1 score) per visit as well as the change from baseline will be presented. An MMRM model will be used to analyze the change from baseline in MFM Domain 1 score with repeat number category, treatment group, visit, and treatment-by-visit interactions as fixed effects and baseline score as a covariate. Within-group LS mean changes from baseline, the associated SEs and 2-sided 95% CIs, treatment differences in LS mean changes from baseline at post-baseline visits and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model and will be provided in the summary table. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. If models using unstructured covariance do not converge, an AR(1) covariance structured will be used instead.

8.4.5. FSHD-HI

The FSHD-HI is an FSHD-specific patient-reported measure of disease burden on activities of daily living, quality of life, and symptom prevalence and severity. It consists of a questionnaire with 116 items developed from qualitative interviews of patients. The measure consists of 14 subscales that measure a patient's perception of their ambulation and mobility, hand function, shoulder and arm function, emotional health, back/chest/abdomen strength, fatigue, pain, eating function, ability to do activities, communication ability, satisfaction in social situations, performance situations, body image and cognition. The 116 items are combined into a total score, the score is then transformed onto a percentage scale, with 100 representing maximal disability,

and lower scores representing decreasing disability. This FSHD-HI total score will be calculated by a separate vendor. This score, along with the 14 subscale scores will be assessed at Baseline, Week 4, Week 12, Week 24, Week 36, Week 48, and Safety Follow-up.

For each treatment, descriptive statistics of the FSHD-HI total and subscale scores per visit as well as the change from baseline will be presented. An MMRM model will be used to analyze the change from baseline in FSHD-HI total score with repeat number category, treatment group, visit, and treatment-by-visit interactions as fixed effects and baseline score as a covariate. Within-group LS mean changes from baseline, the associated SEs and 2-sided 95% CIs, treatment differences in LS mean changes from baseline at post-baseline visits and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model and will be provided in the summary table. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. If models using unstructured covariance do not converge, an AR(1) covariance structured will be used instead. Similar methods will be used to analyze the change from baseline in FSHD-HI subscale scores.

8.4.6. PGIC

The PGIC will be assessed to obtain the subject's rating of overall improvement. The rating includes the following: 1= Very much improved, 2= Much improved, 3= Minimally improved, 4= No change, 5= Minimally worse, 6= Much worse, 7=Very much worse. This will be assessed at Week 4, Week 12, Week 16, Week 24, Week 36, Week 48, and Safety Follow-up.

Responses of 1= Very much improved, 2= Much improved, and 3= Minimally improved will be considered as improved and responses of 4 = No change, 5 = Minimally worse, 6= Much worse, and 7=Very much worse will be considered as not improved. For each treatment, descriptive statistics of PGIC values and PGIC response categories will be presented.

8.5. Inflammatory, Immune, Apoptotic, and Muscle Disease Transcripts

The analysis of these exploratory endpoints will be described in a separate document.

9. Safety Analysis

All summaries of safety data will use the Safety Analysis Set and will be presented by treatment.

9.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions:

- begins on or after the first dose of study drug and before the stop of study drug + 7 days;
- begins before the first dose of study drug and worsens in severity on or after the first dose of study drug and before the stop of study drug + 7 days;
- is completely missing an onset date and end date;

- is completely missing an onset date and the end date is on or after the first dose of study drug.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the AE month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year and the AE end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the AE month and year are the same as the first dose of study drug month and year and the AE end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.
- DD-UKN-YYYY/UK-UKN-YYYY: If the AE year is different from the year of first dose of study drug, assume DD-JAN-YYYY/01-JAN-YYYY of the collected year. If the AE year is the same as the first dose of study drug year and the AE end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug and the AE end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY: Assume DD-DEC-YYYY;
- UK-UKN-YYYY: Assume 31-DEC-YYYY.

All AEs will be classified by SOC and PT according to the MedDRA version 22.0 or higher.

An overview summary of the number and percentage of subjects with any TEAE, serious TEAE, study drug-related TEAE, study drug-related serious TEAE, TEAE leading to treatment discontinuation, TEAE leading to study withdrawal, and AE leading to death will be provided by treatment group. In addition, the number and percentage of subjects with AESI will be presented. Adverse events of special interest for this study include liver tests that meet the criteria for potential drug-induced liver injury (DILI), in accordance with the US Food and Drug Administration (FDA) “Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation”. Further details of liver tests and criteria are described in Section 9.2.2.

9.1.1. Incidence of TEAEs

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided by treatment group. The number and percentage of subjects and the number of events will also be presented by SOC and PT. At each level of subject summarization,

a subject is counted once within each PT if the subject reported one or more events. Percentages will be based on the number of subjects in the Safety Analysis Set. The number of events will be summarized by treatment group.

The summary of TEAEs will also be presented in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the lowest total incidence. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order.

An additional summary will be presented by PT only. This summary will be presented in descending order from the PT with the highest total incidence to the PT with the lowest total incidence.

All AEs will also be presented in a listing.

9.1.2. Relationship of TEAEs to Study Drug

A summary of TEAEs by maximum relationship to study drug will be presented in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are “Unlikely Related”, “Possibly Related”, “Probably Related”, and “Definitely Related”. In the TEAE by maximum relationship table, if a subject reports multiple occurrence of the same TEAE, only the most related occurrence will be summarized. Percentages will be based on the number of subjects in the Safety Analysis Set. All AEs that have a missing relationship will be presented in the summary table as “Definitely Related” but will be presented in the data listing with a missing relationship.

The AE data will be categorized and presented by SOC, PT, and relationship in the same manner to that described in Section 9.1.1.

9.1.3. Severity of TEAE

A summary of TEAEs by maximum severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are “Mild”, “Moderate”, and “Severe”. In the TEAE by maximum severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe occurrence will be summarized. AEs that are missing severity will be presented in tables as “Severe” but will be presented in the data listing with a missing severity. Percentages will be based on the number of subjects in the Safety Analysis Set.

The AE data will be categorized and presented by SOC, PT, and severity in the same manner to that described in Section 9.1.1.

9.1.4. Serious TEAEs

The seriousness of an AE should be assessed independently by the Investigator from the severity of the AE. An SAE is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, is a congenital anomaly/birth defect, requires in-patient hospitalization or prolongation, or results in significant disability.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
SAE data will be presented by SOC and PT in the same manner to that described in Section 9.1.1.

9.1.5. TEAEs Leading to Treatment Discontinuation

A summary of TEAEs that caused treatment discontinuation will be presented in a table. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be based on the number of subjects in the Safety Analysis Set.

TEAE leading to treatment discontinuation data will be presented by SOC and PT in the same manner to that described in Section 9.1.1.

9.1.6. TEAEs Leading to Study Withdrawal

A summary of TEAEs that lead to study discontinuation will be presented in a table. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be based on the number of subjects in the Safety Analysis Set.

TEAE leading to study discontinuation data will be presented by SOC and PT in the same manner to that described in Section 9.1.1.

9.1.7. Death

A summary of TEAEs where the answer to ‘Outcome’ in the AE form is ‘Death Related to Adverse Event’ will be presented in a table. Percentages will be based on the number of subjects in the Safety Analysis Set.

Death data will be presented by SOC and PT in the same manner to that described in Section 9.1.1.

9.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the units provided by the central laboratory (ie, no conversion will be done).

9.2.1. Hematology

The following laboratory tests will be included: hemoglobin (including mean corpuscular volume), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hematocrit, red blood cell count, total white blood count, platelet count, differential blood counts, including basophils, eosinophils, neutrophils, lymphocytes, and monocytes.

Summary tables presenting observed values and changes from baseline will be presented for hematologic tests with numeric values by treatment group for subjects in the Safety Analysis Set. Changes from baseline to each scheduled post-baseline visit will be presented. All hematology data by subject will also be presented in a listing.

The clinical assessment of 'Low', 'Normal', or 'High' relative to the reference range will be summarized in shift tables comparing the baseline results to maximum value post-baseline for those subjects with results at both visits.

All hematology data by subject will be presented in a listing.

9.2.2. Serum Chemistry

The following laboratory tests will be included**:** glucose, sodium, potassium, calcium, inorganic phosphate, total protein, albumin, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, gamma-glutamyl transferase, and creatinine phosphokinase.

Summary tables presenting observed values and changes from baseline will be presented for serum chemistry tests with numeric values by treatment group for subjects in the Safety Analysis Set. Changes from baseline to each scheduled post-baseline visit will be presented. All chemistry data by subject will also be presented in a listing.

The clinical assessment of 'Low', 'Normal', or 'High' relative to the reference range will be summarized in shift tables comparing the baseline results to maximum value post-baseline for those subjects with results at both visits.

Results indicating liver-related abnormalities (i.e., ALT, AST, Total Bilirubin, and/or Alkaline Phosphatase) will also be summarized separately. A newly notable laboratory abnormality is defined as an abnormality observed post baseline that meets the notable criteria in Table 9-1 and that did not exist at baseline. Subjects can still meet the criteria for a newly notable laboratory abnormality if the baseline value is missing. The table below displays the general variables and thresholds of interest. Subjects are considered to have notable laboratory abnormalities if his/her response falls within the specified definitions at least once during the treatment period.

Table 9-1: Notable Criteria for Laboratory Data Abnormalities – Liver Function Tests

Laboratory Variable	SI Units
AST	≥3 x ULN
ALT	≥3 x ULN
Total Bilirubin	≥2 x ULN
Alkaline Phosphatase (ALP)	≤2 x ULN
ALT or AST > 3 x ULN and total bilirubin > 2 x ULN and ALP < 2 x ULN (potential DILI or Hy's law case)	

All chemistry data by subject will be presented in a listing.

9.2.3. Urinalysis

The following laboratory tests will be included*:* leukocytes, blood, nitrite, protein, urobilinogen, bilirubin, pH, specific gravity, ketones, and glucose*.*

Summary tables presenting observed values and changes from baseline will be presented for urinalysis tests with numeric values by treatment group for subjects in the Safety Analysis Set. Changes from baseline to each scheduled post-baseline visit will be presented.

All urinalysis data by subject will be presented in a listing.

9.2.4. Other Laboratory Tests

The following coagulation tests will also be reported: International normalized ratio, prothrombin time, and partial thromboplastin time. These parameters will be presented and summarized in the same manner to that described in Section 9.2.1.

9.3. Vital Sign Measurements

Summary tables will be presented for vital sign data, including pulse rate, respiration rate, blood pressure, and temperature by treatment for subjects in the Safety Analysis Set. Observed results at each visit will be presented. Change from baseline to each post-dose assessment will also be presented. All vital sign data by subject will also be presented in a listing.

9.4. Physical Examination

A table will summarize physical examination results by treatment for the Safety Analysis Set. Status of a body system and any finding associated with the body system as normal, abnormal, or

not done will be captured at screening and safety follow-up. Physical examination results for all subjects will also be presented in a listing.

A separate table will be presented for the summary of neurological examination results. The scores collected in the CRF which is in ordinal scales will be converted into numeric scales according to the convention provided below.

MMT score as collected in the CRF	Numeric Scale
0	0
1	1
2	2
3-	2.67
3	3
4-	3.67
4	4
4+	4.33
5-	4.67
5	5

A total and average of the numeric score will be derived for upper extremity, lower extremity, and all muscle groups.

The following are the components of the upper extremity:

- Deltoid MRC Score Right
- Deltoid MRC Score Left
- Shoulder Abduction MRC Score Right
- Shoulder Abduction MRC Score Left
- Triceps MRC Score Right
- Triceps MRC Score Left
- Biceps MRC Score Right
- Biceps MRC Score Left
- Wrist Extension MRC Score Right
- Wrist Extension MRC Score Left
- Wrist Flexion MRC Score Right
- Wrist Flexion MRC Score Left
- Finger Extension MRC Score Right
- Finger Extension MRC Score Left
- Finger Flexion MRC Score Right
- Finger Flexion MRC Score Left
- Grip MRC Score Right
- Grip MRC Score Left

The following are the components of the lower extremity:

- Hip Flexion MRC Score Right

- Hip Flexion MRC Score Left
- Knee Extension MRC Score Right
- Knee Extension MRC Score Left
- Knee Flexion MRC Score Right
- Knee Flexion MRC Score Left
- Hip Abduction MRC Score Right
- Hip Abduction MRC Score Left
- Hip Adduction MRC Score Right
- Hip Adduction MRC Score Left
- Ankle Dorsiflexion MRC Score Right
- Ankle Dorsiflexion MRC Score Left
- Plantarflexion MRC Score Right
- Plantarflexion MRC Score Left

Total score in the upper extremity is derived as the sum of numeric scores of muscles included in the upper extremity. Total score in the lower extremity is derived as the sum of numeric scores of muscles included in the lower extremity. Total score in all muscle groups is the sum of numeric scores of muscles in the upper and lower extremities plus the numeric score in neck flexion and neck extension.

Average score in the upper extremity is the sum of numeric scores of muscles included in the upper extremity divided by 18. Average score in the lower extremity is the sum of numeric scores of muscles included in the lower extremity divided by 14. Average score in all muscle groups is the sum of numeric scores of muscles in the upper and lower extremities and numeric scores in neck flexion and neck extension divided by 34.

Neurological examination results for all subjects will also be presented in a listing.

9.5. Electrocardiogram

All subjects will have a standard 12-lead ECG performed during the study as clinically indicated. Electrocardiogram data for all subjects will also be presented in a listing.

Descriptive summaries will be provided for the ECG data including ventricular rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec), and QTcF interval (msec) by treatment group for subjects in the Safety Analysis Set. In addition, number and percentage of subjects with normal sinus rhythm will also be presented in a table. Observed results at each visit will be presented. Change from baseline to each post-dose assessment will also be presented.

The number and percentage of subjects with an overall evaluation of ‘Normal’, ‘Abnormal, Not Clinically Significant’, or ‘Abnormal, Clinically Significant’ will be presented for baseline, Week 4, Week 48, End of Treatment, and Safety Follow-up.

A categorical summary of QTcF values and change from baseline at each visit will be presented by number and percentage for the Safety Analysis Set. Categories for reporting absolute QTcF interval are defined as: >450 to 480 msec, >480 to 500 msec, and >500 msec. Change from baseline in QTc interval is classified as: >30 to 60 msec increase from baseline and >60 msec increase from baseline.

ECG data for all subjects will also be presented in a listing.

10. Pharmacokinetics

By-subject listing of pharmacokinetic blood sample and muscle sample collection times as well as derived sampling time deviations will be provided. Losmapimod plasma and muscle concentrations will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, maximum, coefficient of variation) by scheduled time point. Concentrations that are below the limit of quantitation (BLQ) will have a value of LLOQ value divided by 2 in the computation of descriptive statistics. Mean concentration-time data will be graphically presented. All data presentation will use the PK Analysis Set.

Predose samples that are missing will be assigned as missing.

Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics. A concentration value of zero will be included for the computation of arithmetic mean. If 50% or more of the values are BLQ at one scheduled time point, the arithmetic mean will be reported as BLQ.

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

11. Pharmacodynamics

For each treatment, descriptive statistics of natural log (ln) transformed pHSP27 concentrations in blood will be presented at Baseline, Week 16, and Week 36 as well as change from baseline at Week 16 and Week 36. An MMRM model will be used to analyze the change from baseline in ln-transformed pHSP27 in blood with repeat number category, treatment group, visit, and treatment-by-visit interactions as fixed effects and baseline value of ln-transformed pHSP27 in blood as a covariate. Within-group LS mean changes from baseline, the associated SEs and 2-sided 95% CIs, treatment differences in LS mean changes from baseline at post-baseline visits and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model and will be provided in the summary table. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. If models using unstructured covariance do not converge, an AR(1) covariance structured will be used instead. Similar methods will be used to analyze the change from baseline in ln-transformed values of total pHSP27 and ln-transformed values of pHSP27 to total HSP27 ratio in blood. Similar methods will be used to analyze the change from baseline within subgroups identified in Section 4.6 (#1 - #3) to evaluate

consistency of treatment effects across the subgroups. For the repeat category subgroup analysis, the repeat category will be excluded as fixed effect from the model.

Point estimates (i.e., LS means) will be back transformed using the exponential function to tabularly and graphically present the ratio of postbaseline to baseline in pHSP27. Percent change from baseline, calculated as the difference in the ratio of postbaseline to baseline minus 1 times 100, will also be tabularly and graphically presented.

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

12. Interim Analysis

Initially, no interim analysis for efficacy was planned. However, based on protocol version 4.0 (COVID-19 Pandemic Emergency Amendment) dated 10Apr2020, an interim analysis was included to provide timely data to inform the further development of losmapimod for the treatment of FSHD.

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

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

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

The alpha at the time of the IA for sample size ranging from 22 to 32 are provided in Table 12-1

Table 12-1 Alpha at Interim Analysis and Final Analysis for Different Sample Sizes at Interim Analysis (O'Brien Fleming Method)

Interim Analysis Sample Size	Alpha at Interim Analysis	Alpha at Final
22	0.000567	0.049755
23	0.000736	0.049685
24	0.000951	0.049596
25	0.001203	0.049493
26	0.001474	0.049384
27	0.001803	0.049253
28	0.002173	0.049107
29	0.002556	0.048959
30	0.003005	0.048787
31	0.003496	0.048602
32	0.004027	0.048405

The DUX4, PK, demographics, disposition data and sub-group analysis on the DUX4 endpoint (Section 4.6, #1 to #5 and #11)will be presented to the Sponsor as group-level summaries of the unblinded data with associated p-values. The respective tables are indicated in the List of Planned Summary Tables.

13. Safety Review Committee (SRC)

A SRC will be appointed for the study. The primary responsibility of the SRC will be to act in an advisory capacity to the Sponsor to safeguard the interests of trial patients by monitoring patient safety, assess patient risk versus benefit, and assess data quality and general evaluation of the trial progress. Its activities will be delineated in a SRC charter that will define the membership, responsibilities and the scope and frequency of data reviews. The SRC may have an organizational meeting prior to commencement of the trial. The SRC will have meetings where it will review blinded data during a closed session. These meetings will be planned at regular intervals. They may convene ad hoc meetings based on rates of SAEs if safety concerns arise during the trial. After its assessment, the SRC will recommend continuation, modification or termination of the clinical trial.

The blinded team will prepare the safety tables, listings and/or figures using the dummy randomization and materials/kits schedule.

14. References

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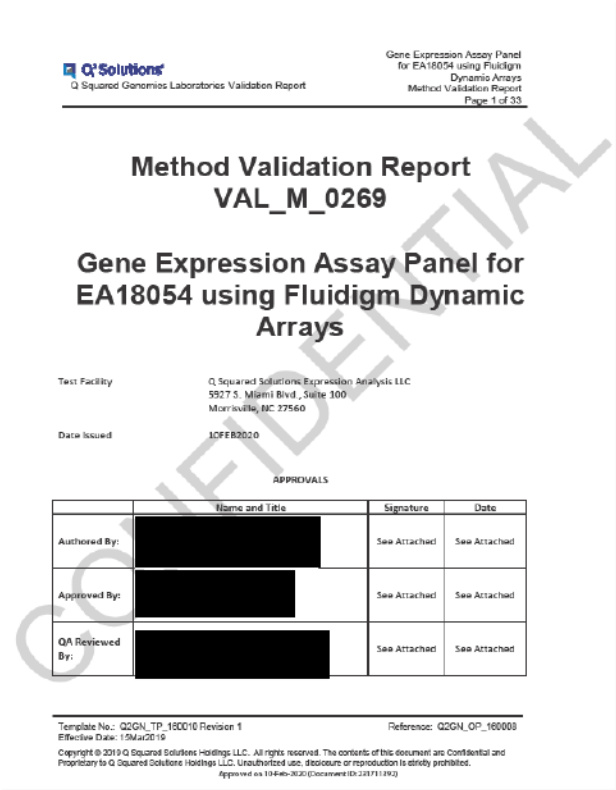
15. Appendices

15.1. The Steps from Raw QPCR Ct to Statistical Analysis

1. Raw Cts from qPCR are determined for DUX4 regulated genes using a validated assay (Fluidigm), described in Appendix 15.2.
2. The raw Cts from the genes are normalized to reference (housekeeping) genes using the process described in Appendix 15.3. The document also describes the method for selecting the reference genes.
3. A mean DUX4 score is created for each subject using the normalized data, at baseline and post-baseline, using the derivation described in Appendix 15.4.
    a. Six DUX4-regulated gene transcripts were selected, a priori, to be in a mean DUX4 score. The process of selection of these 6 genes is detailed in Appendix 15.5.
4. An ANCOVA regression model is then used to test the hypothesis for change in the composite score between treatment arms.

15.2. Validation of the qPCR Assay



Q² Solutions
Q Squared Genomics Laboratories Validation Report

Gene Expression Assay Panel for EA18054 using Fluidigm Dynamic Arrays
Method Validation Report
Page 1 of 33

Method Validation Report
VAL_M_0269

Gene Expression Assay Panel for EA18054 using Fluidigm Dynamic Arrays

Test Facility: Q Squared Solutions Expression Analysis LLC
5927 S. Miami Blvd., Suite 100
Morrisville, NC 27560

Date Issued: 10FEB2020

APPROVALS

	Name and Title	Signature	Date
Authored By:	[redacted]	See Attached	See Attached
Approved By:	[redacted]	See Attached	See Attached
QA Reviewed By:	[redacted]	See Attached	See Attached

Template No.: Q2GN_TP_160010 Revision 1
Effective Date: 15Mar2019

Reference: Q2GN_OP_160008

15.3. QPCR Normalization

Fulcrum Therapeutics

Title

Normalization of qPCR data for Fulcrum Studies FIS-001-2019 and FIS-002-2019

REPORT:

Addenda to FIS-001-2019 and FIS-002-2019 SAPs

INVESTIGATORS: [redacted]

COMPOUND NAME: Losmapimod

LOCATION: [redacted]

AUTHORS: [redacted]

STUDY NUMBER(S): FIS-001-2019 and FIS-002-2019

REPORT DATE: January 22, 2020

15.4. Derivation of DUX4 Score from Delta CT

Select only rows pertaining to the following 6 gene transcripts: CCNA1; KHDC1L; MBD3L2; PRAMEF6; SLC34A2; ZSCAN4

DUX4 Score 1: Mean

Take the mean of delta-CT values across all 6 transcripts, by subject, by timepoint

DUX4 Score 2: Standardized Z-Score Composite

Step 1 (Pre-Treatment data only): (By gene transcript)

I. Calculate Mean (measure of average) of delta CT
II. Calculate standard deviation (measure of variability) of delta CT

Step 2 (Pre-treatment and post-treatment: By gene transcript; by subject)

I. Use variability obtained in Step 1 to calculate standardized score per gene transcript, per patient:

$$Standardized\ Score = (Normalized\ Delta\ Ct\ Value - Mean) \div Standard\ Deviation$$

   a. **Rationale:** Standardize all gene measures to the same scale; reduce the impact of highly variable genes in the final composite measure

II. Calculate mean of standardized scores for each patient, across all genes, by visit.
   a. Each patient's final score is the mean standardized score across multiple transcripts.
   b. This "composite score" is then used in the analysis for change from baseline.

DUX4 Score 3: Median

Take the median of delta-CT values across all 6 transcripts, by subject, by timepoint

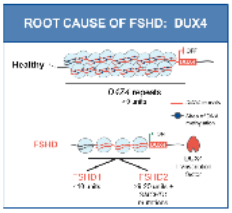
15.5. Selection of 6 gene transcripts

STUDY NUMBER(S): FIS-001-2019
REPORT DATE: April 22, 2020

1.0 BACKGROUND

FSHD is caused by aberrant expression of DUX4, a transcription factor encoded in the D4Z4 macrosatellite repeat array on chromosome 4q35. DUX4 is a master regulator of embryogenesis and it is normally expressed for a very short period of time in the early embryo to then be permanently repressed in later stages during development. Expression of DUX4 and genes activated by this transcription factor in the skeletal muscle of FSHD patients lead to muscle cell death that over time results in significant, progressive disability.

Figure 1: Schematic describing the loss in gene repression caused by contraction of D4Z4 repeats that leads to DUX4 expression.



The evidence that aberrant expression of the DUX4 transcriptional program is the cause of FSHD is the following:

- In people with a permissive DUX4 allele on chromosome 4q35, two very different genetic mutations (a deletion in FSHD1 and a loss of function mutation in FSHD2) converge on causing hypomethylation of the D4Z4 macrosatellite repeat array proximal to the DUX4 gene that enables it to be abnormally turned on
- The aberrant expression of the DUX4 transcriptional program clearly differentiates muscle in FSHD that, based on MRI, is normal (DUX4 activity absent) or affected (DUX4 activity present)

15.6. Derivation of MRI Composite Score

Input to the Statistical Plan for FSHD analysis

Muscle categorization

Each muscle is categorized into one of three categories[1]:

A. 'Normal' muscles are normal appearing (low MFI and MFF, muscle likely unaffected by disease)
B. 'Affected' muscles have a likely disease involvement (intermediate MFI and MFF)
C. 'End-stage' corresponds to that more than 50% of the muscle tissue has been replaced by fat, and most of the functional capacity is likely lost

Muscle category	MFF criteria		MFI criteria
A. Normal	MFF < 50%	AND	MFI < 10%
B. Affected	MFF < 50%	AND	MFI ≥ 10%
C. End-stage	MFF ≥ 50%	-	-

Quality control of measurements

Trained anatomical imaging experts evaluate the signal quality in each muscle. If a muscle is not analyzable, that muscle is marked as not analyzable and no measurements will be extracted from it. For cross-sectional analysis minor quality issues are accepted, but not for longitudinal analysis. Hence, as seen below, we'll use different statistical inclusion parameters depending on if we are doing a cross-sectional or longitudinal analysis.

Statistical inclusion parameters

The muscle categorization and quality control results are summarized in 3 statistical inclusion parameters which will be provided for each muscle:

- Statistical Inclusion Category: Can take the values **A**, **B** or **C**, which correspond to 'Normal', 'Affected' and 'End-stage'. Abbreviated SI_{cat} in equations.
- Statistical Inclusion Cross-sectional: Can take the values **0** or **1** (0 if there are major signal quality issues indicating unreliable measurement, 1 otherwise). Abbreviated SI_{cross} in equations.
- Statistical Inclusion Longitudinal: Can take the values **0** or **1** (0 if there are any signal quality issues, including minor, 1 otherwise). Abbreviated SI_{long} in equations.

Note: In general, if a SI parameter is 'Unable to Assess', 'NA' or '0', that muscle should be excluded from the corresponding data analysis. . As for other muscle measurements, the SI parameters will have a corresponding 'Quality Issues' column – these columns may be ignored.

Whole-body combined measurements

Cross-sectional analysis

MRI-based measurements from multiple muscles is combined to obtain global measurements of disease affection for correlation to disease severity or functional test scores in cross-sectional data:

15.7. Schedule of Study Procedures

15.7.1. Schedule of Study Procedures: Placebo-Controlled Treatment Period

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

Procedure	Screening	Baseline	Week 4	Week 12	Week 16	Week 24	Week 36	Week 48 End of Placebo-Controlled Treatment Period/Start of OLE[a]	ET Visit[b]	Safety Follow-Up 7 Days After the Last Dose of Study Drug[c]
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**-**	**8**
Serum follicle-stimulating hormone[l]	X									
Urine pregnancy test[m]		X	X	X	X	X	X	X	X	X
Weight[e]	X	X						X	X	X
Vital signs[n]	X	X	X	X	X	X	X	X	X	X
Physical examination[o]	X									X
Standard 12-lead ECG[p]	X	X	X					X	X	X
Serum chemistry	X[q]	X	X	X	X	X	X	X	X	X
Hematology	X[q]	X	X	X	X	X	X	X	X	X
Blood sample for coagulation[bb]	X[q]						X			
Urinalysis	X							X	X	X
MSK MRI[r]	X			X				X	X[s]	
Muscle needle biopsy[t]		X			X		X[t]			
PK sampling[u]		X	X	X	X	X	X	X	X	
Target engagement sampling[v]		X			X		X			
[redacted]										
RWS		X	X	X		X	X	X	X	X
TUG (classic and FSHD)		X	X	X		X	X	X	X	X
Manual dynamometry		X	X	X		X	X	X	X	X
MFM Domain 1		X		X		X	X	X	X	

Procedure	Screening	Baseline	Week 4	Week 12	Week 16	Week 24	Week 36	Week 48 End of Placebo-Controlled Treatment Period/Start of OLE[a]	ET Visit[b]	Safety Follow-Up 7 Days After the Last Dose of Study Drug[c]
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**-**	**8**
FSHD-HI questionnaire		X	X	X		X	X	X	X	X
PGIC questionnaire			X	X	X	X	X	X	X	X
Clinic visit	X	X	X	X	X	X	X	X	X	X
Study drug dispensation[x]		X	X	X	X	X[y]	X	X		
Study drug count		X	X	X	X	X	X	X	X	
Concomitant medications[z]	*Continuous from signing the ICF through the safety follow-up visit*									
Concomitant treatments and procedures	*Continuous from signing the ICF through the safety follow-up visit*									
Adverse event monitoring	*Continuous from signing the ICF through the safety follow-up visit*									

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

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

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

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

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

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

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

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

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

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

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

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

[redacted]

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

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

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

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

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

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

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

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

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

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

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

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

[redacted]

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

[y] Subjects who are rolling over into the OLE will be dispensed open label losmapimod at the time of the rollover visit. Subjects may be provided open label losmapimod via courier or shipping service, as applicable.

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

[aa] Large window given to accommodate the COVID-19 pandemic.

[bb] It is optional to perform coagulation studies prior to muscle biopsies. Refer to your institutional guidelines.

15.7.2. Schedule of Study Procedures: Open-Label Extension (Visits will Occur Quarterly Until Study Drug Approval or Study is Discontinued)

Procedure	Week 60 Week 108 Week 156 Week 204	Week 72 Week 120 Week 168 Week 216	Week 84 Week 132 Week 180	Week 96 Week 144 Week 192	ET Visit[a]	Safety Follow-Up 7 Days After the Last Dose of Study Drug
Visit Window (days)[b]	**±7**	**±7**	**±7**	**±7**		**±3**
Weight, height, and BMI[c]		X				
[redacted]						
Urine pregnancy test[e]	X	X	X	X	X	X
Vital signs[f]	X	X	X	X	X	X
Physical examination[g]						X
Standard 12-lead ECG[h]	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X
Hematology	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X
MSK MRI[i]		X		X	X[j]	
PK sampling[k]	X	X	X	X	X	
[redacted]						
RWS	X	X	X	X	X	X
TUG (classic and FSHD)	X	X	X	X	X	X
Manual dynamometry	X	X	X	X	X	X
MFM Domain 1	X	X	X	X	X	
FSHD-HI questionnaire	X	X	X	X	X	X
PGIC questionnaire	X	X	X	X	X	X
Clinic visit	X	X	X	X	X	X
Study drug dispensation[m]	X	X	X	X		

Procedure	Week 60 Week 108 Week 156 Week 204	Week 72 Week 120 Week 168 Week 216	Week 84 Week 132 Week 180	Week 96 Week 144 Week 192	ET Visit[a]	Safety Follow-Up 7 Days After the Last Dose of Study Drug
Study drug count	X	X	X	X	X	
Concomitant medications[n]	*Continuous from signing the ICF through the safety follow-up visit*					
Concomitant treatments and procedures	*Continuous from signing the ICF through the safety follow-up visit*					
Adverse event monitoring	*Continuous from signing the ICF through the safety follow-up visit*					

Abbreviations: BMI, body mass index; ECG, electrocardiogram; ET, early termination; FSHD, facioscapulohumeral muscular dystrophy; FSHD-HI, Facioscapulohumeral Muscular Dystrophy Health Index; ICF, informed consent form; MFM, Motor Function Measure; MRI, magnetic resonance imaging; MSK, musculoskeletal; OLE, open-label extension; PGIC, Patients' Global Impression of Change; PK, pharmacokinetic(s); RWS, Reachable Work Space; TUG, Timed Up and Go.

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

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

[c] Weight and height will be measured and BMI will be calculated once a year (ie, Week 48, Week 96, Week 144, etc.). Weight and height will be measured with shoes off and preferably with the same balance.

[redacted]

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

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

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

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

[redacted]

[j] The MRI at the ET visit will not be repeated if an MRI was completed during the previous 12 weeks.

[k] Blood samples for PK will be collected after dosing at each clinic visit, preferably ≥1 hour after dosing.

[l] Blood samples may be used to aid in the discovery of potential biomarkers of FSHD disease activity and treatment effects.. Serum and plasma samples taken twice a year (ie, every 24 weeks [Week 72, Week 96, Week 120, Week 144, Week 168, etc.]) will be used.

[m] The appropriate amount of study drug supply (losmapimod) will be given to the subject at each applicable visit to allow for dosing until their next scheduled study visit plus additional tablets to cover the visit window or additional study drug will be provided to the subject via a courier, as applicable. Study drug (losmapimod) will be administered as 2 tablets taken twice daily and should be taken with food.

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

15.8. List of Planned Summary Tables

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.1.1	Subject Disposition	FAS	U	5.1	Standard		Y
Table	14.1.2	Protocol Deviations	FAS	U	5.2	Standard		
Table	14.1.3.1	Demographics	FAS	U	6.1	Standard	Y	Y
Table	14.1.3.2	Demographics	Safety Analysis Set	R	6.1	Standard		
Table	14.1.4.1	Baseline Disease Characteristics	FAS	U	6.2	Standard	Y	
Table	14.1.4.2	Baseline Disease Characteristics	Safety Analysis Set	R	6.2	Standard		
Table	14.1.5	Medical History	FAS	U	6.3	Standard		
Table	14.1.6.1	Prior Medications	Safety Analysis Set	U	7.1.1	Standard		
Table	14.1.6.2	Concomitant Medications	Safety Analysis Set	R	7.1.2	Standard		
Table	14.1.7.1	Study Drug Exposure	Safety Analysis Set	U	7.2.1	Standard		
Table	14.1.7.2	Drug Compliance	Safety Analysis Set	U	7.2.2	Standard		
Table	14.2.1.1	Summary of Losmapimod Concentrations by Scheduled Time and Specimen Type	PK Analysis Set	U	10	Efficacy		Y
Table	14.2.1.1.1	Summary of Losmapimod Concentrations by Scheduled Time and Specimen Type	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	10	Efficacy		
Table	14.2.1.2.1	Summary of Target Engagement Estimates in Blood	PD analysis set	U	11	Efficacy	Y	
Table	14.2.1.2.2	Summary of Target Engagement Estimates in Blood by Baseline Repeat Category	PD analysis set	U	11	Efficacy		
Table	14.2.1.2.3	Summary of Target Engagement Estimates in Blood by Baseline Clinical Severity Score	PD analysis set	R	11	Efficacy		
Table	14.2.1.2.4	Summary of Target Engagement Estimates in Blood by Sex	PD analysis set	R	11	Efficacy		
Table	14.2.1.2.3.1	Summary of Target Engagement Estimates	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	10	Efficacy		
Table	14.2.2.1.1	Change from Baseline in DUX4 Activity (DUX4 Score 1)	FAS	U	8.1	Efficacy	Y	Y

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.2.2.1.2	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Baseline Repeat Category	FAS	U	8.1	Efficacy	Y	Y
Table	14.2.2.1.3	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Baseline DUX4 Score 1	FAS	R	8.1	Efficacy	Y	Y
Table	14.2.2.1.4	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Sex	FAS	R	8.1	Efficacy	Y	Y
Table	14.2.2.1.5	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Fat Fraction at Biopsy Site	FAS	R	8.1	Efficacy	Y	Y
Table	14.2.2.1.6	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Total DUX4 Score (DUX4 Score 1)	FAS	R	8.1	Efficacy	Y	Y
Table	14.2.2.1.7	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Subjects Who Completed RWS Protocol With Above Shoulder Movements at Baseline	FAS	R	8.1	Efficacy	Y	
Table	14.2.2.1.8	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Subjects Who Completed RWS Protocol With Above Shoulder Movements All Through the Study	FAS	R	8.1	Efficacy	Y	
Table	14.2.2.1.9	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Subjects Who Completed the Classical TUG, Without an Assisted Device, at Baseline	FAS	R	8.1	Efficacy	Y	
Table	14.2.2.1.10	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Subjects Who Completed the FUG TUG, Without an Assisted Device, at Baseline	FAS	R	8.1	Efficacy	Y	
Table	14.2.2.1.11	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Median MFFtot at Baseline	FAS	R	8.1	Efficacy	Y	
Table	14.2.2.1.12	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Median LMVtot at Baseline	FAS	R	8.1	Efficacy	Y	
Table	14.2.2.1.13	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Median MFItot at Baseline	FAS	R	8.1	Efficacy	Y	
Table	14.2.2.1.14	Change from Baseline in DUX4 Activity (DUX4 Score 1) by Subjects with Non-Censored Laboratory Observations for DUX4 Score at Baseline	FAS	R	8.1	Efficacy	Y	Y
Table	14.2.2.2	Change from Baseline in DUX4 Activity (DUX4 Score 1)	PPS	R	8.1	Efficacy	Y	

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.2.2.2.1	Change from Baseline in DUX4 Activity (DUX4 Score 1)	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.1	Efficacy		
Table	14.2.2.2.2.1	Sensitivity Analysis: Change from Baseline (DUX4 Score 1) in DUX4 Activity	FAS (LOCF)	R	8.1	Efficacy		
Table	14.2.2.2.2.2	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1)	PPS (LOCF)	R	8.1	Efficacy		
Table	14.2.2.2.3.1	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1)	FAS (Placebo Mean Imputation)	R	8.1	Efficacy		
Table	14.2.2.2.3.2	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1)	PPS (Placebo Mean Imputation)	R	8.1	Efficacy		
Table	14.2.2.2.4.1	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1)	FAS (Observed Worst Case Imputation)	R	8.1	Efficacy		
Table	14.2.2.2.4.2	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1)	PPS (Observed Worst Case Imputation)	R	8.1	Efficacy		
Table	14.2.2.2.5.1	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1) by Timepoint	FAS	R	8.1	Efficacy		
Table	14.2.2.2.5.2	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1) by Timepoint	PPS	R	8.1	Efficacy		
Table	14.2.2.2.6.1	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1) by COVID-19 Related Treatment Disruptions	FAS	R	8.1	Efficacy		
Table	14.2.2.2.6.2	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1) by COVID-19 Related Treatment Disruptions	PPS	R	8.1	Efficacy		
Table	14.2.2.2.7.1	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1)	FAS (Excluding Cross-over Subjects)	R	8.1	Efficacy		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.2.2.2.7.2	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1)	PPS (Excluding Cross-over Subjects)	R	8.1	Efficacy		
Table	14.2.2.2.8.1	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1) Excluding Subjects with Censored Laboratory Observations at Baseline	FAS	R	8.1	Efficacy		
Table	14.2.2.2.8.2	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1) Excluding Subjects with Censored Laboratory Observations at Baseline	PPS	R	8.1	Efficacy		
Table	14.2.2.2.9.1	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 2)	FAS	R	8.1	Efficacy		
Table	14.2.2.2.9.2	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 2)	PPS	R	8.1	Efficacy		
Table	14.2.2.2.10.1	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 3)	FAS	R	8.1	Efficacy		
Table	14.2.2.2.10.2	Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 3)	PPS	R	8.1	Efficacy		
Table	14.2.3.1.1.1	Change from Baseline in Composite Muscle Fat Fraction (MFFtot)	FAS	U	8.2	Efficacy	Y	
Table	14.2.3.1.1.1.1	Change from Baseline in Composite Muscle Fat Fraction (MFFtot)	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.2	Efficacy		
Table	14.2.3.1.1.2	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Baseline Repeat Category	FAS	U	8.2	Efficacy		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.2.3.1.1.3	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Baseline Clinical Severity Score	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.4	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Sex	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.5	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Fat Fraction at Biopsy Site	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.6	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Baseline DUX4 Score 1	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.7	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Subjects Who Completed RWS Protocol With Above Shoulder Movements at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.8	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Subjects Who Completed RWS Protocol With Above Shoulder Movements All Through the Study	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.9	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Subjects Who Completed the Classical TUG, Without an Assisted Device, at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.10	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Subjects Who Completed the FUG TUG, Without an Assisted Device, at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.11	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Median MFFtot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.12	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Median LMVtot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.13	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Median MFItot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.1.1.14	Change from Baseline in Composite Muscle Fat Fraction (MFFtot) by Subjects with Censored Laboratory Observations for DUX4 Score at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.1.2	Change from Baseline in Muscle Fat Fraction by Individual Muscles	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.1	Change from Baseline in Composite Lean Muscle Volume (LMVtot)	FAS	U	8.2	Efficacy	Y	

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.2.3.2.1.1.1	Change from Baseline in Composite Lean Muscle Volume (LMVtot)	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.2	Efficacy		
Table	14.2.3.2.1.2	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Baseline Repeat Category	FAS	U	8.2	Efficacy		
Table	14.2.3.2.1.3	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Baseline Clinical Severity Score	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.4	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Sex	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.5	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Fat Fraction at Biopsy Site	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.6	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Baseline DUX4 Score 1	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.7	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Subjects Who Completed RWS Protocol With Above Shoulder Movements at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.8	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Subjects Who Completed RWS Protocol With Above Shoulder Movements All Through the Study	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.9	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Subjects Who Completed the Classical TUG, Without an Assisted Device, at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.10	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Subjects Who Completed the FUG TUG, Without an Assisted Device, at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.11	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Median MFFtot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.12	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Median LMVtot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.2.1.13	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Median MFItot at Baseline	FAS	R	8.2	Efficacy		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.2.3.2.1.14	Change from Baseline in Composite Lean Muscle Volume (LMVtot) by Subjects with Censored Laboratory Observations for DUX4 Score at Baseline by Median MFItot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.2.2	Change from Baseline in Lean Muscle Volume by Individual Muscles	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.1	Change from Baseline in Composite Muscle Fat Infiltration (MFItot)	FAS	U	8.2	Efficacy	Y	
Table	14.2.3.3.1.1.1	Change from Baseline in Composite Muscle Fat Infiltration (MFItot)	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.2	Efficacy		
Table	14.2.3.3.1.2	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Baseline Repeat Category	FAS	U	8.2	Efficacy		
Table	14.2.3.3.1.3	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Baseline Clinical Severity Score	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.4	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Sex	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.5	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Fat Fraction at Biopsy Site	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.6	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Baseline DUX4 Score 1	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.7	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Subjects Who Completed RWS Protocol With Above Shoulder Movements at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.8	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Subjects Who Completed RWS Protocol With Above Shoulder Movements All Through the Study	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.9	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Subjects Who Completed the Classical TUG, Without an Assisted Device, at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.10	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Subjects Who Completed the FUG TUG, Without an Assisted Device, at Baseline	FAS	R	8.2	Efficacy		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.2.3.3.1.11	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Median MFFtot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.12	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Median LMVtot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.13	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Median MFItot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.3.1.14	Change from Baseline in Composite Muscle Fat Infiltration (MFItot) by Subjects with Censored Laboratory Observations for DUX4 Score at Baselineby Median MFItot at Baseline	FAS	R	8.2	Efficacy		
Table	14.2.3.3.2	Change from Baseline in Muscle Fat Infiltration by Individual Muscles	FAS	R	8.2	Efficacy		
Table	14.2.4.1.1	Change from Baseline in Reachable Work Space (RWS) Relative Surface Areas	FAS	U	8.3.1	Efficacy		
Table	14.2.4.1.1.1	Change from Baseline in Reachable Work Space (RWS) Relative Surface Areas	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.1	Efficacy		
Table	14.2.4.1.1.2	Change from Baseline in Reachable Work Space (RWS) Relative Surface Areas by Subjects Who Completed RWS Protocol With Above Shoulder Movements at Baseline	FAS	U	8.3.1	Efficacy		
Table	14.2.4.1.1.3	Change from Baseline in Reachable Work Space (RWS) Relative Surface Areas by Subjects Who Completed RWS Protocol With Above Shoulder Movements All Through the Study	FAS	U	8.3.1	Efficacy		
Table	14.2.4.1.2	Summary of Reachable Work Space (RWS) with >=5% Decline from Baseline by Visit	FAS	U	8.3.1	Efficacy		
Table	14.2.4.1.3	Summary of Reachable Work Space (RWS) with >=2% Decline from Baseline by Visit	FAS	U	8.3.1	Efficacy		
Table	14.2.4.1.4	Summary of Functional Work Space	FAS	U	8.3.1	Efficacy		
Table	14.2.4.2.1	Change from Baseline in Classic Timed Up and Go (TUG) Average Completion Time	FAS	U	8.3.2	Efficacy		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.2.4.2.1.1	Change from Baseline in Classic Timed Up and Go (TUG) Average Completion Time	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.2	Efficacy		
Table	14.2.4.2.1.2	Change from Baseline in Classic Timed Up and Go (TUG) Average Completion Time by Subjects Who Completed the Classical TUG, Without an Assisted Device, at Baseline	FAS	U	8.3.2	Efficacy		
Table	14.2.4.2.2.1	Change from Baseline in FSHD Timed Up and Go (TUG) Average Completion Times	FAS	U	8.3.2	Efficacy		
Table	14.2.4.2.2.1.1	Change from Baseline in FSHD Timed Up and Go (TUG) Average Completion Times	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.2	Efficacy		
Table	14.2.4.2.2.2	Change from Baseline in FSHD Timed Up and Go (TUG) Average Completion Times by Subjects Who Completed the FSHD TUG, Without an Assisted Device, at Baseline	FAS	U	8.3.2	Efficacy		
Table	14.2.4.2.3	Change from Baseline in FSHD Timed Up and Go (TUG) Average Completion Times by Segment	FAS	U	8.3.2	Efficacy		
Table	14.2.4.3.1	Change from Baseline in Average Dynamometry Result	FAS	U	8.3.3	Efficacy		
Table	14.2.4.3.1.1	Change from Baseline in Average Dynamometry Result	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.3	Efficacy		
Table	14.2.4.3.2	Change from Baseline in Maximum Dynamometry Result	FAS	U	8.3.3	Efficacy		
Table	14.2.4.3.2.1	Change from Baseline in Maximum Dynamometry Result	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.3	Efficacy		
Table	14.2.4.3.3	Change from Baseline in Total Average Dynamometry Result; All Muscles Combined, Upper Extremity, Lower Extremity	FAS	U	8.3.3	Efficacy		
Table	14.2.4.4.1	Shift in Motor Function Measure (MFM) Individual Component Score	FAS	U	8.3.4	Efficacy		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.2.4.4.1.1	Shift in Motor Function Measure (MFM) Individual Component Score	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.4	Efficacy		
Table	14.2.4.4.2	Change from Baseline in Motor Function Measure (MFM) Domain 1	FAS	U	8.3.4	Efficacy		
Table	14.2.4.4.2.1	Change from Baseline in Motor Function Measure (MFM) Domain 1	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.4	Efficacy		
Table	14.2.4.5	Change from Baseline in FSHD Health Index (FSHD-HI)	FAS	U	8.3.5	Efficacy		
Table	14.2.4.5.1	Change from Baseline in FSHD Health Index (FSHD-HI)	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.5	Efficacy		
Table	14.2.4.6.1	Patients' Global Impression of Change (PGIC) Improved and Not Improved	FAS	U	8.3.6	Efficacy		
Table	14.2.4.6.1.1	Patients' Global Impression of Change (PGIC) Improved and Not Improved	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.6	Efficacy		
Table	14.2.4.6.2	Patients' Global Impression of Change (PGIC)	FAS	U	8.3.6	Efficacy		
Table	14.2.4.6.2.1	Patients' Global Impression of Change (PGIC)	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	8.3.6	Efficacy		
Table	14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety Analysis Set	U	9.1	Safety	Y	
Table	14.3.1.1.1	Overall Summary of Treatment-Emergent Adverse Events	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.1	Safety		
Table	14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set	U	9.1.1	Safety		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.1.1	Safety		
Table	14.3.1.3	Treatment-Emergent Adverse Events by Relationship to Study Drug	Safety Analysis Set	U	9.1.2	Safety		
Table	14.3.1.3.1	Treatment-Emergent Adverse Events by Relationship to Study Drug	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.1.2	Safety		
Table	14.3.1.4	Treatment-Emergent Adverse Events by Maximum Severity	Safety Analysis Set	U	9.1.3	Safety		
Table	14.3.1.4.1	Treatment-Emergent Adverse Events by Maximum Severity	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.1.3	Safety		
Table	14.3.1.5	Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term	Safety Analysis Set	R	9.1.5	Safety		
Table	14.3.1.5.1	Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.1.5	Safety		
Table	14.3.1.6	Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term	Safety Analysis Set	R	9.1.6	Safety		
Table	14.3.1.6.1	Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.1.6	Safety		
Table	14.3.2.1	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set	R	9.1.4	Safety		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.3.2.1.1	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.1.4	Safety		
Table	14.3.2.2	Adverse Events Leading to Death by System Organ Class and Preferred Term	Safety Analysis Set	R	9.1.7	Safety		
Table	14.3.2.2.1	Adverse Events Leading to Death by System Organ Class and Preferred Term	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.1.7	Safety		
Table	14.3.4.1.1	Change from Baseline in Hematology	Safety Analysis Set	U	9.2.1	Safety		
Table	14.3.4.1.1.1	Change from Baseline in Hematology	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.2.1	Safety		
Table	14.3.4.1.2	Shift from Baseline in Hematology	Safety Analysis Set	U	9.2.1	Safety		
Table	14.3.4.1.2.1	Shift from Baseline in Hematology	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.2.1	Safety		
Table	14.3.4.2.1	Change from Baseline in Chemistry	Safety Analysis Set	R	9.2.2	Safety		
Table	14.3.4.2.1.1	Change from Baseline in Chemistry	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.2.2	Safety		
Table	14.3.4.2.2	Shift from Baseline in Chemistry	Safety Analysis Set	R	9.2.2	Safety		
Table	14.3.4.2.2.1	Shift from Baseline in Chemistry	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.2.2	Safety		
Table	14.3.4.2.3	Summary of Clinically Notable Laboratory Results by Visit - Chemistry (Liver)	Safety Analysis Set	U	9.2.2	Safety		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.3.4.2.3.1	Summary of Clinically Notable Laboratory Results by Visit - Chemistry (Liver)	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.2.2	Safety		
Table	14.3.4.3	Change from Baseline in Coagulation	Safety Analysis Set	R	9.2.3	Safety		
Table	14.3.4.3.1	Change from Baseline in Coagulation	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.2.3	Safety		
Table	14.3.4.4	Change from Baseline in Urinalysis	Safety Analysis Set	R	9.2.3	Safety		
Table	14.3.4.4.1	Change from Baseline in Urinalysis	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.2.3	Safety		
Table	14.3.5.1	Change from Baseline in Vital Signs by Visit	Safety Analysis Set	U	9.3	Safety		
Table	14.3.5.1.1	Change from Baseline in Vital Signs by Visit	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.3	Safety		
Table	14.3.5.2.1	Physical Examination	Safety Analysis Set	U	9.4	Safety		
Table	14.3.5.2.1.1	Physical Examination	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.4	Safety		
Table	14.3.5.2.2	Neurological Examination Results	Safety Analysis Set	U	9.4	Safety		
Table	14.3.5.2.2.1	Neurological Examination Results	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.4	Safety		
Table	14.3.5.3.1	Change from Baseline in Electrocardiogram Results	Safety Analysis Set	U	9.5	Safety		
Table	14.3.5.3.1.1	Change from Baseline in Electrocardiogram Results	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.5	Safety		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Table	14.3.5.3.2	Electrocardiogram Interpretation by Visit	Safety Analysis Set	U	9.5	Safety		
Table	14.3.5.3.2.1	Electrocardiogram Interpretation by Visit	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.5	Safety		
Table	14.3.5.3.3	Summary of QTc Values	Safety Analysis Set	U	9.5	Safety		
Table	14.3.5.3.3.1	Summary of QTc Values	Open-label losmapimod (Pre-COVID-19) Analysis Set	R	9.5	Safety		

15.9. List of Planned Data Listings

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Listing	16.2.1	Subject Disposition	All Screened Subjects	U	5.1	Standard		
Listing	16.2.2	Protocol Deviations	FAS	U	5.2	Standard		
Listing	16.2.3	Analysis Set	All Screened Subjects	U	5.1	Standard		
Listing	16.2.4.1	Demographics and Baseline Disease Characteristics	FAS	U	6.1	Standard		
[redacted]								
Listing	16.2.4.3	Medical History	FAS	U	6.3	Standard		
Listing	16.2.4.4	Prior and Concomitant Medications	Safety Analysis Set	U	7.1.1 and 7.1.2	Standard		
Listing	16.2.4.5	Physical Examination	Safety Analysis Set	U	9.4	Safety		
Listing	16.2.4.6	Neurological Examination Result	Safety Analysis Set	U	9.4	Safety		
Listing	16.2.5.1	Study Drug Accountability	Safety Analysis Set	U	7.2.1	Standard		
Listing	16.2.5.2	Study Drug Administration	Safety Analysis Set	U	7.2.2	Standard		
Listing	16.2.5.3.1	Individual Losmapimod Concentration	PK Analysis Set	U	10	Efficacy		

TLF	Table Number	Title	Analysis Set	Unique (U)/ Repeat (R)	Section	Efficacy/ Safety/ Standard	Topline	IA
Listing	16.2.5.3.2	Target Engagement Estimates	PD Analysis Set	U	10	Efficacy		
Listing	16.2.6.1.1	DUX4 Activity (Normalized Delta CT Value)	FAS	U	8.1	Efficacy		
Listing	16.2.6.1.2	DUX4 Score	FAS	U	8.1	Efficacy		
Listing	16.3.6.2	Fat Fraction, Lean Muscle Tissue Volume, and Muscle Fat Infiltration	FAS	U	8.2	Efficacy		
Listing	16.3.6.3.1.1	Reachable Work Space	FAS	U	8.3.1	Efficacy		
Listing	16.3.6.3.1.2	Functional Work Space	FAS	U	8.3.1	Efficacy		
Listing	16.3.6.3.2.1	Classic Timed Up and Go (TUG)	FAS	U	8.3.2	Efficacy		
Listing	16.3.6.3.2.2	Optimized Timed Up and Go (TUG)	FAS	U	8.3.2	Efficacy		
Listing	16.3.6.3.3	Muscle Strength by Handheld Quantitative Dynamometry	FAS	U	8.3.3	Efficacy		
Listing	16.3.6.3.4	Motor Function Measure (MFM) Domain 1	FAS	U	8.3.4	Efficacy		
Listing	16.3.6.3.5	Facioscapulohumeral Muscular Dystrophy Health Index (FSHD-HI)	FAS	U	8.3.5	Efficacy		
Listing	16.3.6.3.6	Patient Global Impression of Change (PGIC)	FAS	U	8.3.6	Efficacy		
Listing	16.2.7.1	Adverse Events	Safety Analysis Set	U	9.1	Safety		
Listing	16.2.7.2	Serious Adverse Events	Safety Analysis Set	R	9.1	Safety		
Listing	16.2.7.3	Adverse Events Leading to Treatment Discontinuation	Safety Analysis Set	R	9.1	Safety		
Listing	16.2.7.4	Adverse Events Leading to Study Withdrawal	Safety Analysis Set	R	9.1	Safety		
Listing	16.2.7.5	Deaths	Safety Analysis Set	R	9.1	Safety		
Listing	16.2.8.1	Laboratory Results – Hematology	Safety Analysis Set	U	9.2.1	Safety		
Listing	16.2.8.2.1	Laboratory Results – Chemistry	Safety Analysis Set	R	9.2.2	Safety		
Listing	16.2.8.2.2	Laboratory Results of Subjects with Incidence of ALT/AST $\geq$3 x ULN and Total Bilirubin $\geq$2 X ULN and ALP <2 x ULN	Safety Analysis Set	R	9.2.2	Safety		
Listing	16.2.8.3	Laboratory Results – Urinalysis	Safety Analysis Set	R	9.2.3	Safety		
Listing	16.2.8.4	Laboratory Results – Coagulation	Safety Analysis Set	R	9.2.4	Safety		
Listing	16.2.8.5	Vital Sign Results	Safety Analysis Set	U	9.3	Safety		
Listing	16.2.8.6	Electrocardiogram Results	Safety Analysis Set	U	9.5	Safety		

15.10. List of Planned Figures

Figure Number	Title	Analysis Set	Unique (U)/ Repeat (R)	SAP Section	Efficacy/ Safety/ Standard	Topline	IA
14.2.1	LS Mean (+/- SE) Change from Baseline in DUX4 Activity by Visit	FAS	U	8.2	Efficacy		
14.2.2.1	LS Mean (+/- SE) Change from Baseline in Muscle Fat Fraction by Visit	FAS	R	8.2	Efficacy		
14.2.2.2	LS Mean (+/- SE) Change from Baseline in Lean Muscle Volume by Visit	FAS	R	8.2	Efficacy		
14.2.2.3	LS Mean (+/- SE) Change from Baseline in Muscle Fat Infiltration by Visit	FAS	R	8.2	Efficacy		
14.2.3	Mean (+/- SE) Plasma Concentrations by Treatment by Visit	PK Analysis Set	U	10	Efficacy		
14.2.4.1	LS Mean (+/- SE) in Target Engagement Estimates by Treatment by Visit	PD Analysis Set	R	10	Efficacy		
14.2.4.2	Mean Percent Change from Baseline in Target Engagement Estimates by Visit	PD Analysis Set	U	10	Efficacy		

Fulcrum Therapeutics

FIS-002-2019

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

25Feb2021

Final Statistical Analysis Plan Addendum
(Placebo-Controlled Treatment Period)

Prepared by:

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Upon review of this document, including the shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can b[redacted]

DocuSigned by:
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1. Introduction

The purpose of this addendum to the final statistical analysis plan (SAP), dated 28May2020, is to describe the additional analyses that will be performed as well as to provide details on the analyses that will no longer be performed. In addition, this document will also correct some typos in both SAP and protocol.

2. Analysis Set

2.1. Pharmacodynamics Analysis Set

The Pharmacodynamic Analysis Set definition is updated to:

The PD Analysis Set will consist of all subjects who receive at least 1 dose of study drug and have evaluable PD data.

2.2. Per Protocol Analysis Set

The following are considered as significant protocol deviations in the study that may have a substantial impact on the primary endpoint. Thus, subjects in Full Analysis Set who satisfy any of the following criteria will be excluded from the Per Protocol Analysis Set.

1) Study drug compliance of below 80% before the post-baseline muscle biopsy assessment, which is either on Week 16 or Week 36.
2) Certain major protocol deviation identified from the protocol deviation tracker before database lock.
3) Certain prohibited medications.
4) Violation of inclusion/exclusion criteria.

3. General Statistical Considerations

3.1. Reporting Conventions

Presentation of continuous and quantitative variables will also include standard errors (SE).

3.2. Subgroup

For the subgroup analysis, RWS will be presented according to protocol type instead of just presenting subjects who have above shoulder movements.

1. Protocol Type (High or Low - for Subjects Who Completed RWS Protocol With Above Shoulder Movements or Below Shoulder Movements at Baseline).
2. Protocol Type (High or Low - for Subjects Who Completed RWS Protocol With Above Shoulder Movements or Below Shoulder Movements All Through the Study).

Subgroup no. 8, subjects completing the classical TUG, without an assisted device at baseline, will be updated to also consider subjects with assisted device at baseline. Hence, the subgroup presentation will be based according to use or non-use of assisted device at baseline for subjects who completed the classical TUG.

In the same manner, subgroup no. 9, subjects completing the FSHD TUG, without an assisted device, at baseline, will be updated to consider subjects with assisted device at baseline. Hence, the subgroup presentation will be based according to use or non-use of assisted device at baseline for subjects who completed the FSHD TUG.

Subgroup no. 10, MFF_{tot}, LMV_{tot} and MFI_{tot} with thresholds at the median of observed baseline data, will be based on the Longitudinal Reference Value at Screening.

4. Treatment Compliance

Additional categories for compliance will be included and the existing categories will be updated as follows:

- <40%
- 40-<60%
- 60-<80%
- 80-<120%
- >120%

5. Efficacy Analysis

5.1. Mixed Effects Model for Repeated Measures

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

5.2. Change from Baseline in DUX4 Activity in Skeletal Muscle at Week 16 or Week 36

Fold change will be presented in Table 14.2.2.1.1 (Change from Baseline in DUX4 Activity (DUX4 Score 1) Full Analysis Set, Table 14.2.2.1.2 (Change from Baseline in DUX4 Activity (DUX4 Score 1) by Baseline Repeat Category Full Analysis Set), Table 14.2.2.1.6 (Change from Baseline in DUX4 Activity (DUX4 Score 1) by Baseline DUX4 Score 1 Full Analysis Set), and Table 14.2.2.2.5.1 (Sensitivity Analysis: Change from Baseline in DUX4 Activity (DUX4 Score 1) by Timepoint Full Analysis Set). Fold change is the difference in the natural log (ln) transformed values of DUX 4 Score 1 at Week 36 or Week 16 DUX4 Score 1 and Baseline; then using the exponential function to return the computation to the original scale. The summary of fold change will include n, mean, SD, SE, median, minimum, maximum, and geometric mean. Geometric mean is derived as the arithmetic mean of the ln-transformed values of fold change of DUX4 Score 1; then using the exponential function to return the computation to the original scale. For the repeat category subgroup analysis, the repeat category will be excluded as fixed effect from the model.

In addition, an ANCOVA model will be used to analyze the change from baseline in the ln-transformed value of DUX4 Score 1, with repeat number category and treatment group as fixed effects and ln-transformed baseline DUX4 Score 1 in affected skeletal muscle as a covariate. Then, the point estimates which include within-group least-squares (LS) means and 2-sided 95% CIs will be back transformed using the exponential function to return the values to the original scale as the ratio of means and the associated 2-sided 95% CIs.

An additional sensitivity analysis will be done using the highest two expression transcripts. The DUX4 Score 1 of highest two expression transcript is derived as the mean of 2 genes or more (if there is a tie in values) with the highest expressing values at baseline. Similar methods in Section 8.2 of the SAP will be used to analyze the change from baseline in the DUX4 activity of highest two expression transcripts

5.3. MSK MRI Muscle Fat Fraction, Lean Muscle Volume and Muscle Fat Infiltration

The cross-sectional composite scores will be used to correlate the results with Clinical Outcome Assessments (i.e. TUG and RWS). Only summary statistics will be presented for these parameters.

The cross-sectional results will be further presented by extremity i.e. upper extremity, lower extremity, and total results. The convention that will be used to get extremity equivalent of the cross-sectional results is provided in Table 5-3.

Table 5-3. Extremity Equivalent of MRI Cross-sectional Results.

MRI Cross-sectional Results	Equivalent Extremity
FSHD TUG Cross-sectional	Lower extremity (LE)
RWS Right Cross-sectional	Right upper extremity (RUE)
RWS Left Cross-sectional	Left upper extremity (LUE)
RUE + LUE	Upper extremity (UE)
LE + RUE + LUE	Total

In addition, Spearman correlation coefficients will be used to assess relationships between the by extremity MRI results and classical and FSHD TUG and RWS results by visit. The Spearman correlation coefficient and p-value will be calculated within each treatment and presented in a table. This will also be graphically presented using scatterplots. Specifically, the following relationships will be assessed:

- LE vs. FSHD-TUG
- LE vs. Classical TUG
- RUE vs. RWS
- LUE vs. RWS
- UE vs. RWS

- TOTAL vs. FSHD-TUG
- TOTAL vs. Classical TUG
- TOTAL vs. RWS

The longitudinal composite scores are used to measure the change from baseline at each post-baseline visit. This is the result that will be used in the MMRM model.

5.4. Reachable Work Space With and Without Weights

The % change/year in RSA will be analyzed. A linear mixed-effects model will be used to analyze the total RSA, with treatment group as a fixed effect, and intercept, time and treatment-by-time interaction as random effects, and with adjustment for repeat number category and region (EU, USA, and Canada). Within-group LS mean of slope and the associated SEs, intercept and the associated SE, differences in the LS mean of slope and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the linear mixed-model and will be provided in the summary table. In addition, the % change/year will be presented and will be derived as [(slope*365)/baseline]*100 where baseline is the LS mean of the intercept. Difference in % change/year between treatments will also be presented.

A separate model will be run with and without weights and for the dominant and non-dominant hand. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. Similar methods will be used to analyze the change from baseline in RSA for each quadrant.

The analysis related to functional work space (FWS) will no longer be done. According to the vendor, majority of the sessions were collected on normal speed and the table on FWS to show subjects belonging to normal or low speed will not give much information. In addition, the listing to show the detected will also be removed since this data was removed by the vendor.

5.5. FSHD TUG

An MMRM model will also be used to analyze the change from baseline in the sum of the 3 FSHD TUG segments average completion time with repeat number category, treatment group, visit, and treatment-by-visit interaction as fixed effects and baseline value as a covariate. Within-group LS mean changes from baseline, the associated SEs and 2-sided 95% CIs, treatment differences in LS mean changes from baseline at post-baseline visits and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model and will be provided in the summary table. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. If models using unstructured covariance do not converge, an AR(1) covariance structure will be used instead.

5.6. PGIC

The PGIC will be further analyzed. An MMRM model will be used to analyze the PGIC with repeat number category, treatment group, visit, and treatment-by-visit interaction as fixed effects. Within-group LS mean changes from baseline, the associated SEs and 2-sided 95% CIs, treatment differences in LS mean changes from baseline at post-baseline visits and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model and will be provided in the summary table. An unstructured covariance matrix will be used to model the correlation among repeated measurements within each subject. If models using unstructured covariance do not converge, an AR(1) covariance structure will be used instead.

In addition, a spaghetti plot will be presented to show the PGIC score within subject over time.

6. Pharmacodynamics Analysis

An ANCOVA model instead of MMRM model will be used to analyze the target engagement parameters.

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