STATISTICAL ANALYSIS PLAN

Title: Statistical Analysis Plan for 1821-FSH-301, A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled, 48-Week, Parallel-Group Study of the Efficacy and Safety of Losmapimod in Treating Patients with Facioscapulohumeral Muscular Dystrophy (REACH)

Compound Name/Number: Losmapimod

Effective Date:

Subject: Facioscapulohumeral Muscular Dystrophy

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TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
CI	Confidence interval
CLT	Central limit theorem
CSP	Clinical study protocol
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
[redacted]	[redacted]
ET	Early termination
FAS	Full Analysis Set
FSHD	Facioscapulohumeral muscular dystrophy
FSHD1	Facioscapulohumeral muscular dystrophy type 1
FSHD2	Facioscapulohumeral muscular dystrophy type 2
GCP	Good Clinical Practice
ICH	International Council for Harmonization
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
LLOQ	Lower limit of quantification
LMV	Lean muscle volume
LME	Linear mixed-effects model
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities

MFF	Muscle fat fraction
MFI	Muscle fat infiltration
MI	Multiple imputation
MMRM	Mixed-effects model for repeated measures
MRI	Magnetic resonance imaging
Neuro-QoL	Quality of Life in Neurologic Disorders
Neuro-QoL-UE	Quality of Life in Neurologic Disorders – Upper Extremity
[redacted]	[redacted]
PD	Pharmacodynamic(s)
PFS	Physical Function Scale
PGIC	Patient Global Impression of Change
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PR	ECG measurement
PRO	Patient-reported outcome
PT	Preferred term
Q	Quadrant
QoL	Quality of life
QT	ECG measurement
QTc	QT interval corrected
QTcF	QT interval corrected for heart rate by Fridericia's formula
RSA	Relative surface area
RWS	Reachable workspace
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
SLS	Symptoms and Limitations Scale
TEAE	Treatment-emergent adverse event
UE	Upper extremity
ULN	Upper limit of normal
WB	Whole-body
WHO DD	World health organization drug dictionary

TRADEMARK INFORMATION

SAS®	SAS (Statistical Analysis Software) is a registered trademark of SAS Institute Inc.

REVISION HISTORY

Version	Date	Summary of revisions

1. INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is a serious, rare, progressive, and debilitating neuromuscular disease, characterized by muscle weakness and eventual loss of muscle function. The progression of the disease significantly impacts activities of daily living (ADLs), independence, self-esteem, and mental status, with some patients experiencing pain and lost ability to function or work. No therapy has been proven to reduce disease severity or delay the progression of the disease; therefore, there is a high unmet need for an effective therapy for FSHD.

This study (REACH) is a Phase III double-blind, randomized, placebo-controlled trial of losmapimod, an orally bioavailable small molecule inhibitor of the p38α/β mitogen-activated protein kinase (MAPK). The study is being conducted in 2 parts: a 48-week placebo-controlled treatment period (Part A) and an open-label extension (OLE, Part B) to allow patients to continue receiving losmapimod after completion of Part A. Prior Phase I and II studies have shown that losmapimod has potential to be a safe and effective therapeutic in slowing the progression of FSHD.

This Statistical Analysis Plan (SAP) provides details of the summaries and analyses to be performed to report the findings of Part A of the study. It should be read in conjunction with the Clinical Study Protocol (CSP); 1821-FSH-301, v5.1,21 December 2023. A separate SAP will be written to describe the planned analyses for Part B.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 Primary objective

The primary objective of the study is to evaluate the efficacy of losmapimod for the treatment of FSHD on disease progression assessed by RWS quantification of total relative surface area (RSA) Q1-Q5 with 500 g wrist weight, averaged over both arms.

2.1.2 Secondary objectives

The secondary objectives are:

- To evaluate Patient Global Impression of Change (PGIC) relative to placebo.
- To evaluate efficacy of losmapimod to slow accumulation of fat in muscle-by-muscle fat infiltration (MFI) with whole-body (WB) musculoskeletal (MSK) magnetic resonance imaging (MRI) relative to placebo.
- To evaluate relative change from baseline in shoulder strength by hand-held quantitative dynamometry relative to placebo.
- To evaluate the change in Quality of Life in Neurological Disorders: Upper Extremities (Neuro-QoL-UE) relative to placebo.
- To assess safety and tolerability of losmapimod in patients with FSHD.

- To evaluate relative change from baseline in muscle strength by hand-held quantitative dynamometry, relative to placebo.

2.1.4 Safety objectives

These are included in the Secondary Objectives (see 2.1.2).

2.2 STUDY ESTIMANDS

2.2.1 Primary estimand

The estimand of the primary analysis is the mean difference in the change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 between treatment groups, where average is applied over both arms. This evaluation will be carried out on the Full Analysis Set (FAS) (as per the ICH E9 (R1) [1]), which will consist of all randomized patients with FSHD type 1 (FSHD1) and FSHD type 2 (FSHD2) who receive at least one dose of study drug in the placebo-controlled treatment period. All observed data will be included in the primary analysis, including data collected after intercurrent events (as described in ICH E9 (R1) Addendum 2017), i.e., treatment discontinuation or a change in concomitant use of FSHD symptomatic medication. The change from baseline in average total RSA Q1-Q5 with 500 g wrist weight will be summarized by treatment group at each post-baseline visit. A mixed-effects model for repeated measures (MMRM) will be used as the primary analysis to analyze change from baseline in average total RSA Q1-Q5 with 500 g wrist weight (see 8.3.1, 10.2.1.1).

2.3 STUDY ENDPOINTS

2.3.1 Primary endpoint

Change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48, where average is applied over both arms.

2.3.2 Secondary endpoints

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

2.3.3 Exploratory endpoints

[redacted]

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

[redacted]

Abbreviations: MFI = muscle fat infiltration; [redacted].

2.4 STATISTICAL HYPOTHESES

2.4.1 Primary hypotheses

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

The alternative hypothesis for the primary endpoint is that the mean change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48, where average is applied over both arms, differs between the 2 treatment groups.

2.4.2 Multiple testing strategy

To control the overall type I error rate, the primary endpoint and secondary efficacy endpoints will be tested in sequence as follows:

1. The primary endpoint will be tested at 2-sided significance level α=0.05.

2. If a statistically significant result is obtained for the primary endpoint (test 1), change from baseline in WB longitudinal composite MFI in B muscles at Week 48 and relative change from baseline in average shoulder abductor strength by hand-held quantitative dynamometry at Week 48 will be tested using the Bonferroni procedure, i.e., each will be tested at 2-sided α = 0.025 (test 2).

   - If both tests are significant, a statistically significant result is obtained from test 2. The remaining significance level from test 2 = 0.05.
   - If only one of the 2 tests is significant, a statistically significant result is obtained from test 2. The remaining significance level from test 2 = 0.025.
   - If neither test is significant, a statistically significant result is not obtained from test 2.

3. If a statistically significant result is obtained from test 2, PGIC at Week 48 will be tested at the remaining significance level from test 2 (test 3).

4. If a statistically significant result is obtained from test 3, change from baseline in Neuro-QoL-UE at Week 48 will be tested at the remaining significance level from test 3, which is equal to the remaining significance level from test 2.

In recognition of the complexities of this rare disease and the novelty of this research field, in case the result of the primary analysis (MMRM) of the primary endpoint is on the boundary of statistical significance, but at least one of the following is true:

- results from most sensitivity analyses are nominally significant,
- result of PGIC at Week 48 is nominally significant,
- result of Change from baseline in WB longitudinal composite MFI in B muscles at Week 48 is nominally significant,

AND

- results from most of the remaining secondary and exploratory efficacy endpoints are directionally favorable to losmapimod,

the totality of evidence will be utilized to support the decision making.

3. STUDY DESIGN

3.1 STUDY DESIGN

Part A of this study is a global, randomized, double-blind, placebo-controlled, parallel-group, multi-center Phase III study with a [redacted] screening period, a 48-week treatment period, and safety follow-up visits [redacted] and [redacted] after last dose.

A total of approximately 230 patients with FSHD will be randomized 1:1 to receive 15 mg orally of losmapimod (n~115) or placebo (n~115) tablets twice daily (BID) with food for 48 weeks (see Figure 1 of protocol for a design schematic). Approximately 210 patients with genetically confirmed FSHD1 and 20 patients with genetically confirmed FSHD2 will be randomized.

- For the FSHD1 cohort, randomization will be stratified by the number of FSHD repeats (1- 3 versus 4-9) to ensure that an equal number of patients are allocated to treatment and placebo within each FSHD repeat number category.
- The FSHD2 cohort will be separately randomized to ensure that an equal number of patients will be allocated to treatment and placebo. Randomization will not be stratified for the FSHD2 cohort.

During the treatment period in Part A, patients will be asked to attend the study clinic at each scheduled visit (see Appendix B below).

Scheduled visits may be split over 2 days if required, with a maximum of 5 business days between visits. Unscheduled visits may be performed if clinically indicated.

See Section 4 of the protocol for inclusion and exclusion criteria.

For patients who do not continue in the Open Label extension, safety follow-ups of [redacted] and [redacted] are implemented once a patient takes the last dose of study drug.

3.2 RATIONALE OF STUDY DESIGN

See Section 3.2 of the protocol for full details of the rationale for the study design.

4. TIMING OF PLANNED ANALYSES

4.1 INTERIM ANALYSES

No formal interim analysis is planned during Part A. Safety and a limited set of statistics summarizing efficacy will be presented at periodic Independent Data Monitoring Committee (IDMC) meetings, without unblinding of the sponsor and vendor teams involved with the analyses described in this SAP.

4.2 FINAL ANALYSIS

The planned final analysis will be performed following the end of Part A of the study, and when all required database cleaning activities for Part A data have been completed, and the database has been declared clean and locked by data management. This is after all patients who have decided to continue into the OLE have had their Week 48 visit; and after all other patients have completed their safety follow-up visit.

5. SAMPLE SIZE CONSIDERATIONS

The target population for this clinical trial is patients with FSHD1 and FSHD2. The clinical trial will reflect the current epidemiologic information about FSHD, with patients with FSHD1 making up approximately 95% of the study population and the other 5% being people living with FSHD2.

Assuming the within-group standard deviation (SD) of change is 0.08, a sample size of 210 patients with FSHD1 (105 patients per group) will be needed to provide at least 95% power with a 2-sided t-test at 0.05 significance level to detect a difference of 0.05 between losmapimod and placebo for the primary endpoint. An additional approximately 20 patients with FSHD2 will be recruited. The primary analysis will include patients with FSHD1 and FSHD2. Premature withdrawal and missing data are discussed in 9.1.

For the secondary efficacy endpoints of change from baseline in WB longitudinal composite MFI of B Muscles and PGIC at Week 48, assuming the within-group SDs are 0.72 and 1.0 respectively, a sample size of 210 patients with FSHD1 will provide at least 95% power with a 2-sided t-test at 0.025 significance level to detect a difference of 0.5 and 0.6 respectively between losmapimod and placebo.

For the secondary efficacy endpoint of relative change from baseline in average shoulder abductor strength at Week 48, assuming the within-group SD is 46, a sample size of 210 patients with FSHD1 will provide at least 75% power with a 2-sided Wilcoxon rank-sum test at 0.025 significance level to detect a difference of 20.2 between losmapimod and placebo.

In the above calculations, the assumed treatment differences and SDs are based on results from an ongoing Phase 2 study, Study FIS-002-2019 (ReDUX4). It is also assumed that 10% of the study population has missing Week 48 data. All power calculations were performed using the POWER Procedure of SAS® Version 9.4.

6. ANALYSIS POPULATIONS

6.1 FULL ANALYSIS SET

The FAS will consist of all patients with FSHD1 or FSHD2 who are randomized and receive at least 1 dose of study drug in the placebo-controlled treatment period. All analyses using the FAS will group patients according to randomized treatment, regardless of which treatment the patient actually received.

6.2 SAFETY ANALYSIS SET

The safety analysis set will consist of all patients who receive any study drug. All analyses using the safety analysis set will group patients according to treatment actually received, regardless of which treatment the patient was randomized to. If a patient receives both losmapimod and placebo, the patient will be assigned to the losmapimod group in the safety analysis set.

6.3 PHARMACOKINETIC ANALYSIS SET

The pharmacokinetic (PK) analysis set will consist of all patients who receive at least 1 dose of losmapimod and have non-missing PK data for losmapimod.

7. PROTOCOL DEVIATIONS

Protocol deviations are defined as any change, divergence, or departure from the study design in the CSP.

Significant deviations are protocol deviations that affect important efficacy and safety assessments (as applicable), the safety or mental integrity of a patient, or the scientific value of the trial/project.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1 STANDARD SUMMARY STATISTICS

Continuous data will be summarized using descriptive statistics (n, mean, standard deviation (SD), standard error (SE), median, first quartile, third quartile, minimum, and maximum). Categorical data will be summarized using the count and percentage in each category. When count data are presented, in cases where the count is zero, the percentage will not be displayed, in order to draw attention to the non-zero counts. A row denoted 'Missing' will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will usually be the number of patients in that treatment group within the analysis set of interest (i.e., including patients with missing data). Exceptions to this are when binary or categorical variables are derived from changes from baseline, where the denominator is all patients within the analysis set of interest with non-missing baseline. . Percentages will be displayed to 1 decimal place, except in the case of 100% which will be presented with no decimal places.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported in the raw data. Mean, median, quartiles, 95% CI, SD and SE will be displayed to one level of precision greater than the data collected. P-values will be rounded to four decimal places. A p-value below 0.0001 will be reported as "<0.0001." A p-value above 0.9999 will be reported as ">0.9999". Data will be presented in summary tables, listings, and figures. Where appropriate, an estimation approach will be taken, and point estimates and confidence intervals (CIs) of interest will be constructed. Patients will be identified in the listings by patient identification number. Summary statistics will be presented by treatment arm and/or overall (if required). In the case where the number of patients included in an analysis is 0, no statistics will be presented; if only one patient is included, then only n, and mean will be presented.

All analyses will be conducted using SAS® Version 9.4 or higher.

8.2 STRATA AND COVARIATES

Patients will be randomly assigned at the baseline visit (Day 1) to receive losmapimod (active drug) or placebo using a 1:1 allocation ratio. Randomization will be stratified to ensure that treatment allocation is balanced across 3 strata based on FSHD repeat number category and FSHD type:

- FSHD 1, repeat numbers 1-3
- FSHD 1, repeat numbers 4-9
- FSHD 2

Inferential models will be adjusted for the above 3-level FSHD repeat number category (except subgroup analyses by FSHD Repeat Number Category). If the stratification category used at randomization is different from the correct category, the stratification category used in analyses will be the category used at randomization for the primary analyses of the primary endpoint and alpha-protected secondary endpoints (see 2.4.2), while the correct category will be applied in the sensitivity analyses of the primary endpoint and alpha-protected secondary endpoints, and the correct category will be applied in all other efficacy analyses. If the number of patients with non-missing data in any level of the FSHD repeat number category < 5 in either treatment group in any inferential analysis, the data from that level in both treatment groups will not be included in that inferential analysis. If such a situation occurs in at least 2 of the 3 levels, the inferential analysis will be performed on data from all patients without adjusting for the 3-level FSHD repeat number category. All inferential models will include a fixed effect for region: North America / Europe (except subgroup analyses by region). If the number of patients with non-missing data in either region < 5 in either treatment group in any inferential analysis, the inferential analysis will be performed on data from all patients without adjusting for region.

8.3 STANDARD COMPARISON METHODS

8.3.1 Primary and secondary endpoint analyses

Continuous endpoints with multiple post-baseline assessments will be analyzed using mixed-effects models for repeated measures (MMRM). Models will include terms for treatment group, visit,

treatment group by visit interaction, baseline value, baseline value by visit interaction, stratification category (FSHD repeat number category: FSHD 1, 1-3; FSHD 1, 4-9; FSHD 2; see 8.2), and region (North America, Europe). An unstructured covariance matrix will be used to model the correlations between repeated measurements within each patient. If the unstructured covariance matrix results in a lack of convergence, the first-order autoregressive covariance structure followed by the compound symmetric covariance structure will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom [2, 3]. Windowing (see 9.5.1) will be applied to ensure no more than one measurement per target visit window, per patient. Least-square (LS) mean, standard error, 2-sided 95% CI, and a 2-sided within-group p-value will be presented for each treatment group, at each visit. The difference in LS means between treatment groups (Losmapimod 15 mg BID – Placebo BID), the 2-sided 95% CI of the difference, and a 2-sided p-value will be presented at each visit.

In addition, certain continuous endpoints with multiple post-baseline assessments will be analyzed using a linear mixed-effects model (LME, see 10.2). In these models the response variable is the absolute measurement, at baseline and post-baseline assessments. Models will include terms for treatment group, time, treatment group by time interaction, FSHD repeat number category (FSHD 1, 1-3; FSHD 1, 4-9; FSHD 2; see 8.2), and region (North America, Europe). Intercept and time will be fitted as random effects. In this model, 'time' is time from first dose normalized over the treatment period of 48 weeks (335 days). It is derived as follows:

Time = (Assessment/event date – Date of first dose) / 335

The treatment effect will be assessed over the entire treatment period (i.e., 48 weeks) for each treatment group. Data to be included (scheduled and unscheduled) will be selected through windowing. An unstructured covariance matrix will be used to model the correlations between repeated measurements within each patient. If the unstructured covariance matrix results in a lack of convergence, the first-order autoregressive covariance structure followed by the compound symmetric covariance structure will be used. LS mean, SE and 2-sided 95% CI for the slope and intercept, and a 2-sided p-value for the slope, will be presented for each treatment group. The difference in LS mean slopes between treatment groups (Losmapimod 15 mg BID – Placebo BID), the 2-sided 95% CI of the difference, and a 2-sided p-value will be presented. In addition, the average percentage change per year (annualized percentage change) will be presented for each treatment group. This is derived as [(slope/baseline)*(365/335)*100], where baseline is the LS mean intercept, slope is the LS mean slope and 335 is the planned duration of treatment with study drug in days minus 1. The difference in average percentage change per year between treatment groups (Losmapimod 15 mg BID – Placebo BID) will also be presented.

Least squares means derived from the MMRMs will be plotted over time for both treatment groups with error bars showing standard errors. Annualized percentage changes estimated from LMEs will be presented as line charts.

For all MMRMs and LMEs fitted, model assumptions will be checked by examining plots of residuals. Given the sample size of the study and the nature of the variables investigated, the central limit theorem (CLT) is highly likely to guarantee that the analysis of means is appropriate. However, if the

distributions of the data strongly imply the CLT isn't appropriate, the analysis may rely on nonparametric methods or transformations of the data.

In the case that a model does not converge under any of the three covariance structures, analysis will consist of descriptive statistics only.

[redacted]

8.3.3 Pharmacokinetic analyses

See 10.5.1 below.

8.4 Statistical significance

See Section 2.4.2 for a summary of significance thresholds for the primary and secondary endpoints. All other statistical tests will be 2-sided and performed using a 0.05 significance level.

8.5 Examination of subgroups

Subgroup analyses of the primary and secondary efficacy endpoints will be conducted. Subgroups to be analyzed are:

- Correct FSHD type 1 repeat categories 1-3; FSHD type 1 repeat categories 4- 9; FSHD type 2
- Baseline clinical severity score (Ricci score 2- 3 and 3.5- 4)
- Region (North America and Europe)
- Sex (Male and Female)
- Age (<45 years old and ≥ 45 years old)
- Baseline weight (<77kg vs ≥ 77kg)

The by-site analysis of the primary endpoint will also be performed.

Note: models will be fitted for all subgroups, but in the case of failure to converge due for example to small sample size, model results will not be presented.

9. DATA HANDLING CONVENTIONS

9.1 Premature withdrawal and missing data

Patients who prematurely discontinue study treatment will be encouraged to remain in the study and continue with all other aspects of the study. Patients who decide to discontinue study treatment

prematurely and not continue with all other aspects of the study will be considered to have withdrawn from the study.

The primary analysis of the primary endpoint will use a mixed-effects model based on restricted maximum likelihood estimation. The assumption will be made that, conditional on fixed and random effects, data are missing at random; therefore no imputation of missing data will be performed. The robustness of the analysis will be evaluated by sensitivity analyses with missing post-baseline values imputed using several imputation algorithms (see 10.2.1.2).

9.2 BASELINE AND CHANGE FROM BASELINE

For all endpoints, the baseline value is defined as the last non-missing value obtained prior to the first dose of study treatment.

For continuous laboratory variables, electrocardiogram (ECG) data and vital signs, if two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average will be used as the baseline value. In the scenario where there are two assessments on day 1, one with time recorded and the other without time recorded, the one with time recorded will be selected as baseline. Where safety data will be summarized over time, time on study will be calculated in relation to date of first study treatment.

In all summaries, change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change (relative change) from baseline will be calculated as:

100 x (Post-baseline value - Baseline value) / (Baseline value)

9.3 DERIVED AND TRANSFORMED DATA

9.3.1 General derivations

9.3.1.1 Average

Where an average is required, but some data are missing, the average is the mathematical mean of the non-missing value(s).

9.3.1.2 Multiple measurements at one time point

All data will be included in the relevant listings.

For summary tables and figures, if two assessments are assigned to the same visit, the assessment closest to the target day for that window (see Section 9.5.1) will be used. Where two assessment dates are equidistant from the target visit date, the later assessment will be included for analysis.

9.3.1.3 Study day

The study day for assessment and event dates are derived from the date of first dose of the study drug (Day 1).

If the assessment/event date is before the date of first dose, then the study day is defined as:

(Assessment/event date) – (Date of first dose)

If the assessment/event date is on or after the date of first dose, then the study day is defined as:

(Assessment/event date) – (Date of first dose) + 1

Missing assessment/event dates

Handling of partial or missing medical history, AE, prior medication, prior procedure, concomitant medication, and concomitant procedure dates is described below in the relevant derivation sections.

All other assessment/event dates should not be partial or missing. Querying should resolve missing dates prior to database lock. In the event of a partial or missing date at database lock, the assessment date will be imputed by visit date.

9.3.1.4 On-treatment

For patients that do not prematurely discontinue treatment, all post-baseline measurements on or before the end of the Week 48 window are considered on-treatment.

For patients that do prematurely discontinue treatment, only measurements that are taken whilst a patient is taking the study treatment will be on-treatment measurements. More specifically if:

(Assessment date) – (Date of first dose) + 1 > 0; and
(Date of last dose) + 2 – (Assessment date) ≥ 0

9.3.1.5 MRI data

The objectives of the study relate to whole body longitudinal composite MFI and MFF. In addition, exploratory analyses are planned for whole body longitudinal composite lean muscle volume (LMV); analysis of each muscle MFI, MFF and LMV; and RWS cross-sectional composite MFI, MFF and LMV. MRI data are complex, and an intermediate step of derivation is carried out prior to statistical analysis. Derivations for this intermediate step may be found in Appendix C. The section below gives derivations relevant to the statistical analysis using the dataset that will be analyzed. These derivations are common to MFI, MFF and LMV endpoints.

Muscle categories

A, B, C muscle category codes are assigned to each muscle at baseline by the MRI vendor based on MFF and MFI and are applied throughout the study:

MFF Criteria		MFI criteria	Muscle Category	Code
MFF < 50%	and	MFI < 10%	Normal	A
MFF < 50%	and	MFI ≥ 10%	Affected	B
MFF ≥ 50%	-	-	End-stage	C

where:

A. Normal = a muscle that appears normal and is most likely not affected by disease.
B. Affected = a muscle that is more likely to have disease involvement, but which still retains some functional capacity.
C. End-stage = a muscle that is most likely to have loss of functional capacity.

Whole-body Longitudinal composite endpoints

These endpoints relate to measurements of change from baseline in LMV, MFI and MFF. These are specific to three muscle group categorizations: A, B, A+B. Note that baseline is measured during screening. If there is more than one screening measurement, then the last available assessment prior to first dose of treatment should be used. For the analysis of these endpoints four measures are required:

(1) Baseline whole body longitudinal LMV, MFI and MFF are variables with the label of type:

Lngtdl [*Y*] Ref Scrn [*Muscle categories included*] [*unit*]

where *Y*=MFI, MFF or LMV; *unit* = percentage points(pp) when Y=MFI or MFF; and *Muscle category included* = A, B, or A+B; and *unit* = liters (L) when Y=LMV; with Visit Name = 'Screening'.

(2) Change from baseline whole body longitudinal LMV, MFI and MFF are variables with the label of type:

Lngtdl [*Y*] Chng from Scrn [*Muscle categories included*] [*unit*]

where *Y*=MFI, MFF or LMV; *unit* = percentage points(pp) when Y=MFI or MFF; and *Muscle category included* = A, B, or A+B; and *unit* = liters (L) when Y=LMV; with Visit Name = '24 weeks' or '48 weeks'.

Change from baseline validity: At weeks 24 and 48, reference LMV is assessed using reference screening LMV ($LMV(t)_{REF}$); and reference screening muscle count ($N(t)_{REF}$) , where t=24 or 48. $N(t)_{REF}$ is the total number of individual muscles assessed at time t. These are labelled in the raw data as:

Lngtdnl LMV Ref Scrn [*Muscle categories included*]
Lngtdnl LMV Ref Scrn Mscl Cnt [*Muscle categories included*]

If a patient's reference LMV is too small, then change from baseline should be coded as missing per instruction from the MRI vendor. $LMV(t)_{REF}$ is considered too small if:

- $LMV(t)_{REF} < 0.25L$ when $N(t)_{REF} \geq 2$; or
- $LMV(t)_{REF} < 0.5L$ when $N(t)_{REF} = 1$

(3) Reference screening whole body longitudinal LMV, MFI and MFF for a muscle group are measured at weeks 24 and 48. These are labelled:

Lngtdnl [*Y*] Ref Scrn [*Muscle categories included*]

where *unit* = percentage points(pp) when Y=MFI or MFF; and *unit* = liters (L) when Y=LMV.

(4) Absolute whole body longitudinal LMV, MFI and MFF for a muscle group measured at weeks 24 and 48 are derived from Reference screening and Change from baseline as:

Absolute for Y = Reference screening for Y at time t + Change from baseline for Y at time t

where Y=MFI, MFF or LMV, and t=24 or 48 weeks.

Individual muscle measurements

There are 36 muscles measured, 18 on each side of the body:

- Infraspinatus
- Subscapularis
- Supraspinatus
- Teres Minor
- Biceps Brachii
- Deltoideus
- Triceps Brachii
- Latissimus Dorsi/Teres Major
- Pectoralis Major
- Rhomboideus
- Serratus Anterior
- Spinal Erectors Th1-Sacrum
- Trapezius
- Adductors
- Gastrocnemius Medialis
- Hamstrings
- Quadriceps
- Tibialis

LMV, MFI and MFF are measured for each muscle at screening, 24 and 48 weeks. These are labelled as:

[*Muscle Name*] [*measurement Type*] [*Unit of Measurement*]

E.g., "Left Infraspinatus Muscle Fat Fraction (MFF) [%]."

Change from baseline is derived at 24 and 48 weeks as defined in 9.2 above.

Missing data

All MRI missing data where a scan is known to have taken place will be queried prior to database lock. For signal quality issues, see Appendix C.

9.3.2 Study population

Analysis populations are defined in Section 6.

9.3.2.1 Patient disposition

The total number of patients screened is the total number of unique patients recorded in the consent forms. These forms also define the total number of patients who gave informed consent.

Patients who consent but are ineligible are recorded in the Inclusion/Exclusion criteria form.

9.3.2.2 Demographics and baseline characteristics

Demographics and baseline characteristics are recorded in the following eCRF forms: Demographic Data; Height, Weight and BMI; FSHD History; and [redacted]. Most of these data are collected at screening. Weight is measured at screening and baseline: the measure taken closest to day 1 should be used.

9.3.2.3 Medical history

Medical history is recorded in the Relevant Medical History form of the eCRF. Partial or missing dates will not be imputed.

9.3.2.4 Concomitant medications/procedures

All medications or procedures 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 or procedure is defined as any medication or procedure that is taken prior to the first dose of study drug regardless of when the medication or procedure ended. A concomitant medication or procedure is defined as any medication or procedure continued or newly received on or after the date of first dose of the study drug.

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

- Medications with missing or partially missing start dates will have 2000 imputed for the missing year, January for the missing month, and 1 for the missing day.
- Medications with missing or partially missing stop dates will have 2050 imputed for the missing year, December for the missing month, and the last day of the month for the missing day.

For the purpose of listings, missing date data will not be imputed. For example, a date with a missing day but known to be in October 2023 will be presented as ??/OCT/2023. Where medications or procedures are ongoing, a stop date will not be presented.

9.3.2.5 Treatment exposure and compliance

The following will be derived from data collected in the Study Drug Accountability form of the eCRF:

For each visit post baseline:

- Number of tablets taken = Number of tablets dispensed at previous visit – Number of tablets returned for the visit
- Duration = (date of last dose) – (date of first dose) + 1.
- Tablets Prescribed = Duration x 2
- Study drug compliance (%) = 100 x (Number of tablets taken) / (Number of tablets prescribed)

For the whole study:

- Treatment Duration = (Date of last dose) – (Date of first dose) + 1
- Cumulative dose is the total number of tablets taken across all study days times 15 mg
- Average daily dose is the cumulative dose divided by the total treatment duration
- Total number of tablets taken = Sum of numbers of tablets taken over all visits
- Total number of tablets prescribed = Sum of tablets prescribed over all visits
- Overall study drug compliance (%) = 100 x (Total number of tablets taken) / (Total number of tablets prescribed)

If “Number of tablets returned” is missing, the Number of tablets returned will be assumed to be 0 in the calculations of treatment exposure and compliance but will be presented as missing in the listings.

9.3.3 Efficacy derivations

9.3.3.1 Primary endpoint

Change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48, where the average is applied over both arms.

The RWS (total RSA Q1-Q5) measurements required for the analysis of the primary endpoint are those assessed at baseline and at weeks 4, 12, 24, 36 and 48, on both the dominant and non-dominant arms. At each visit the RWS for each arm (Left and Right) is the sum of the 5 RSA measurements: Q1+Q2+Q3+Q4+Q5, where the weight used is 500g. The average total RSA is the average of the two totals:

Average = Mean of (Total for Left Arm with 500g weight, Total for Right Arm with 500g weight)

Change from baseline is derived as specified in 9.2. above.

Note: the average over both arms per visit needs to be calculated before computing changes from baseline.

If an arm is not tested for RWS, and the reason code is W='Weakness related', then the RWS for that arm should be imputed as 0.

Because the RWS data are used in the primary endpoint analysis for this study, Fulcrum or its designated vendor will perform additional cleaning of these data. Fulcrum or its designated vendor will use the following criterion to identify potentially invalid data points: post-baseline data points that show a change (increase or decrease) >50% from the previous result on total RSA Q1-Q5. Records meeting this criterion will be sent to the RWS vendor for further investigation. After blind review, the RWS vendor will communicate to Fulcrum or its designated vendor any records that are deemed invalid because of problems with the software and should therefore not be included in the analysis. These rare sessions, if any, will be flagged by the RWS vendor, and their associated results, including total RSA Q1-Q5, total RSA Q1-Q4, sum of Q1 and Q3, and all 5 individual quadrants, will be removed from the RWS analysis (also see 9.3.3.3).

9.3.3.2 Secondary endpoints

PGIC at Week 48

PGIC is a single-item rating scale. Patients will be asked to rate their overall status relative to baseline: 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, 7 = Very much worse. The PGIC is measured at weeks 4, 12, 24, 36 and 48. Missing values are treated as missing.

Change from baseline in whole-body (WB) longitudinal composite muscle fat infiltration (MFI) (B muscles) at Week 48

This endpoint is derived for B-muscles as described in 9.3.1.3, where Y=MFI.

Relative change from baseline in average shoulder abductor strength by hand-held quantitative dynamometry at Week 48

Shoulder abductor strength is measured three times on each arm at baseline, weeks 4, 12, 24, 36, and 48, and a mean value is recorded in the EDC. At each timepoint, the average mean for the two arms will be derived, and a relative change of this average from baseline will be derived as specified in 9.2. above.

Missing values will be treated as missing.

Change from baseline in Neuro-QoL-UE Function at Week 48

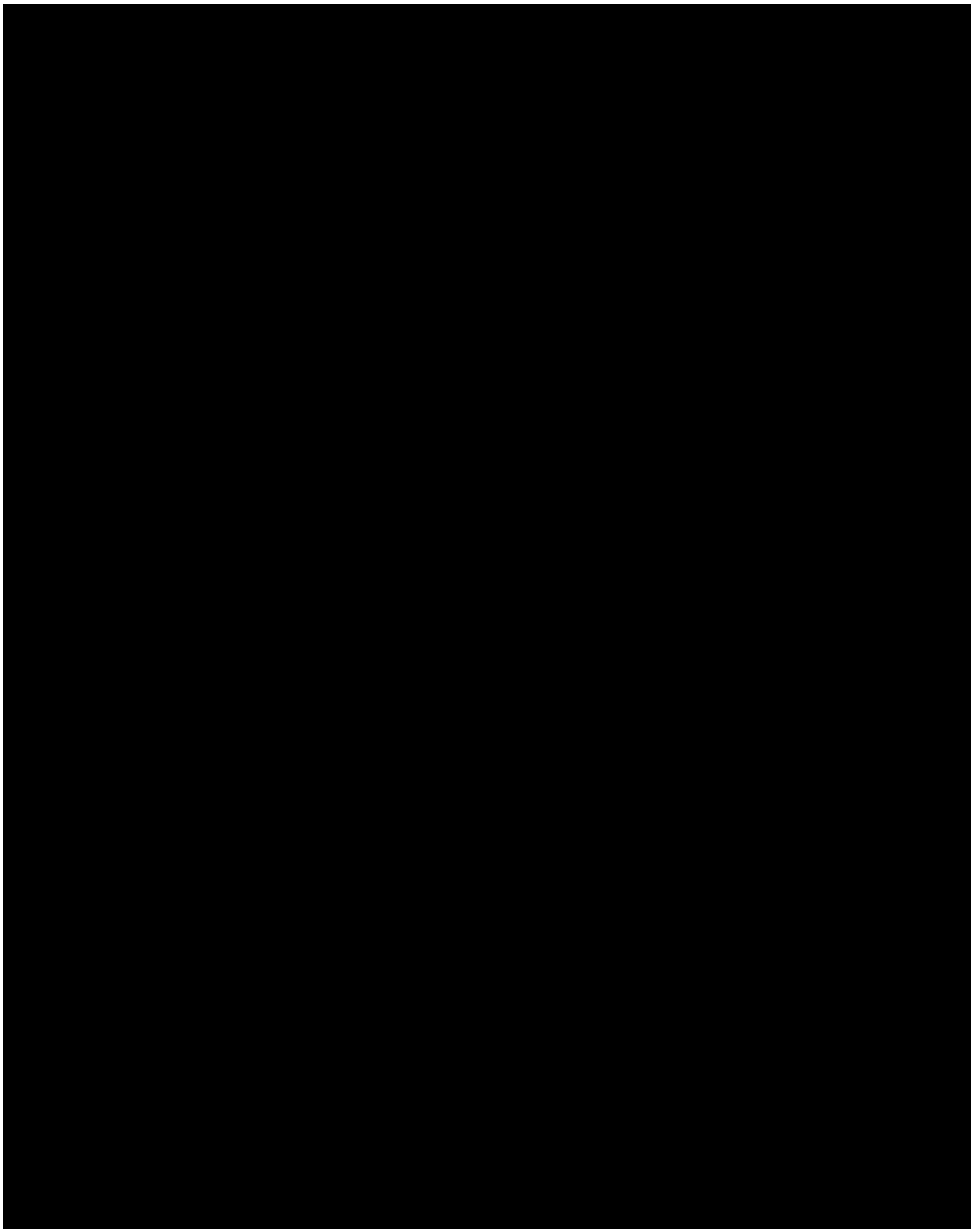
The Neuro-QoL-UE is a 20-item questionnaire, from which a single scale is derived. It is measured at baseline and at weeks 4, 12, 24, 36 and 48. The Neuro-QoL-UE measures ability across fine motor and activities of daily living involving digital, manual, and reach-related function and self-care. Responses are divided into 5 ordinal levels (1 = unable to do, 2 = with much difficulty, 3 = with some difficulty, 4 = with a little difficulty, 5 = without any difficulty). The endpoint is derived as:

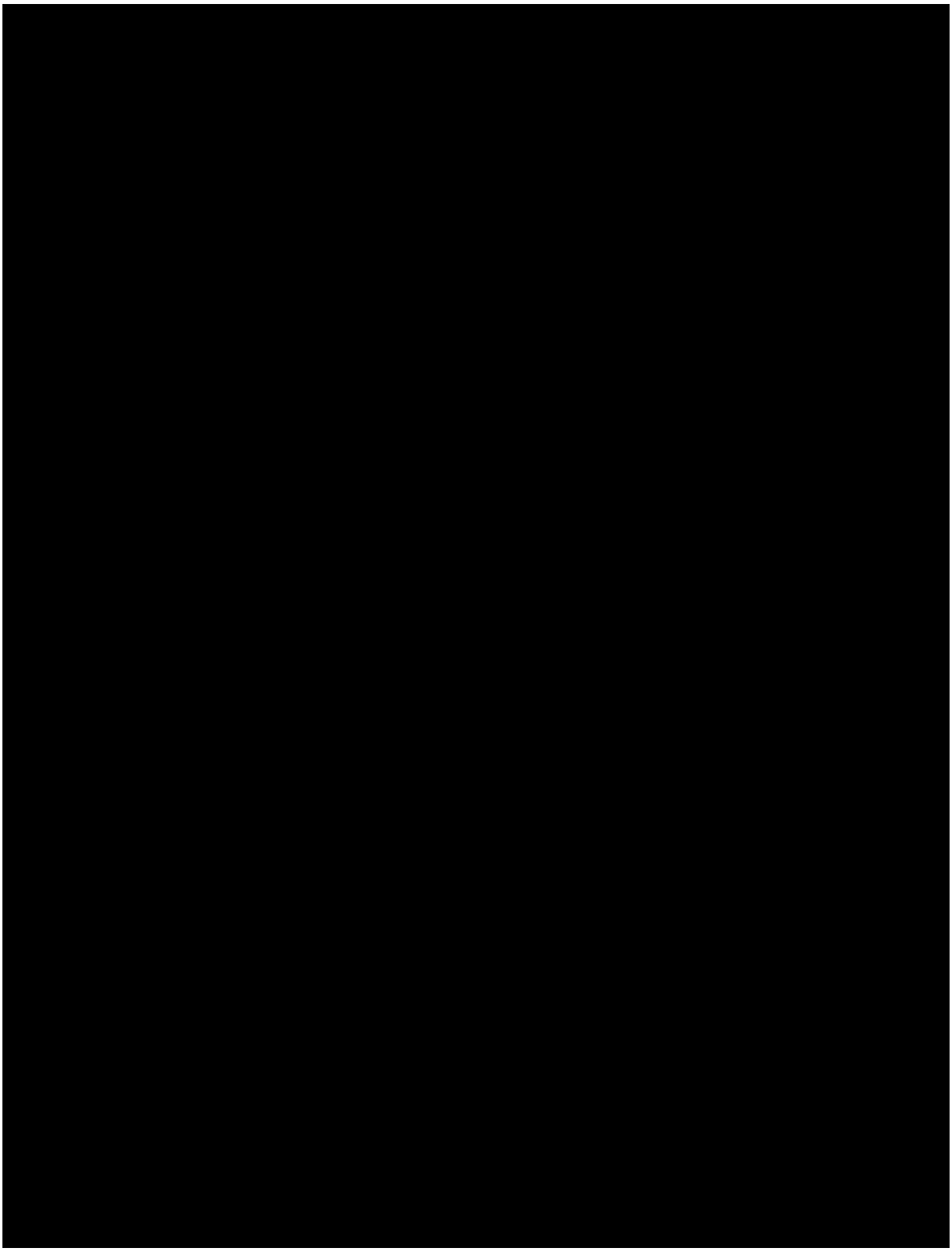
20 x (Sum scores from all items answered) / (Number of items answered)

The Neuro-QoL-UE will be recorded as missing if fewer than 10 items are answered. The score ranges from 20-100, with higher scores reflecting better upper extremity fine motor function.

Change from baseline is derived as specified in 9.2. above.

[redacted]





[redacted]

Change and relative change from baseline in muscle strength by hand-held quantitative dynamometry

There are eight dynamometry outcomes measured at baseline and at weeks 4, 12, 24, 36 and 48. They relate to 4 assessment areas:

[1] Average dominant shoulder abductor strength (kg)
[2] Average non-dominant shoulder abductor strength (kg)
[3] Average dominant hand grip strength (kg)
[4] Average non-dominant hand grip strength (kg)
[5] Maximum dominant shoulder abductor strength (kg)
[6] Maximum non-dominant shoulder abductor strength (kg)
[7] Maximum dominant hand grip strength (kg)
[8] Maximum non-dominant hand grip strength (kg)
[9] Average shoulder abductor strength (kg)
[10] Average hand grip strength (kg)
[11] Total average muscle strength (kg)

[1] to [8] are variables in the dataset which need to be mapped from left and right to dominant/non-dominant for each patient. [9] and [10] are the means of [1]-[2] and [3]-[4] respectively. [11] is the mean of [9]-[10]. If either [9] or [10] is missing, [11] becomes missing. Change from baseline and relative change from baseline will be derived for all 11 measures (as specified in 9.2. above).

Missing values will be treated as missing.

[redacted]

[redacted]

Sub-Neuro-QoL

A sub-scale called Sub-Neuro-QoL will be derived for the purpose of exploratory analysis, using the following five items from the Neuro-Qol-UE: NQUEX03 (using a spoon); PAF9 (picking up clothes); PFA47 (pulling up trousers); NQUEX04 (putting on a shirt); and NQUEX05 (taking off a shirt). This is derived as:

5 x (Sum scores from all items answered) / (Number of items answered)

The Sub-Neuro-QoL will be recorded as missing if fewer than 3 items are answered. The score ranges from 5-25, with higher scores reflecting higher independence in performing tasks.

[redacted]

9.3.4 Safety derivations

9.3.4.1 Adverse events

Adverse events (AEs) and serious adverse events (SAEs) will be collected from the time of signature of the informed consent form (ICF), until after either the 7-Day follow-up period is completed or up to 30 days after the patient has stopped study treatment, whichever is later.

All AEs and SAEs are recorded in the Adverse Event Form.

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 on or before the stop of study drug + 35 days
- begins before the first dose of study drug and worsens on or after the first dose of study drug and on or before the stop of study drug + 35 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 and on or before the stop of study drug + 35 days.

Stop of study drug is recorded in the End of Treatment form as the Date of Last Dose.

Missing start and stop dates for TEAEs will be handled as follows:

- ??-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-???-YYYY/??-???-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 in the case of AEs that are non ongoing 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:

- ??-MMM-YYYY: Assume the last day of the month
- DD-???-YYYY: Assume DD-DEC-YYYY
- ??-???-YYYY: Assume 31-DEC-YYYY.

If the imputed end date is greater than either the study cutoff date or date of death, then assume the minimum of study cutoff date and date of death.

The following classifications are contained within the eCRF and do not require derivation:

- MedDRA version 24.1 or higher coding of System Order Class (SOC) and Preferred Term (PT)
- Common Terminology Criteria for Adverse Event (CTCAE) grade version 5.0
- Classification of AEs as SAEs
- SAE criteria
- Relationship of AEs
- AE of special interest (AESI)
- Outcome
- Action taken

An AE is deemed related to study drug if it is classified as Possibly, Probably or Definitely related. AEs that have missing relatedness (after data querying) will be assumed to be related to study treatment.

Severity of AE is derived from CTCAE coding. Codes 1 and 2 represent Mild and Moderate severity, respectively, and codes 3-5 represent Severe severity. Where CTCAE code is missing, severity will be categorized as Missing.

AESI are defined as potential drug-induced liver injuries. These will be derived from laboratory liver tests where:

(1) A patient has (ALT ≥ 3*ULN) and (Total bilirubin ≥ 2*ULN) and (ALP < 2*ULN) or;
(2) A patient has (AST ≥ 3*ULN) and (Total bilirubin ≥ 2*ULN) and (ALP < 2*ULN)

where ALT = alanine aminotransferase; ALP = alkaline phosphatase; ULN = upper limit of normal; and AST = aspartate aminotransferase.

These should also be recorded in the EDC as AEs, but this source will not be used to identify AESIs.

9.3.4.2 Clinical laboratory evaluations

For continuous laboratory data: values of the form "< *x*" (i.e., below the limit of quantification) will be imputed as *x* divided by 2 in the computation of descriptive statistics. Laboratory values that are recorded in the form "> x" (i.e., above the limit of quantification) will be imputed as *x* in the computation of descriptive statistics. Raw formats will be presented in listings.

Urinary glucose will be treated as continuous, with the value 'Negative' imputed as 0.

9.3.4.3 Vital signs

No derivations are required for absolute values of vital sign endpoints.

9.3.4.4 Electrocardiogram (ECG)

Where three screening measurements of QtCF are carried out (in the case that QtCF is >450 for males or >470 for females), QtCF at screening will be the average of the three assessments. No further derivations are required for ECG endpoints.

9.4 CLINICAL PHARMACOLOGY

9.4.1 Pharmacokinetics

Concentrations that are below the limit of quantitation (BLQ) will be derived as the lower limit of quantification (LLOQ) value divided by 2 in the computation of descriptive statistics.

9.5 ASSESSMENT TIME WINDOWS

9.5.1 Definition of permissible time windows

All study visits from baseline to Week 48 have a window of +/- 7 days inclusive in the schedule of assessments. For the purpose of efficacy, PK and safety analysis, visit windows will be treated as continuous, from the midpoint between two consecutive study visits:

Visit	Window
Screening	From enrollment to randomization

Baseline	Day of randomization, or date of last non-missing value obtained prior to the first dose of study treatment.
Week 4	Days 15 to 56
Week 12	Days 57 to 126
Week 24	Days 127 to 210
Week 36	Days 211 to 294
Week 48	Days 295 to the earliest of Day 357 or Day of OLE Study Drug Dose 1

Data collected after the first dose of study treatment up to and including Day 14 will be treated as unscheduled. Where there is more than one measurement within a visit window, the visit closest to the target visit date will be included for analysis. Where two visits are equidistant to the target visit date, the later visit will be included for analysis. Data collected during visits that are excluded because another is closer to the target visit date will be treated as out-of-window observations.

Efficacy and PK data from both scheduled and unscheduled visits and from Early Termination visit will go through the above windowing process. Similarly, safety data from scheduled visits, from Early Termination visit and from Safety Follow-up visit will go through the above windowing process.

9.5.2 Methods for handling out-of-window observations

Out-of-window observations will be treated as unscheduled visits. Unscheduled visit data will be excluded from by-visit summaries, but included in the following: efficacy analyses through windowing (see 9.5.1); listings; and in identifying min/max/worst results for laboratory data analyses, etc.

10. STATISTICAL ANALYSES AND METHODOLOGY

10.1 STUDY POPULATION

10.1.1 Disposition of patients

Patient disposition will be summarized for patients screened (pre-randomization disposition) and for the FAS (post randomization disposition). Summaries of patients screened, signed ICF, included/excluded in study will be summarized overall. Patients who received study drug, visits attended, patients' treatment status in the study (completed / discontinued, and reasons for discontinuations), patients' participation status (completed / discontinued and reasons for discontinuation), and who rollover into Part B will be summarized by treatment group and overall.

Screen failures will be summarized by reason for screen failure and presented in a listing.

Patient disposition will be presented in a listing. Patient inclusion/exclusion in the FAS, and safety analysis set will be presented in a listing, by FSHD type.

10.1.2 Protocol deviations

Protocol deviations are classified as Significant or Not Significant, according to a Study Deviation Rules document. Significant protocol deviations will be summarized by deviation type (ICH/GCP, Efficacy, Safety) for all FAS patients, by treatment group. All protocol deviations will be listed, and listings will specify deviation type and whether significant or not significant.

10.1.3 Demographic and baseline characteristics

The following data will be summarized descriptively by treatment group and overall:

- Demographics: Sex, Age in years, Race, Ethnicity
- Height (cm), Weight (kg), BMI (kg/m^2)
- Dominant hand
- FSHD Type, Correct FSHD repeat number and category, FSHD repeat number category used for randomization
- [redacted]
- FSHD history: Age of first symptoms (years), First symptoms, Age of diagnosis (years), Current pain related to FSHD

Analyses are based on the FAS. All demographic and baseline data will be presented by patient in a listing, by FSHD type and treatment group.

10.1.4 Relevant medical history

Relevant medical history (excluding data collected in the FSHD medical history form) will be MedDRA coded. The number and percentage of patients experiencing relevant medical history prior to enrolling into the study will be summarized by SOC and PT; by treatment group and overall. Analyses are based on the FAS.

All relevant medical history data will be presented by patient in a listing, by FSHD type and treatment group.

10.1.5 Concomitant medications/procedures

Prior and concomitant medications will be summarized by treatment group and overall, for patients in the safety analysis set. Medications are coded using World Health Organization (WHO) drug dictionary (DD) 2021Sep or later and Anatomical Therapeutic Chemical (ATC) Code. Prior and concomitant medications will be summarized by ATC class (level 2) and generic (preferred) name. All prior and concomitant medications and procedures will be presented by patient in a listing, by FSHD type and treatment group.

10.1.6 Treatment exposure and compliance

Exposure and study drug accountability (compliance) will be presented for patients in the Safety Analysis Set.

Study drug exposure

Descriptive statistics will be used to summarize duration of exposure both as a continuous measure in days and weeks and by category: < 8 weeks, ≥ 8 weeks, ≥ 16 weeks, ≥ 24 weeks, ≥ 36 weeks, ≥ 48 weeks, average daily dose, and cumulative dose.

Study drug accountability

Descriptive statistics will be used to summarize compliance as a continuous measure, and by category: < 80%, 80-120%, ≥ 120%. Drug accountability will be presented in a listing, presented by FSHD type, treatment, and patient. For each patient, first dose date, last dose date, and treatment duration will be presented; and at each time-point, for dispensed study drug: bottle number, date and study day tablets were dispensed, and number of tablets dispensed; for returned study drug: date returned, number of tablets returned. The following treatment compliance data will be presented: Number of tablets taken, number of tablets prescribed, duration, and compliance.

10.2 EFFICACY ANALYSES

Efficacy analyses are based on the FAS. The primary and secondary efficacy analyses will also be split by subgroup of the FAS.

10.2.1 Primary efficacy analysis

10.2.1.1 Change from baseline in average total RSA Q1-Q5 with 500 g wrist weight, where average is applied over both arms

For each treatment, descriptive statistics of RWS results (total RSA Q1-Q5) per visit as well as the change from baseline will be presented.

An MMRM will be used to analyze the primary endpoint. The primary analysis of the primary endpoint will be based on the MMRM. See 8.3.1 for analysis methods, where change from baseline in RWS is fitted as the dependent variable for the MMRM. An LME will be also be fitted, where the dependent variable is average total RSA Q1-Q5 with 500g weight, measured at baseline and each post-baseline visit.

Least squares means derived from the MMRM will be plotted over time for both treatment groups with error bars showing standard errors. Annualized percentage changes estimated from the LME will be presented as line charts.

Derived RWS at each time-point, by dominant and non-dominant arm and as an average of both, will be presented by patient in a listing, by FSHD type and treatment group.

10.2.1.2 Other analyses of the primary endpoint

The cumulative distribution plot of change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 will be plotted by treatment group. Missing change values are imputed by the worst value per treatment group. Additionally, a bar chart showing the percentage of patients by response categories (e.g., <-0.25, ≥-0.25 to < -0.2, ≥-0.2 to <-0.15, ≥-0.15 to <-0.1, ≥-0.1 to <-0.05, ≥-0.05 to <0, ≥0 to <0.05, ≥0.05 to <0.1, ≥0.1 to <0.15, ≥0.15 to <0.2, ≥0.2 to <0.25, ≥0.25, in percentage points) of change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 will be plotted by treatment group. Missing change values are included in the worst category (e.g., change <-0.25). A waterfall plot of change from baseline in average total RSA Q1-Q5 with 500g weight at Week 48 will be plotted, this is a plot of best to worst change from baseline for all subjects with a non-missing change from baseline, by treatment group. A responder plot showing the cumulative percentage of patients by response categories (<-0.25, ≥-0.25, ≥-0.2, ≥-0.15, ≥-0.1, ≥-0.05, ≥0, ≥0.05, ≥0.1, ≥0.15, ≥0.2, and ≥0.25 in percentage points) of change from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 will be plotted by treatment group. Missing change values are included in the worst category (e.g., change <-0.25).

The relative change from baseline in average total RSA Q1-Q5 with 500 g wrist weight will also be analyzed using the Wilcoxon rank-sum test, stratified by the FSHD repeat number category (see 8.2). The Hodges-Lehmann estimate of the associated treatment difference and asymptotic nonparametric

95% confidence interval as described by Hollander and Wolfe (1999)[5] will be computed. Median relative change from baseline will be plotted by treatment group.

Descriptive statistics will be presented by site.

A binary analysis may be carried out should meaningful score differences (MSDs) be determinable. An MSD is a measure of clinically meaningful within-patient change, which will be explored for change from baseline at 48 weeks in average total RSA Q1-Q5 with 500 g wrist weight, following the draft FDA guidance [6]. This exploration will be conducted by the sponsor's designated vendor. If the MSDs can be determined, for each treatment group, the number and percentage of patients at or above an MSD and the number and percentage of patients below the MSD will be presented. A patient with a missing change from baseline in average total RSA Q1-Q5 with 500 g wrist weight will be considered as below the MSD. The proportion of patients at or above MSDs at Week 48 will be compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by FSHD repeat number category, and a two-sided p-value will be presented. Similar analysis will be performed using the lower bounds of MSDs as cut-off points as well as 0 as a cut-off point.

In addition, the analysis described in 10.2.1.1 will be repeated for the following:

(1) Sensitivity analyses (see below)
(2) For certain subgroups (listed in Section 8.5)

Sensitivity Analysis 1: MMRM with on-treatment measurements only

This sensitivity analysis of the primary endpoint will be similar to that used for the primary analysis of the primary endpoint. The key difference is that, for patients who prematurely discontinue study treatment, this MMRM will include only the measurements up to 2 days (inclusive) after the last dose of study drug.

Sensitivity Analyses 2, 3 and 4: MMRM with missing data imputed

In the primary analysis of the primary endpoint, missing data are assumed to be missing at random. To minimize the amount of missing data, patients who prematurely discontinue study treatment will be encouraged to remain in the study and continue with all remaining scheduled study visits for efficacy assessments.

To assess the impact of missing data and the assumption that data are missing at random, 3 multiple imputation (MI) algorithms will be applied if 10% or more of the patients have missing changes from baseline in average total RSA Q1-Q5 with 500 g wrist weight at Week 48 in either treatment group. A missing change from baseline in average total RSA Q1-Q5 with 500 g wrist weight will be imputed starting from the first visit with a missing change value, for which every change value at every subsequent visit through Week 48 is also missing. For intermediate missing data, i.e., missing change values that fall between two non-missing ones, it is reasonable to assume that they are missing at random and therefore will not be imputed.

If a patient discontinues the study because of death, the patient's missing values of average total RSA Q1-Q5 with 500 g wrist weight after the last non-missing value will be imputed as 0, the lowest possible value of average total RSA Q1-Q5 with 500 g wrist weight. It will be used to derive changes from baseline.

Other missing values after the last non-missing value will be classified as missing category 1 or missing category 2 as follows:

- Missing category 1: A patient discontinues the study because of adverse events, noncompliance, or investigator discretion, or because a patient requires a prohibited medication.
- Missing category 2: A patient discontinues the study for other reasons or completes the study but has missing value(s) at the last or last several visits.

Sensitivity Analysis 2: MMRM with discontinuation reason-based MI

For missing values in missing category 1: The missing changes from baseline after the last non-missing change value will be imputed as random values drawn from a normal distribution with mean equal to the 25th percentile of the non-missing changes from baseline at the given visit and with variance estimated using the non-missing changes at that visit from the same treatment group.

For missing values in missing category 2: The missing changes from baseline after the last non-missing change value will be imputed as random values drawn from a normal distribution with mean equal to the mean of the non-missing changes from baseline at the given visit and with variance estimated using the non-missing changes at that visit from the same treatment group.

This process will be repeated 20 times to form 20 imputed datasets. The same MMRM model as is used for the primary endpoint analysis will be applied to each imputed dataset to estimate mean change from baseline for each treatment group, and the difference between treatment groups in mean change from baseline at Week 48. These 20 model results will be combined using the SAS procedure MIANALYZE to obtain MI estimates with SE, 2-sided 95% CI, and 2-sided p-value.

Sensitivity Analysis 3: MMRM with placebo-based MI

For missing values in missing category 1: The missing changes from baseline after the last non-missing change value will be imputed as random values drawn from a normal distribution with mean equal to the mean of the non-missing placebo group changes from baseline at the given visit and with variance estimated using the non-missing changes at that visit from the placebo group.

For missing values in missing category 2: The missing changes from baseline after the last non-missing change value will be imputed as random values drawn from a normal distribution with mean equal to the mean of the non-missing changes from baseline at the given visit and with variance estimated using the non-missing changes at that visit from the same treatment group.

This process will be repeated 20 times to form 20 imputed datasets. The same MMRM model as is used for the primary endpoint analysis will be applied to each imputed dataset to estimate mean change from baseline for each treatment group, and the difference between treatment groups in

mean change from baseline at Week 48. These 20 model results will be combined using the SAS procedure MIANALYZE to obtain MI estimates with SE, 2-sided 95% CI, and 2-sided p-value.

Sensitivity Analysis 4: MMRM with tipping point MI

The missing changes from baseline after the last non-missing change value will be imputed as random values drawn from a normal distribution with mean equal to the mean of the non-missing changes from baseline at the given visit and with variance estimated using the non-missing changes at that visit from the same treatment group.

For missing values in missing category 1 of patients in the losmapimod group, a delta that is equal to *m* times the difference in LS means between treatment groups (Losmapimod 15 mg BID – Placebo BID) at the given visit obtained from the primary MMRM analysis will be subtracted from their imputed values, with *m* starting from 0%, 10%, 20%, .., and up to 100% or higher, until conclusion from the primary MMRM analysis is overturned, or it becomes clinically meaningless to go even higher.

For each *m*, this process will be repeated 20 times to form 20 imputed datasets. The same MMRM model as is used for the primary endpoint analysis will be applied to each imputed dataset to estimate mean change from baseline for each treatment group, and the difference between treatment groups in mean change from baseline at Week 48. These 20 model results will be combined using the SAS procedure MIANALYZE to obtain MI estimates with SE, 2-sided 95% CI, and 2-sided p-value. Complete the tipping point MI analysis with different m's as described in the above paragraph.

In applying the above-mentioned 3 MI algorithms, missing changes from baseline in average total RSA Q1-Q5 with 500 g wrist weight will be imputed from normal distributions. The underlying normality assumption of changes from baseline will be checked using a normal probability plot, p-value from the Shapira-Wilk test, and skewness and kurtosis of non-missing changes at Week 48 for each treatment group. The homogeneity of variances will be checked using the Levene test and Brown-Forsythe test on non-missing changes at Week 48. In case the change data significantly deviate from the normality assumption, they will be fitted against a distribution, and missing changes will be sampled from the fitted distribution.

Sensitivity analysis 5: Nonparametric rank repeated measures analysis of covariance (ANCOVA)

This sensitivity analysis of the primary endpoint will evaluate the robustness of the primary analysis of the primary endpoint against model assumptions of normal residuals and linear relationship between the response and covariates. The rank two-way repeated measures ANCOVA will be applied upon rank transformed response and rank transformed covariates. Here, the response is change from baseline in average total RSA Q1-Q5 with 500 g wrist weight, the two factors are treatment group and visit, and the covariates are baseline value of average total RSA Q1-Q5 with 500 g wrist weight, baseline value by visit interaction, stratification category, and region. Ranks are applied at each visit within the FAS, not within each treatment group. The generalized estimating equation technique will be employed to construct rank tests [7].

Sensitivity Analysis 6: MMRM adjusting for correct FSHD repeat number category

This sensitivity analysis of the primary endpoint will be similar to that used for the primary analysis of the primary endpoint. The key difference is that, for patients with stratification category used at randomization being different from the correct category, this MMRM will adjust for the correct category.

10.2.2 Secondary efficacy analyses

10.2.2.1 Patient Global Impression of Change (PGIC)

This endpoint will follow the same method of analysis as for the primary endpoint (see 10.2.1.1), but no LME will be fitted. No baseline PGIC term will be fitted in the MMRM since this is not applicable at baseline.

Additionally, PGIC will be summarized using counts and percentages of patients in each of the 7 levels and will be compared between treatment groups using the Wilcoxon rank-sum test, stratified by the FSHD repeat number category.

The number and percentage of patients reporting improvement, i.e., PGIC of 3 or less, and those without reporting improvement, i.e., PGIC of 4 or more, will also be presented for each treatment group. A patient with a missing PGIC value will be considered as not reporting improvement. The proportion of patients reporting improvement at Week 48 will be compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by FSHD repeat number category.

Similar analysis will be performed for the number and percentage of patients without reporting worsening, i.e., PGIC of 4 or less, and those reporting worsening, i.e., PGIC of 5 or more, with between-treatment comparison using the Cochran-Mantel-Haenszel test stratified by FSHD repeat number category. A patient with a missing PGIC value will be considered as reporting worsening.

A sensitivity analysis of this endpoint will be carried out using the MMRM based on the on-treatment measurements up to 2 days (inclusive) after the last dose of study drug for patients in the FAS. Another sensitivity analysis will adjust for correct FSHD repeat number category (see 10.2.1.2).

The analysis will be repeated for each subgroup listed in Section 8.5.

PGIC scores will be presented by patient in a listing, by FSHD type and treatment group.

10.2.2.2 Change from baseline in whole body (WB) longitudinal composite MFI (B muscles)

This endpoint will follow the same method of analysis as for the primary endpoint (see 10.2.1.1) using an MMRM. The primary analysis of this endpoint will be based on the MMRM. An LME will also be fitted as defined in 10.2.1.1, where the dependent variable is absolute WB composite MFI, measured at baseline and each post-baseline visit.

Additionally, this endpoint will be analyzed using the Wilcoxon rank-sum test, stratified by the FSHD repeat number category (see 8.2). The Hodges-Lehmann estimate of the associated treatment

difference and asymptotic nonparametric 95% confidence interval will be computed. Median change from baseline will be plotted by treatment group.

A sensitivity analysis of this endpoint will be carried out based on the on-treatment measurements up to 2 days (inclusive) after the last dose of study drug for patients in the FAS. Another sensitivity analysis will adjust for correct FSHD repeat number category (see 10.2.1.2).

The analysis will be repeated for each subgroup listed in Section 8.5.

All WB longitudinal composite endpoint data and cross-sectional composite data (MFI/MFF/LMV) will be presented by patient in a listing, by FSHD type and treatment group.

10.2.2.3 Relative change from baseline in average shoulder abductor strength by hand-held quantitative dynamometry at Week 48

This endpoint will be analyzed using the Wilcoxon rank-sum test, stratified by the randomization stratification factor (see 8.2). The Hodges-Lehmann estimate of the associated treatment difference and asymptotic nonparametric 95% confidence interval will be computed. Median relative change from baseline will be plotted by treatment group.

A sensitivity analysis of this endpoint will be carried out based on the on-treatment measurements up to 2 days (inclusive) after the last dose of study drug for patients in the FAS. Another sensitivity analysis will adjust for correct FSHD repeat number category (see 10.2.1.2).

The analysis will be repeated for each subgroup listed in Section 8.5.

All dynamometry data will be presented by patient in a listing, by FSHD type and treatment group.

10.2.2.4 Change from baseline in Neuro-QoL-UE

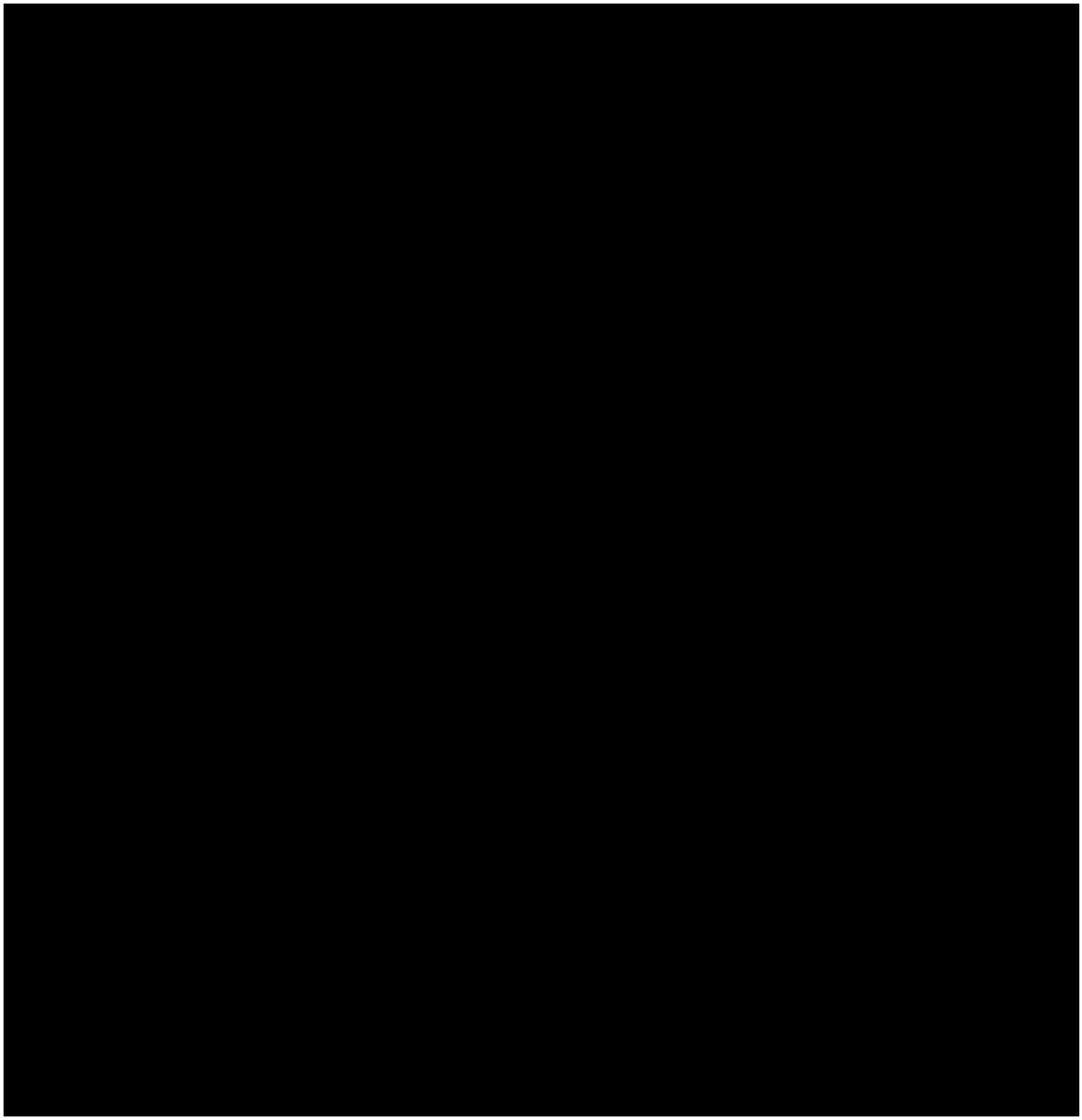
This endpoint will follow the same method of analysis as for the primary endpoint (see 10.2.1.1) using an MMRM. The primary analysis of this endpoint will be based on the MMRM. An LME will also be fitted as defined in 10.2.1.1, where the dependent variable is absolute Neuro-QoL-UE, measured at baseline and each post-baseline visit.

A sensitivity analysis of this endpoint will be carried out based on the on-treatment measurements up to 2 days (inclusive) after the last dose of study drug for patients in the FAS. Another sensitivity analysis will adjust for correct FSHD repeat number category (see 10.2.1.2).

The analysis will be repeated for each subgroup listed in Section 8.5.

Neuro-QoL-UE scores will be presented by patient in a listing, by FSHD type and treatment group.

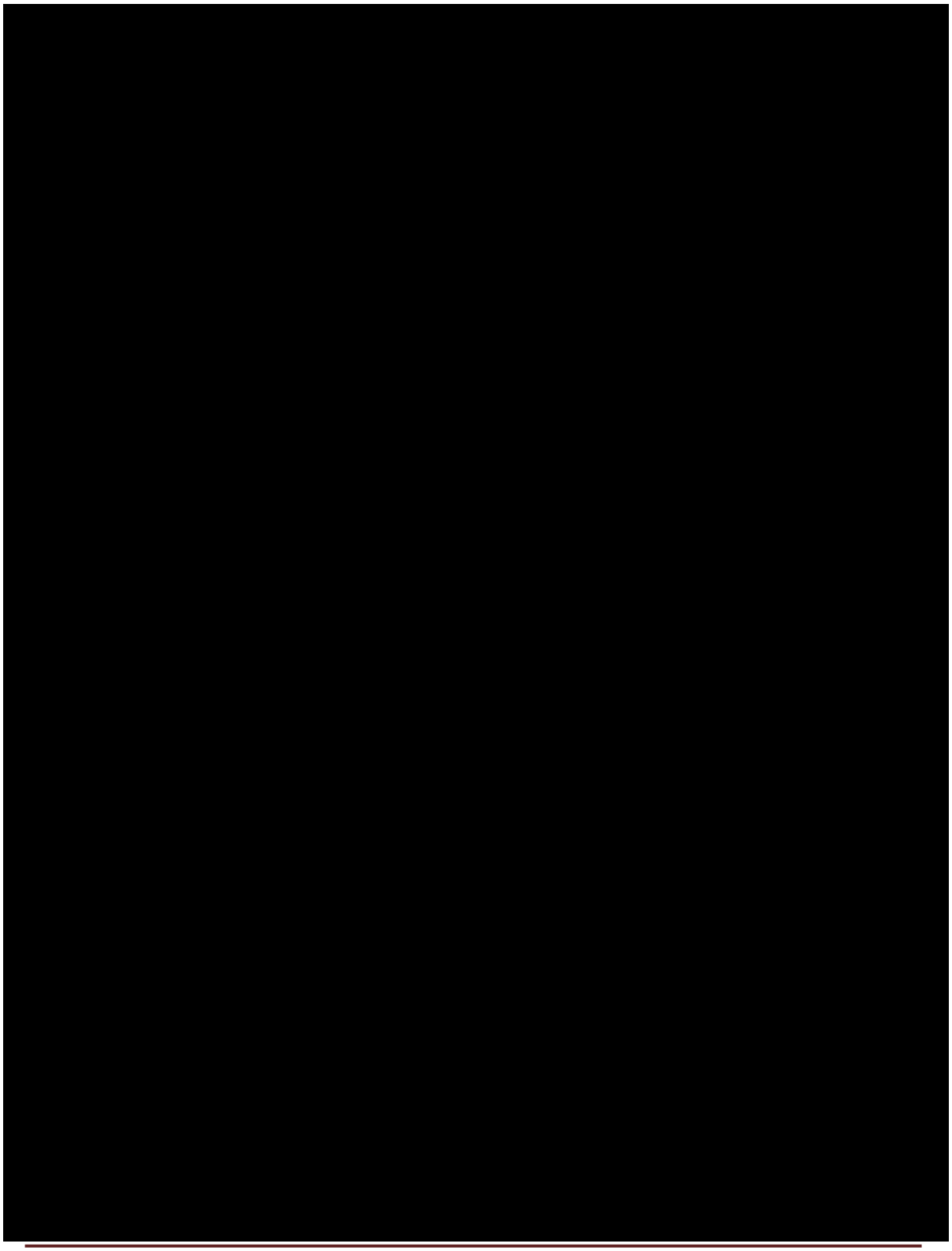
[redacted]

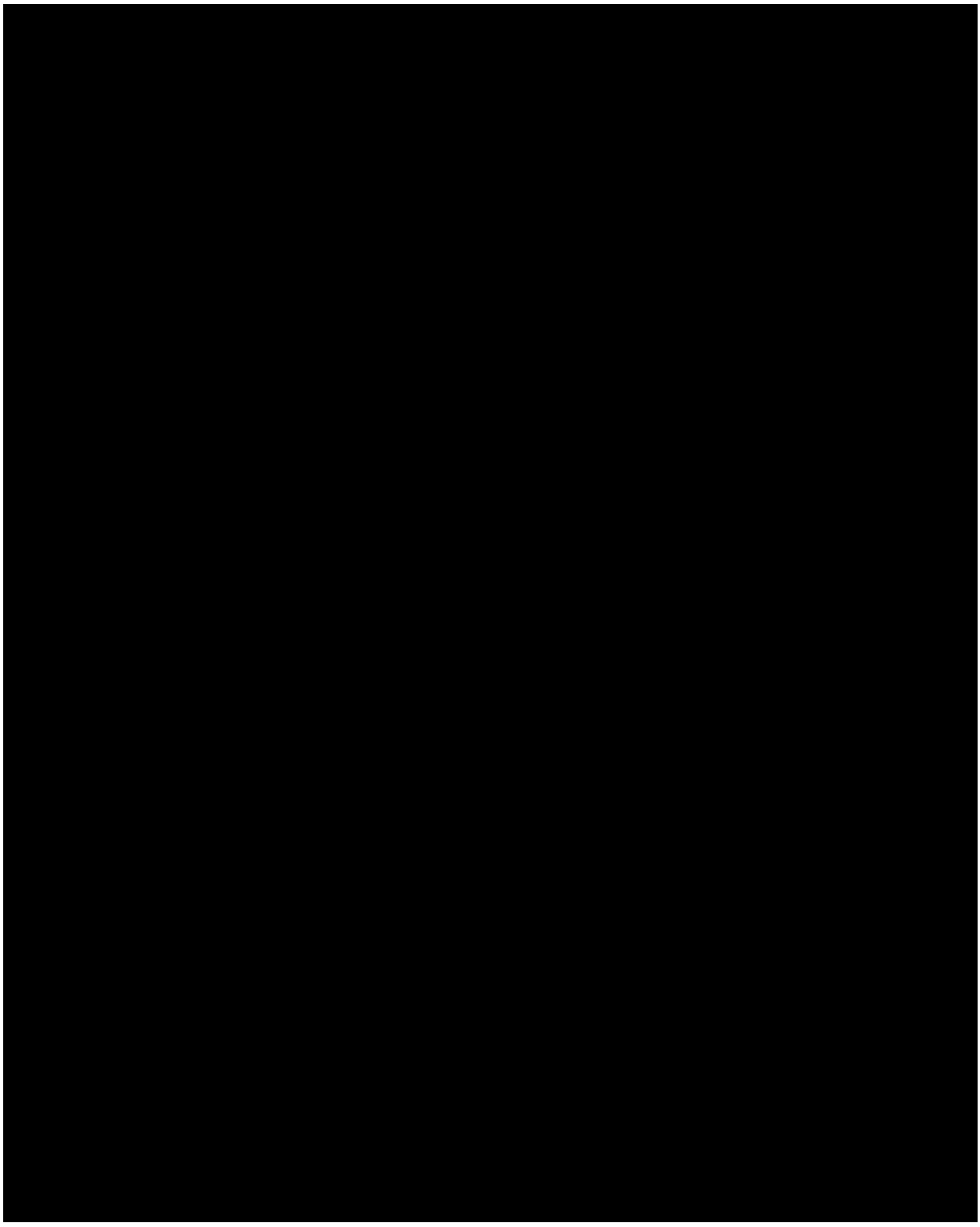


10.2.3.4 Change from baseline in Neuro-QoL individual items

Each of the 20 items of the Neuro-QoL questionnaire will be analyzed as for the primary endpoint (see 10.2.1.1) using an MMRM, but no LME will be fitted.

Neuro-QoL-UE item scores will be presented by patient in a listing, by FSHD type and treatment group.





[redacted]

10.2.3.11 Changes from baseline in muscle strength by hand-held dynamometry

A separate analysis will be carried out for each of the 11 dynamometry measures listed in 9.3.3.3 above, expressed as (a) a change from baseline, and (b) a relative change from baseline. Changes from baseline will follow the same method of analysis as for the primary endpoint (see 10.2.1.1). Relative changes from baseline will follow the same method of analysis as for the secondary endpoint of relative change from baseline in average shoulder abductor strength (see 10.2.2.3). All 22 measures modelled will be presented by patient in a listing, by FSHD type and treatment group.

[redacted]

[redacted]

10.2.3.14 Correlation between RWS with weight and dynamometry

Spearman correlation coefficient, with 95% CI and p-value, will be calculated between the average total RSA Q1-Q5 with 500 g wrist weight and the following dynamometry measures at baseline and each post-baseline visit, by treatment group:

- Average shoulder abductor strength (kg)
- Average hand grip strength (kg)
- Total average muscle strength (kg)

This analysis will be repeated for the change from baseline and relative change from baseline in the average total RSA Q1-Q5 with 500 g wrist weight versus change from baseline and relative change from baseline in each dynamometry measure, respectively, at each post-baseline visit, by treatment group.

A corresponding scatterplot will be presented for each correlation.

10.2.3.15 Correlation between RWS with weight and patient-reported outcomes

Spearman correlation coefficient, with 95% CI and p-value, will be calculated between the average total RSA Q1-Q5 with 500 g wrist weight and the following patient reported outcomes at baseline and each post-baseline visit, by treatment group:

- Neuro-QoL-UE
- Sub-Neuro-QoLUE

[redacted]

[redacted]

- PGIC, [redacted]

[redacted]

10.3 SAFETY ANALYSES

The safety analysis will consist of an assessment of adverse events, serious adverse events, clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations.

The safety analyses will be based on the Safety Analysis Set and summarized by treatment group. Safety data collected at unscheduled visits and local laboratory data will be excluded from by-visit summaries using descriptive statistics for continuous variables, but included in listings and in identifying min/max/worst results for laboratory data analyses, etc.

10.3.1 Treatment-emergent adverse events

The number and percentage of patients with at least one TEAE in the following categories will be presented by treatment group:

- Any TEAE
- TEAE related to study drug
- TEAE with a CTCAE grade of 3 or higher
- TEAE with a CTCAE grade of 3 or higher, related to study drug
- TEAE leading to discontinuation of study drug
- TEAE leading to withdrawal from study
- TEAE with an outcome of death
- TEAE with an outcome of death, possibly related to study drug
- TEAE of special interest (AESI)

The number and percentage of patients with at least one TEAE will be summarized by SOC and PT, by treatment group. The total number of TEAEs observed within each category will be reported.

The number and percentage of patients with at least one TEAE will be summarized by maximum CTCAE grade. Maximum CTCAE grade will also be presented by SOC and PT, by treatment group.

The number of TEAEs will be presented by relationship (5 levels: definitely related, probably related, possibly related, unlikely related, not related) to study drug, by treatment group. Numbers and percentages of patients with at least one TEAE will be summarized by highest level of relationship, overall and by SOC and PT.

All AEs will be listed. Listings will be presented by FSHD type and treatment. They will include patient age, sex, race, country, SOC, PT, AE description as reported in eCRF, start, and stop dates and study days, duration in days, outcome (Recovered/Resolved, Recovering/Resolving, Not recovered/Not resolved, Recovered/Resolved with sequelae, Fatal), severity (Mild, Moderate, Severe, Life-threatening), action (Drug interrupted, Drug withdrawn, Not applicable, Other (Specify), relationship, whether it resulted in study discontinuation, and seriousness/if yes, SAE criteria. TEAEs will be flagged.

10.3.2 Deaths and serious adverse events

The number and percentage of patients with at least one SAE in the following categories will be presented:

- Any SAE
- SAE related to study drug

The number of SAEs will be presented by treatment group. Numbers and percentages of patients with at least one SAE will be summarized by SOC and PT. All SAEs will be listed in the same way as AEs.

Deaths will be listed by FSHD type and treatment group, and include date of death, primary cause of death, relatedness and whether an autopsy was performed.

10.3.3 Adverse events leading to discontinuation of investigational product and/or withdrawal from the study

The number of TEAEs leading to discontinuation of study drug will be presented by treatment group. Numbers and percentages of patients with at least one TEAE leading to study drug discontinuation will be summarized by SOC and PT, and also by maximum CTCAE grade.

The number of TEAEs leading to withdrawal from the study will be presented by treatment group. Numbers and percentages of patients with at least one TEAE leading to withdrawal from the study will be summarized by SOC and PT, and also by maximum CTCAE grade.

All AEs leading to discontinuation of study drug will be listed in a single listing, in the same way as AEs. AEs leading to withdrawal from study are flagged in the AE listing.

10.3.4 Other adverse events of special interest

The number of AEs identified as AESIs will be presented by treatment group. Numbers and percentages of patients with at least one such AESI will be presented. AESIs will be listed in the same way as AEs.

The number and percentage of patients with laboratory tests that potentially flag a drug-induced liver injury (DILI):

- (ALT ≥ 3ULN; Total bilirubin ≥ 2ULN; and ALP < 2ULN)
- (AST ≥ 3ULN; Total bilirubin ≥ 2ULN; and ALP < 2ULN)

will be presented for each test type, treatment group and visit; the number and percentage of patients with a potential DILI will be presented by treatment group and visit. Denominators for percentages are the number of patients in treatment group with normal baseline result and non-missing result for given parameter and visit. ALT, AST, total bilirubin, and ALP will be listed for each potential DILI, by treatment group, patient, and visit. In addition, the number and percentage of patients with ALT ≥ 3ULN, AST ≥ 3ULN and total bilirubin ≥ 2ULN will be presented separately for each treatment group and visit. These results will be listed, including the result dividing by the ULN.

10.3.5 Clinical laboratory evaluations

Laboratory data (hematology, biochemistry, and urinalysis) will be presented as follows:

For each timepoint (baseline, weeks 4, 12, 24, 36 and 48, and the safety follow-up visit) absolute values and change from baseline will be summarized with standard summary statistics (see Section 8.1), by treatment group.

For the following hematology (hemoglobin, red blood cell count, hematocrit, total white blood cell count, # lymphocytes, neutrophils, basophils, eosinophils, and platelet count), biochemistry (total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase), and urinalysis (glucose, blood and protein) parameters: shift from baseline will be tabulated for all patients with a baseline value as well as at least one post-baseline measurement, by treatment group: the number and percentage of patients at baseline classified as low, normal or high and overall will be presented; and the shift from baseline category to (a) lowest post-baseline category; and (b) highest post-baseline category. For parameters which have classifications in both the high and low direction, these will be summarized separately.

Hematology, biochemistry and urinalysis data will be presented in separate listings, by treatment group and FSHD type. Each listing will present patients' data by visit. Patients' 3 highest and 3 lowest results outside of the normal range for each variable will be flagged in the listings. Data from unscheduled visits and any early termination (ET) visit will be included in this assessment of low and high results.

10.3.6 Vital signs and physical examination

Patient's vital signs (pulse rate, respiration rate, systolic blood pressure, diastolic blood pressure and temperature) will be presented as follows:

For each timepoint (baseline, weeks 4, 12, 24, 36 and 48, and the safety follow-up visit) absolute values and change from baseline will be summarized with standard summary statistics (see Section 8.1), by

treatment group. Weight will be presented in a similar way, but only at baseline, weeks 24 and 48, and the safety follow-up visit.

An on-treatment summary of vital signs will be presented. A low category and one or two high categories are pre-specified as follows:

Vital Signs Parameter	Low category	High Categories
Systolic blood pressure (mmHg)	< 90	> 140 to ≤ 160 > 160
Diastolic blood pressure (mmHg)	< 50	> 90 to ≤ 100 > 100
Pulse rate (bpm)	< 60	> 100
Temperature (°C)	< 36.0	> 38.0
Respiratory rate (breaths/min)	< 12	> 20
Body weight	≥ 7% decrease from baseline while on-treatment	≥ 7% increase from baseline

For each measurement type the number and percentage of patients: in each category at baseline (except body weight); with minimum on-treatment measurement in the lowest category; and with maximum on-treatment measurement in the highest category/categories will be presented.

All vital signs data will be presented by patient in a listing, by FSHD type and treatment group.

All physical examination data will be presented by patient in a listing, by FSHD type and treatment group.

10.3.7 Electrocardiogram (ECG)

Each patient's maximum on-treatment QTcF interval will be categorized as ≤ 450, > 450 to ≤ 480, > 480 to ≤ 500, > 500. The number and percentage of patients in each category will be presented by treatment group. Each patient's maximum on-treatment change from baseline in QTcF interval will be categorized as < 0, ≥ 0 to ≤ 30, > 30 to ≤ 60, >60. The number and percentage of patients in each category will be presented by treatment group.

All ECG data will be presented by patient in a listing, by FSHD type and treatment group

10.4 Clinical Pharmacology

10.5 Pharmacokinetics

Pharmacokinetics analyses are based on the pharmacokinetic analysis set.

10.5.1.1 Plasma concentrations of losmapimod

Plasma PK concentrations for losmapimod at weeks 4 and 48 at two collection times (pre-dose, and 4 hours post dose) will be summarized with the following descriptive statistics: n, mean, standard

deviation (SD), coefficient of variation (CV, %), geometric mean, geometric CV (%), median, minimum, and maximum. The number of decimal places for statistics will be as specified in Section 8.1; and CV (%) and geometric CV (%) will be displayed to 1 decimal place. Plasma concentrations will be presented graphically by collection time using boxplots. Plasma concentrations of losmapimod will be presented by patient in a listing, by FSHD type.

11. CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSIS

None

12. REFERENCES

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5. Hollander, M. and Wolfe, D. A. *Nonparametric Statistical Methods*, 2nd edn, Wiley, New York, 1999.
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APPENDIX A – LIST OF TABLES, LISTINGS AND FIGURES

See *Ph3 1821-FSH-301-FinalAnalysisShell-FINAL-v1.0.pdf*.

APPENDIX B – SCHEDULE OF ASSESSMENTS PART A: PLACEBO-CONTROLLED TREATMENT PERIOD SCHEDULE OF ASSESSMENTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX C – ADDITIONAL MRI DERIVATION DETAIL

AMRA MRI data, derivations, and analysis rules for REACH Study 1821-FSH-301:

MRI DATA FOR INDIVIDUAL MUSCLES:

MRI tests will be performed at Screening, Week 24, and Week 48 and a total of 36 individual muscles from 4 main body regions (i.e., neck, arm, torso, and leg) will be assessed (See **Attachment A**). Eighteen (18) muscles come from the Left side of the body and 18 come from the Right side. For the MRI analysis, results from Left and Right muscles will be designated as Dominant and Non-Dominant muscles in accordance with the patient's reported arm dominance (as collected on the CRF).

For each individual muscle, trained anatomical imaging experts from the Vendor (AMRA) will calculate the muscle tissue measurements (Lean Muscle Volume [LMV], Muscle Fat Fraction [MFF], and Muscle Fat Infiltration [MFI]), assign a muscle category code (A, B, or C), and evaluate the MRI signal quality for any potential issues that may affect the results. Individual muscle category and MRI signal quality will be used to determine eligibility of a muscle for the MRI analysis.

AMRA derives these results for each individual muscle and provides this set of 3 muscle tissue measurements plus 3 Statistical Inclusion (SI) variables:

- **LMV** is a measure of the lean ('fat-free') muscle tissue volume. Results are reported in liters (L).
- **MFF** is a measure of the overall fattiness of the muscle. MFF results are reported as percentages ranging from 0% (representing no fat) to 100% (representing a completely fat-replaced muscles).
- **MFI** is the fat fraction in the leaner ('fat-free') parts of the muscle and is a proxy for the quality of the portion of the muscle that may still retain a relevant amount of functionality. MFI results are reported as percentages with expected values ranging from 0% to 50%.
- **SI Category (SI_{cat})**: A, B, C muscle category codes are assigned based on MFF and MFI:

MFF Criteria		**MFI criteria**	**Muscle Category**	**SI_{cat}**
MFF < 50%	and	MFI < 10%	Normal	A
MFF < 50%	and	MFI ≥ 10%	Affected	B
MFF ≥ 50%	-	-	End-stage	C

where:

A. Normal = a muscle that appears normal and is most likely not affected by disease.
B. Affected = a muscle that is more likely to have disease involvement.
C. End-stage = a muscle that is most likely to have loss of functional capacity.

- **SI Cross-sectional Quality Flag (SI_{cross})**: with values of 0 or 1 (where 0 = presence of a **major** signal quality issue indicating an unreliable measurement; and 1 = signal quality is otherwise acceptable

for the Cross-sectional analysis). If SI_{cross} = 0, the muscle will not be included in the Cross-sectional analysis.

- **SI Longitudinal Quality Flag (SI_{long})**: with values of 0 or 1 (where 0 = presence of **major or minor** signal quality issues; and 1 = signal quality is otherwise acceptable for the Longitudinal analysis). If SI_{long} = 0, the muscle will not be included in the Longitudinal analysis.

Planned REACH Study Objectives for Individual MRI Results (Exploratory)

In accordance with the Protocol schedule of assessments, AMRA will provide the set of derived results for each individual muscle per subject per MRI performed at Screening, Week 24, and Week 48. Fulcrum will use the individual muscle results from AMRA to support exploratory objectives:

- Change from baseline in MRI Individual Muscle Measures (MFI, MFF, LMV) at Week 48.

MRI DATA FROM COMBINED MUSCLE GROUPS:

In addition to providing the individual muscle MRI measures and signal quality flags, AMRA also provides a comprehensive set of highly derived composite results from multiple sets of combined muscle groups. AMRA calculates composite MRI results for 2 purposes:

1. Cross-sectional analysis (to evaluate status of disease at a specific point in time).
2. Longitudinal analysis (to evaluate progression of disease over time).

MRI CROSS-SECTIONAL ANALYSIS DATA

For cross-sectional analysis, AMRA calculates composite results from groups of individual muscles in body regions that are associated with a particular functional test. For example, cross-sectional composite results from Dominant Neck + Arm + Torso MRI muscle groups may be used for analysis of correlation with RWS functional test results in the Dominant Arm.

AMRA provides the derived cross-sectional results as a set of 3 total composite measurements:

- **LMV_{tot}:** total cross-sectional composite LMV = calculated sum of LMV values from all eligible muscles (SI_{cross} = 1) in the specified cross-sectional body region. LMV_{tot} values are reported in L.
- **MFI_{tot}:** total cross-sectional composite MFI = calculated ratio (proportion) based on the sum of all LMV-adjusted MFI values from all eligible muscles (SI_{cross} = 1) in the cross-sectional body region. MFI_{tot} ratio values are then converted and reported as percentages.
- **MFF_{tot}:** total cross-sectional composite MFF = calculated ratio (proportion) based on the difference between 1 (indicating all fat-replaced) and the proportion of lean-to-total muscle volume (**LMV_{tot} / TMV_{tot}**), where **LMV_{tot}** is the sum of LMV values and **TMV_{tot}** is the sum of TMV values from all eligible muscles (SI_{cross} = 1) in the cross-sectional body region. MFF_{tot} ratio values are also converted and reported as percentages.

These are the equations AMRA uses to derive these cross-sectional composites:

$$LMV_{tot} = \sum_{i \in muscles} SI_{cross,i} \cdot LMV_i$$

$$MFI_{tot} = \frac{\sum_{i \in muscles} SI_{cross,i} \cdot MFI_i \cdot LMV_i}{\sum_{i \in muscles} SI_{cross,i} \cdot LMV_i}$$

$$MFF_{tot} = 1 - \frac{\sum_{i \in muscles} SI_{cross,i} \cdot LMV_i}{\sum_{i \in muscles} SI_{cross,i} \cdot TMV_i}$$

Note: AMRA does not directly provide TMV values for each individual muscle in the data transfer. However, TMV (L) may be calculated from the LMV (L) and MFF (ratio) values using the formula:

TMV = LMV / (1-MFF)

[redacted]

MRI LONGITUDINAL ANALYSIS DATA

Longitudinal analysis uses AMRA-derived MRI results from whole-body groups of muscles that are defined using **SI_{cat}** (muscle category) and **SI_{long}** (longitudinal signal quality flag) values as follows:

- **B Muscles**: all individual muscles with SI_{cat} = B and SI_{long} = 1 at Screening (Baseline).
- **A Muscles**: all individual muscles with SI_{cat} = A and SI_{long} = 1 at Screening (Baseline).
- **A+B Muscles**: all individual muscles with SI_{cat} = (A or B) and SI_{long} = 1 at Screening (Baseline).

Important Note: once an individual muscle is assigned to a particular Longitudinal Analysis Muscle Group at Screening (Baseline), the muscle will continue to be followed as such throughout the study. For example, muscles assigned to the **B Muscles** group at Screening (Baseline) will continue to be included in the **B Muscles** group at subsequent visits, regardless of any Post-baseline change in muscle category (e.g., even if a Post-baseline SI_{cat} shifts from B to either A or C, the muscle will still be included in the **B Muscles** group). However, if signal quality at a subsequent visit is deemed unacceptable for Longitudinal analysis (i.e., if Post-baseline SI_{long} shifts from 1 to 0), results from that muscle will not be included in the Longitudinal composite results for that muscle group at that Post-baseline visit (but may still be eligible to be included again at a later visit, if signal quality issues resolve and SI_{long} shifts back from 0 to 1).

Longitudinal Composites: Derived Results From AMRA

For each separate Longitudinal Muscle Group (e.g., B Muscles, A Muscles, A+B Muscles), AMRA provides a set of highly derived longitudinal composite measurements from all eligible muscles at Screening, Week 24, and Week 48 as follows:

- **At Screening**: AMRA provides a derived set of initial study-level **Reference Screening** values at the Screening Visit, based on the number of muscles eligible for longitudinal analysis (SI_{long} = 1), and reports these longitudinal composite results as LMV_{tot} (unit = L), MFF_{tot} (unit = %), and MFI_{tot} (unit = %). In addition, AMRA provides a total LMV muscle count (n) of the number of eligible muscles with a non-missing LMV value at the Screening visit.
- **At Week 24**: AMRA provides a derived set of visit-level **Change from Reference Screening** results. These visit-level results comprise an overall count of muscles that are still eligible for analysis at Week 24, plus 4 visit-level Reference Screening values, and 4 visit-level Change from Reference Screening values as follows:
    - (Step 1) AMRA calculates the Week 24 **Reference Screening** values based on the set of muscles that are still eligible (SI_{long} = 1). (Note: if new signal quality issues are identified, the eligible muscle count will change and the Reference Screening values will be updated; otherwise, if the muscle count has not changed, the Reference Screening values at Week 24 remain the same as the initial study-level Reference Screening values at Screening). AMRA also refers to these as **Reference Timepoint 1** (TP1) values and provides them as a set of 4 results: Reference Screening LMV muscle count, LMV_{tot}, MFI_{tot}, and MFF_{tot}.

- (Step 2) AMRA calculates the **Week 24** actual values based on the same set of muscles eligible at this visit. AMRA also refers to these as **Timepoint 2** (TP2) values. Note: these TP2 results are interim values that AMRA uses for the calculations but does not directly provide them in the MRI data transfer to Fulcrum (see additional details below in the Section for Post-Data Transfer Processing Steps).
- (Step 3) AMRA derives the Week 24 **Change from Reference Screening** values using the Week 24 TP1 and TP2 values (from Steps 1 and 2 above). AMRA provides these change results in the data transfer as a set of 4 highly derived longitudinal composite results:
  - absolute change in LMV_{tot} (unit = L),
  - relative change in LMV_{tot} (unit = %),
  - absolute change in MFF_{tot} (unit = percentage points),
  - absolute change in MFI_{tot} (unit = percentage points).

- **At Week 48:** AMRA repeats the process (as noted above for Week 24) and provides a similar set of visit-level **Reference Screening** and **Change from Reference Screening** at Week 48 values in the data transfer to Fulcrum. Note: for the Week 48 visit, AMRA also includes an extra set of composites that are calculated using Week 24 as the Reference TP1 instead of Screening. However, for the double-blind placebo-controlled portion of the study, this extra set of Reference Week 24-as-TP1 results will not be used; only Reference Screening TP1-based results will be used for this portion of the study.

Longitudinal Composites: Post-Data Transfer Processing Steps

Once AMRA provides the highly derived longitudinal composite results, Fulcrum will perform some additional post-data transfer processing steps to prepare the longitudinal results for analysis.

Calculate Actual TP2 Analysis Values

Since AMRA does not directly provide the actual TP2 values, these analysis values will be calculated in accordance with a rule provided by AMRA, which is a standard sum of the visit-level values:

TP2 = (Reference TP1 + Absolute Change from Reference TP1)

Apply LMV-based Inclusion Criteria

AMRA provides instructions for Fulcrum to use on each set of visit-level composite values to determine the overall final eligibility of the results for the Longitudinal analysis. AMRA has determined that the reliability of results from a longitudinal analysis requires an adequate level of LMV_{tot} from a sufficient number of muscles. Consequently, if longitudinal LMV_{tot} is below a certain threshold value and the

LMV muscle count is too low, AMRA recommends that the entire set of longitudinal results from that visit should be reset to missing and should not be included in the longitudinal analysis.

So, for each set of visit-level longitudinal results, Fulcrum will check the AMRA derived data and ensure that at least 1 of the 2 following inclusion criteria are met (as instructed by AMRA):

To be included, the Reference Screening (TP1) LMV_{tot} and LMV muscle count must be either:

- at least 25 cl (0.25 L) with measurements from at least 2 muscles, **or**
- at least 50 cl (0.50 L) with measurement(s) from at least 1 muscle.

If the Reference Screening TP1 values do not meet at least 1 of the 2 LMV-based criteria, the entire set of results for all 3 composite measures (LMV_{tot}, MFI_{tot}, and MFF_{tot}) at that visit will be reset to missing and excluded from the longitudinal analysis. Fulcrum will apply these post-data transfer steps to the AMRA data at all visits (Screening, Week 24, and Week 48).

Planned REACH Study Objectives for MRI Longitudinal Results (Secondary and Exploratory)

Per the Protocol schedule, AMRA will provide longitudinal MRI composite results at Screening, Week 24, and Week 48. Fulcrum will use the longitudinal results from AMRA to support 1 planned secondary objective and several planned exploratory objectives.

Longitudinal MRI Secondary Efficacy Endpoint:

- Change from baseline in WB MRI Longitudinal Composite MFI (MFI_{tot}) in B Muscles at Week 48.

AMRA calculates and provides the longitudinal composite results for this secondary endpoint. Fulcrum applies the LMV-based inclusion criteria rules (as instructed by AMRA) and determines the final set of evaluable longitudinal results.

AMRA first identifies the longitudinal analysis set of **B Muscles** (i.e., muscles with SI_{cat} = B at Baseline with SI_{long} = 1) and derives the composite measurements at each visit.

Absolute Change from Baseline in MFI_{tot} in B Muscles at Week 48 is described here using AMRA terminology and equations:

- Baseline MFI_{tot} = AMRA-derived Reference Screening TP1 value for MFI_{tot} at Week 48 (unit: %).
- Absolute Change from Baseline MFI_{tot} at Week 48 = AMRA-derived MFI_{tot} Change from Reference Screening at Week 48 value (unit: percentage points).

The equation AMRA uses to calculate absolute change in MFI_{tot} at Week 48 for B Muscles is:

$$\Delta MFI_{tot} = \frac{\sum_{i \in SI_{cat,tp1=B}} SI^{comb}_{long,i} \cdot MFI_{i,tp2} \cdot LMV_{i,tp2}}{\sum_{i \in SI_{cat,tp1=B}} SI^{comb}_{long,i} \cdot LMV_{i,tp2}} - \frac{\sum_{i \in SI_{cat,tp1=B}} SI^{comb}_{long,i} \cdot MFI_{i,tp1} \cdot LMV_{i,tp1}}{\sum_{i \in SI_{cat,tp1=B}} SI^{comb}_{long,i} \cdot LMV_{i,tp1}}$$

Note: AMRA uses SI_{long} values combined from both timepoints to ensure only reliable results from evaluable muscles with acceptable MRI signal quality are included:

$$SI_{long}^{comb} = SI_{long,tp1} \cdot SI_{long,tp2}$$

[redacted]

Absolute change in LMV_{tot} (L):

$$\Delta LMV_{tot} = \sum_{i \in SI_{cat,tp1=B}} SI_{long,i}^{comb} \cdot \left(LMV_{i,tp2} - LMV_{i,tp1}\right)$$

Relative change in LMV_{tot} (%):

$$\Delta LMV_{tot}^{relative} = \sum_{i \in SI_{cat,tp1=B}} SI_{long,i}^{comb} \cdot \left(\frac{LMV_{i,tp2} - LMV_{i,tp1}}{LMV_{i,tp1}}\right)$$

Absolute change in MFF_{tot} (pp):

$$\Delta MFF_{tot} = \left(1 - \frac{\sum_{i \in SI_{cat,tp1=B}} SI_{long,i}^{comb} \cdot LMV_{i,tp2}}{\sum_{i \in SI_{cat,tp1=B}} SI_{long,i}^{comb} \cdot TMV_{i,tp2}}\right) - \left(1 - \frac{\sum_{i \in SI_{cat,tp1=B}} SI_{long,i}^{comb} \cdot LMV_{i,tp1}}{\sum_{i \in SI_{cat,tp1=B}} SI_{long,i}^{comb} \cdot TMV_{i,tp1}}\right)$$

Important note regarding AMRA terminology:

AMRA uses non-standard variable names for the longitudinal composite results. These will be mapped to standard variable names for the analysis:

AMRA Variable:	**Analysis Variable:**
Reference Screening (TP1) at the Screening Visit	Study-level Baseline Value (BASE at Screening)
Reference Screening (TP1) at Visit Week xx	Visit-level Baseline Value (BASE at Visit Week xx)
Week xx (TP2) at Visit Week xx	Visit-level Actual Value (AVAL at Visit Week xx)

Change from Reference Screening at Visit Week xx	Visit-level Absolute Change (CHG at Visit Week xx)
Change from Reference Screening at Visit Week xx, (%)	Visit-level Percent Change (PCHG at Visit Week xx)

ATTACHMENT A:

Individual Muscle Locations:

Left and Right muscles from the following 18 locations will be assessed.

Neck muscles:

- Infraspinatus
- Subscapularis
- Supraspinatus
- Teres Minor

Arm muscles:

- Biceps Brachii
- Deltoideus
- Triceps Brachii

Torso muscles:

- Latissimus Dorsi/Teres Major
- Pectoralis Major
- Rhomboideus
- Serratus Anterior
- Spinal Erectors Th1-Sacrum
- Trapezius

Leg muscles:

- Adductors
- Gastrocnemius Medialis
- Hamstrings
- Quadriceps
- Tibialis Anterior