**Protocol Number: SMT C11005**

**Official Title:** PhaseOut DMD: A Phase 2 Clinical Study to Assess the Activity and Safety of Utrophin Modulation with SMT C1100 in Ambulatory Paediatric Male Subjects with Duchenne Muscular Dystrophy (SMT C11005)

**NCT Number: NCT02858362**

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# Statistical Analysis Plan

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| **Sponsor:** | Summit (Oxford) Limited |
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| **Title** | PhaseOut DMD: A Phase 2 Clinical Study to Assess the Activity and Safety of Utrophin Modulation with SMT C1100 in Ambulatory Paediatric Male Subjects with Duchenne Muscular Dystrophy (C11005) |
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# 1.0 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Summit (Oxford) Limited Protocol SMT C11005, titled 'PhaseOut DMD: A Phase 2 Clinical Study to Assess the Activity and Safety of Utrophin Modulation with SMT C1100 in Ambulatory Paediatric Male Subjects with Duchenne Muscular Dystrophy (C11005)'.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using Protocol Version 5.0 dated 24-Feb-2017 and CRF version dated 24-Aug-2017. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Please note that the study has both magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) assessments, however, in the protocol they were collectively referred to as MRI assessments. In this SAP information from the protocol (e.g. objectives and endpoints) still refers to MRI, but in other places that relate to the reporting of the study MRS is also mentioned, where appropriate.

# 2.0 Study Objectives

## 2.1 Primary Objectives

The primary objectives for this study are:

- To investigate changes in leg MRI in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To investigate the relationships between changes in leg MRI with plasma concentrations of SMT C1100 and its metabolites in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To assess the safety and tolerability of SMT C1100 and its metabolites in paediatric patients with DMD

## 2.2 Secondary Objectives

The secondary objectives for this study are:

- To investigate changes in utrophin expression and muscle fibre regeneration in muscle, in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To investigate the relationships between changes in utrophin expression and fibre regeneration in muscle and safety parameters with plasma concentrations of SMT C1100 and its metabolites in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To investigate changes in pulmonary function tests in paediatric subjects with DMD, following treatment with SMT C1100
- To investigate the relationships between changes in pulmonary function tests with plasma concentrations of SMT C1100 and its metabolites in paediatric subjects with DMD, following treatment with SMT C1100

## 2.3 Exploratory Objectives

The exploratory objectives for this study are:

- To investigate changes in functional measures, in paediatric patients with DMD, following treatment with SMT C1100, including the relationship between functional measures and exposure
- To investigate changes in paediatric outcomes data collection instrument (PODCI) scores in paediatric patients with DMD, following treatment with SMT C1100, including the relationship between PODCI scores and exposure

- To investigate changes in blood biomarkers in paediatric patients with DMD, following treatment with SMT C1100, including the relationship between blood biomarkers and exposure
- To investigate changes in cardiac MRI tests in paediatric subjects with DMD, following treatment with SMT C1100 (Cohort 3)
- To investigate the relationships between changes in cardiac MRI with plasma concentrations of SMT C1100 and its metabolites in paediatric subjects with DMD, following treatment with SMT C1100 (Cohort 3)

# 3.0 Study Design

This is a Phase 2, open-label study to assess the activity and safety of utrophin modulation with SMT C1100 administered orally twice-daily (bid) in ambulatory paediatric male patients with DMD. In Cohort 1, approximately 30 patients with DMD will be administered 2.5 g bid of SMT C1100 microfluidised aqueous suspension formulation (F3). In Cohort 2, approximately 10 patients will be administered 1 g bid of SMT C1100 as a powder for oral suspension (F6). In Cohort 3, approximately 15 patients, who have previously received SMT C1100, but who are not eligible for Cohorts 1 or 2, will be administered 2.5 g bid of SMT C1100 F3.

Cohort 1 will be conducted in a multi-centre setting in both the United Kingdom (UK) and the United States of America (USA). Cohorts 2 and 3 will only be conducted at specific centres in the USA and UK respectively. All three cohorts have a Screening and Baseline Phase of up to 28 days, a 48-week open label Treatment Phase and a 30-day Safety Follow up Phase.

Following completion of the initial 48-weeks of the open label Treatment Phase, subjects will be eligible to consider receiving SMT C1100 until either SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued. All subjects will receive the same formulation as they had previously been receiving, twice-daily.

## 3.1 Sample Size Considerations

A suitable number of potential subjects will be screened in order that 55 subjects successfully meet the inclusion and exclusion criteria and continue into the Treatment Phase. Thirty subjects are expected to be enrolled in Cohort 1, approximately 10 in Cohort 2 and approximately 15 in Cohort 3. The sample size is not based upon statistical powering, but the number is considered to be sufficient to initially explore the endpoints and their relationship with SMT C1100 exposure.

Subjects who withdraw or who are withdrawn during the Treatment Phase may be replaced if the study has not yet reached full enrolment at the time of withdrawal. Subjects who withdraw or who are withdrawn due to an adverse event (AE) considered related to SMT C1100 will not be replaced.

Efforts will be made, in Cohorts 1 and 2, to balance the study populations and attempt to have at least 50% of boys with a fat: water fraction greater than or equal to 0.15. Efforts will also be made such that half of the boys are greater than or equal to 8 years of age. Such attempts will be made manually rather than via an automatic system; achieving these recruitment goals will be attempted but complete balance will not be enforced.

All subjects will be eligible to be rolled into the extension phase.

## 3.2 Randomization

Not applicable, as all study subjects will receive open-label SMT C1100.

# 4.0 Study Endpoints

## 4.1 Primary Endpoints

- Change from baseline to Weeks 12, 24, 36 and 48 in MRI leg muscle parameters (Cohorts 1 and 2)
- SMT C1100 and metabolite plasma concentrations at Weeks 1 (Days 1 and 7, as applicable (Cohorts 2 and 3 only)), 4, 8 (Cohorts 1 and 2 only), 12, 24, 36 and 48
- Safety data including:
  - Treatment emergent AEs

## 4.2 Secondary Endpoints

- Change from baseline to Week 24 or 48 in utrophin expression via muscle biopsy analysis (Cohorts 1 and 2)
- Change from baseline to Week 24 or 48 in muscle regeneration biomarkers via muscle biopsy analysis (Cohorts 1 and 2)
- Change from baseline to Weeks 12, 24, 36 and 48 (Cohorts 1 and 2) and from baseline to Weeks 1, 24 and 48 (Cohort 3) in pulmonary function tests
- Safety data including:
  - Vital signs (systolic and diastolic blood pressure and heart rate)
  - Physical examination
  - Twelve-lead electrocardiogram (ECG)
  - Echocardiogram (ECHO)
  - Pulmonary function tests:
    - Forced expiratory volume in 1 second ($FEV_1$)
    - Forced vital capacity (FVC)
    - Maximum inspiratory pressure (MIP)
    - Maximum expiratory pressure (MEP)
    - Peak expiratory flow (PEF)
    - Peak cough flow (PCF) (Cohort 3)
    - Sniff nasal inspiratory pressure (SNIP) (Cohort 3)
  - Safety laboratory evaluations (clinical chemistry, haematology, (all 3 Cohorts) coagulation (Cohort 2 and Cohort 3) parameters and urinalysis (all 3 Cohorts))

## 4.3 Exploratory Endpoints

- Change from baseline to Week 12, 24, 36 and 48 for Cohorts 1 and 2 and from baseline to Week 24 and 48 for Cohort 3 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in 6MWD

- Change from baseline to Week 12, 24, 36 and 48 for Cohorts 1 and 2 and from baseline to Week 24 and 48 for Cohort 3 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in North Star Ambulatory Assessment (NSAA) global score
- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in timed function tests (10 meter run/walk, time to stand)
- Change from baseline to Week 12, 24, 36 and 48 for Cohorts 1 and 2 and from baseline to Week 24 and 48 for Cohort 3 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in paediatric outcomes data collection instrument (PODCI) scores
- Change from baseline to Week 12, 24, 36 and 48 for Cohorts 1 and 2 and from baseline to Week 24 and 48 for Cohort 3 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in Performance of Upper Limbs (PUL)
- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) and measured at 6-monthly intervals for the duration of the Extension Phase of blood biomarkers, e.g., creatine kinase, matrix metallopeptidase 9 and other biomarkers
- Change from baseline to Week 48 (in the main phase of the study) and measured at 12-monthly intervals for the duration of the Extension Phase in cardiac MRI parameters (Cohort 3)
- Change from baseline in MRI leg muscle parameters measured at 6-monthly intervals for the duration of the Extension Phase (Cohorts 1 and 2)
- SMT C1100 and metabolite plasma concentrations measured at 6-monthly intervals for the duration of the Extension Phase
- Change from baseline in pulmonary function tests measured at 6-monthly intervals for the duration of the Extension Phase

It should be noted that subjects in Cohort 3 may not be able to perform all of the functional tests at baseline. Therefore the subjects included in the analyses for these tests will be test specific and based upon their baseline ability to perform the test.

# 5.0 Definitions and Study Assessments

## 5.1 Definitions

**Baseline**

Unless stated otherwise, the baseline is defined as the last non-missing assessment prior to the first administration of investigational medicinal product (IMP). If the assessment time is missing while the assessment date is the same date as the first administration of investigation product, a scheduled pre-dose assessment will be considered as baseline.

**Change from Baseline**

Change from baseline is defined as (value at post-baseline visit – value at baseline). Similarly percentage change from baseline is defined as 100 x (change from baseline)/baseline.

**Concomitant and Prior Medication**

Prior medications are defined as medications with a start date prior to first dose of IMP. Concomitant medications are defined as any medications ongoing at the start of IMP treatment or with a start date on or after the first IMP dose date. Consequently, medications ongoing at the start of IMP will be reported as both prior and concomitant medications.

**Study Day 1**

The first day IMP is administered.

**Study Day**

Study day is defined as the number of days from Study Day 1.

- Before Study Day 1, Study Day = (Date of Interest – Date of Study Day 1)
- On or After Study Day 1, Study Day = (Date of Interest – Date of Study Day 1) + 1

Therefore the day prior to Study Day 1 is Study Day -1.

**Study Visit**

For by-visit summaries, data will be assigned to visits using windowing (see below). If more than one actual visit (including the early termination or unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the latest visit with non-missing data will be considered for analysis.

| Study Analysis Visit | Target Day | Study Day | Interval (days) |
|---|---|---|---|
| Baseline | 1 | ≤1* | NA |
| Day 7 (Cohorts 2 & 3 only) | 7 | 5 to 9 | 5 |
| Week 4 | 28 | 21 to 38 | 18 |
| Week 8 | 56 | 49 to 66 | 18 |
| Week 12 | 84 | 67 to 112 | 46 |
| Week 24 | 168 | 140 to 196 | 57 |
| Week 36 | 252 | 224 to 280 | 57 |
| Week 48 | 336 | 308 to 364 | 57 |
| Week 60 | 420 | 392 to 448 | 57 |
| Week W | W x 7 | (W x 7 -28) to (W x 7 +28) | 57 |
| *And so forth for 3 monthly visits* | | | |

* Must be prior to dosing if time of assessment is recorded.

Windowing will not be used for the biopsy data as there is only one measurement post dose.

These visit windows will be reviewed and may be updated. Any assessments that fall outside of these windows will be reviewed on a case-by-case basis, and decisions on their handling will be fully documented prior to reporting.

Data will be included in analyses regardless of the duration of time since their last dose of study treatment and the assessment. However additional summaries may be generated excluding subjects if their assessment is performed several weeks after their last prior study dose. This will be reviewed on a case-by-case basis as the decision will be dependent on the assessment and the likely impact of the exclusion on the interpretation of the results.

Data collected outside these windows will only be listed.

## 5.2 Efficacy Assessments

All of the efficacy endpoints will be assessed at baseline, end of study, and Weeks 12, 24, 36 and 48 during the first 48 weeks and then 6 monthly during the extension phase. If a subject withdraws from the study prematurely they will also be assessed at the termination visit.

The 6MWT will also be conducted at screening.

In the sections below reference is made to reasons for not performing an assessment or not completing an assessment. Different approaches will be taken for dealing with the missing data dependent on whether or not the reason is related to the subject's medical condition (i.e. informative). A reason of 'Subject physically unable' will be regarded as informative, whilst 'Site staff/facility unavailable' is not informative. Other reasons will require a team review on a case-by-case basis.

### 5.2.1 Six-Minute Walk Distance

The total distance walked during six-minutes will be recorded in the eCRF. Subjects in both Cohorts 1 and 2 are required to be ambulatory at Baseline. If the subject is unable to perform the assessment after Day 1 or is unable to complete it, the reason will be recorded. For an assessment not completed the duration of time walked will also be recorded.

If the reason given for not performing the assessment or not completing the assessment is related to the subject's medical condition (i.e. informative) the 6MWD will be taken as zero or the recorded 6MWD respectively. However, if the reason is not deemed to be related to their medical condition (i.e. non-informative) then the distance will be taken as missing.

The use of orthoses or aids will also be recorded. The 6MWD recorded will still be used in analyses, but the use of orthoses or aids will be summarized.

The number of falls or times the follower provides support will also be recorded. This will not impact the use of the 6MWD recorded, but will be summarized separately.

The %-predicted 6MWD will be calculated using the equation proposed by Geiger (2007):

Male 6MWD=196.72+ (39.81 x age) – (1.36 x age$^2$) + (132.28 x height), where age is age at assessment (not integer age) in years and height is height at assessment in meters.

Changes from baseline will be calculated for 6MWD and %-predicted 6MWD. Baseline will be the average of the pre-dose measurements.

The following velocities of change (change per month) will also be calculated for both the 6MWD and the %-predicted 6MWD:

- Baseline to Week 12
- Week 12 to Week 24
- Week 24 to Week 36
- Week 36 to Week 48

And

- Baseline to Week 24
- Week 24 to Week 48

… and so forth when reporting the extension phase data

The time till a 10% reduction in 6MWD will be determined for each subject. The occurrence of this reduction will have to be confirmed by the next visit attended.

### 5.2.2 North Star Ambulatory Assessment

The NSAA is a functional scale specifically designed for ambulant patients affected by DMD. It is designed to test 17 activities (see Appendix 2) with scores of 0, 1 or 2 for each activity; a higher score indicating fewer limitations due to DMD. The total score will be derived as the sum of the scores from the 17 activities, and hence has the range 0-34. If the NSAA was performed but some of the activity scores are missing, then the worst score of the adjacent visits will be used to calculate the total score. For example, if the Week 24 NSAA was performed but some of the activities were missing then the worst score for the corresponding activity at Week 12 and 36 will be used.

The NSAA linearized score will also be derived (Mayhew 2013) where the NSAA scale is converted to a 0-100 scale using 16 of the activities (excludes 'lifts head').

The time to rise from the floor (time to stand) and the 10-Metre run/walk time are also collected with this assessment and are described in sections below as independent endpoints.

If the subject is unable to perform the assessment the reason will be recorded. If the reason given for not performing the assessment is related to the subject's medical condition (i.e. informative) the activity score will be taken as zero, otherwise it will be taken as missing.

Changes from baseline in the total score and the linearized score will be calculated.

The following velocities of change (change per month) will also be calculated for the total and linearized scores:

- Baseline to Week 12
- Week 12 to Week 24
- Week 24 to Week 36
- Week 36 to Week 48

And

- Baseline to Week 24
- Week 24 to Week 48

… and so forth when reporting the extension phase data

Loss of ambulation will be determined by a score of 0 with the 'walk' activity in the NSAA. To ensure the subject's disease has truly reached this level, subsequent visits will also need to have a score of 0.

The number of functions (0, 1, 2…) a subject has lost ("unable"), compared to baseline, will also be determined at each visit. Again, to ensure, that the subject's disease has truly reached this level subsequent visits will also need to have a score of 0.

### 5.2.3 10-Metre Run/Walk

The 10-metre run/walk should be performed once at each visit and only repeated if the evaluator deems it to be spurious. The protocol incorrectly states that the test should be repeated after a 10 minute rest and both times recorded on the eCRF. The error was documented in a file note (SMTC11005-006 Dated: 05Oct2017). As a consequence, the majority of patients only have one test performed at a visit however if there is a repeat test then the shortest time (duration) of the completed tests will be used in analyses. If the subject is unable to perform the assessment or is unable to complete it, the reason will be recorded. For an assessment not completed the distance and duration of time walked will also be recorded.

If the reason given for not performing at any assessment or not completing any assessment is related to the subject's medical condition (i.e. informative) the time will be taken as the worst score recorded (over all subjects and assessments) whilst on treatment or the derived time adjusted for the distance recorded respectively.

The derived time adjusted for the distance = (10/distance in metres) x time recorded.

Changes from baseline will be calculated.

The following velocities of change (change per month) will also be calculated:

- Baseline to Week 12
- Week 12 to Week 24
- Week 24 to Week 36
- Week 36 to Week 48

And

- Baseline to Week 24
- Week 24 to Week 48

… and so forth when reporting the extension phase data

### 5.2.4 Time to stand

The time to stand is recorded as part of the NSAA. If the subject is unable to perform the NSAA the reason will be recorded. If the time to stand is missing and the response to rise from floor activity with the NSAA is "unable" then the time to stand will be considered informative missing and taken as the worst time recorded (over all subjects and assessments). Otherwise, if the reason given for not performing the assessment is related to the subject's medical condition (i.e. informative) the time to stand will be taken as the worst time recorded, otherwise it will be taken as missing.

Changes from baseline will be calculated.

The following velocities of change (change per month) will also be calculated:

- Baseline to Week 12
- Week 12 to Week 24
- Week 24 to Week 36
- Week 36 to Week 48

And

- Baseline to Week 24
- Week 24 to Week 48

… and so forth when reporting the extension phase data

### 5.2.5 Paediatric Outcomes Data Collection Instrument (PODCI)

The PODCI will be completed by the parent/carer. It consists of 86 questions from which five scales and one global scale are calculated (see Appendix 3). The five scales are:

1) Upper extremity and physical function core scales;

2) Transfer and basic mobility core scale,

3) Sports and physical functioning core scale,

4) Pain/comfort core scale and

5) Happiness core scale.

For each scale the mean score (referred to as the "mean of items") will be calculated. If a question contained within a scale is not answered, that question is not included in the calculation of the mean score. For each scale there is a minimum number of questions that have to be answered, otherwise the score is considered missing.

The scale's mean score is standardized into a score ranging between 0-100, where a higher score indicates fewer limitations due to DMD. The Standardized Score will be used in analyses.

The global functioning scale is calculated by taking the mean of the "standardized scores" from the following scales:

1) Upper extremity and physical function,
2) Transfer and basic mobility,
3) Sports and physical functioning and
4) Pain/comfort.

The scoring algorithms can be found in Appendix 4.

No imputation will be used for missing PODCI scores.

Changes from baseline will be calculated for each scale standardized score and the global functioning scale score.

### 5.2.6 Performance of the Upper Limbs

The PUL assessment (Version 2) was specifically designed to assess upper limbs in patients with DMD. It includes 22 items subdivided into high level shoulder (6 items), middle level elbow (9 items) and distal level wrist and hand (7 items) dimensions to test shoulder, elbow, and distal upper limb performance reflecting functional tasks (see Appendix 4). Prior to assessing these 22 items an entry level score (entry item) is determined. For weaker subjects, a low score on the entry item means high level items do not need to be performed with the shoulder dimension. Each item is scored on a 0-2 scale, except Items 15 and 22 which are scored as either 0 or 1. For all items a higher score indicates better performance. Each dimension will be scored separately with a maximum score of 12 for the shoulder level, 17 for the elbow level, and 13 for the distal level. A total score can be achieved by adding the three level scores (max global score 42).

If the subject is unable to perform the assessment the reason will be recorded. If the reason given is related to the subject's medical condition (i.e. informative) the score will be taken as 0, otherwise the score will be taken as missing.

Changes from baseline will be calculated for each dimension and the total score.

## 5.3 Pharmacodynamic Assessments

### 5.3.1 Leg MRI/MRS (Cohorts 1 and 2)

The following leg muscle MRI/MRS parameters will be measured at Baseline and Weeks 12, 24, 36 and 48 during the first 48 weeks and then 6 monthly during the extension phase:

- MRS method
    - Fat Fraction in the Vastus Lateralis (MRS_FF_VL)
    - Fat Fraction in the Soleus (MRS _FF_SOL)

- Water Transverse Relaxation Time (1H2O-T2) in the Vastus Lateralis (MRS _T2_VL)
- Water Transverse Relaxation Time (1H2O-T2) in the Soleus (MRS _T2_SOL)

- 8 point Dixon method
  - Fat Fraction in the Vastus Lateralis (DIX_FF _VL)
  - Fat Fraction in the Soleus (DIX_FF _SOL)
  - Fat Fraction in the Biceps Femoris (DIX_FF_BFLH)
- MRI method
  - Proton Transverse Relaxation Time (T2) in the Vastus Lateralis (MRI_T2_VL)
  - Proton Transverse Relaxation Time (T2) in the Soleus (MRI_T2_SOL)
  - Proton Transverse Relaxation Time (T2) in the Biceps Femoris (MRI_T2_BFLH)

The MRS parameters from the Vastus Lateralis and Soleus are considered the primary MRI/MRS parameters for the study.

The fat fractions are reported as percentages, whilst T2 parameters are reported in ms.

Imputation will not be used for any missing data.

If a subject withdraws from the study prematurely they will also be assessed at the termination visit if not performed in the last 6 weeks.

Changes from baseline will be calculated.

The following velocities of change (change per month) will also be calculated for the MRS fat fraction measurements:

- Baseline to Week 12
- Week 12 to Week 24
- Week 24 to Week 36
- Week 36 to Week 48

And

- Baseline to Week 24
- Week 24 to Week 48

… and so forth when reporting the extension phase data

### 5.3.2 Cardiac MRI (Cohort 3)

MRI parameters will be measured at Baseline and then annually (every 48 weeks). Information concerning the MRI parameters will be added in a later version of the SAP.

### 5.3.3 Fibre Regeneration [via Biopsy] (Cohorts 1 and 2)

Parameters will be measured from biopsies at Baseline and once post-dose, at either 24 weeks or 48 weeks. If a subject withdraws from the study prematurely they may also have a biopsy at the termination visit if they haven't already had their second biopsy.

At each time-point two samples will be taken.

Imputation will not be used for any missing data.

#### 5.3.3.1 Developmental Heavy Chain Myosin (MHCd), Utrophin Expression and Fibre Diameter

Each sample will have, where possible, 3 sections assessed – different sections will be used for the Myosin and Utrophin assays. For each of these sections the following will be determined from the Myosin assay:

- Percentage of MHCd positive fibres (%MHCd positive)
- Percentage of fibres with 0, 1, 2 and 3 MHCd intensity
- MHCd heterogeneity score
- Fibre diameter - mean
- Fibre diameter – standard deviation

For the other sections the following will be determined from the Utrophin assay:

- Utrophin intensity – mean
- Utrophin intensity – standard deviation
- Utrophin intensity – mean, where utrophin expression is ≥75% around the fibre
- Utrophin intensity – standard deviation, where utrophin expression is ≥75% around the fibre
- Percentage of fibres with 0, 1, 2 and 3 Utrophin intensity
- Utrophin heterogeneity score

In addition to these parameters the percentage of Utrophin positive fibres (%UT positive) will be derived as (100 - % of fibres with 0 intensity).

The total number of fibres will also be recorded for both assays, but this is only information concerning the assay and isn't to assess treatment effect.

If there was a technical issue with the assay a value may be excluded from analyses. This exclusion has to be justified and documented by the pathologist/technician following their assessment of the stained image.

For each subject at each time-point the average will be calculated across sections for each sample and then the average will be calculated from the two sample averages. Changes from baseline will then be calculated from these averages.

#### 5.3.3.2 % Necrosis/Inflammation, % Regeneration, %Fat and %Collagen

For each biopsy sample the % of necrosis / inflammation, % regeneration, %fat and %collagen will be estimated by semi-quantitative pathology assessment. Note that a single section stained with haematoxylin and eosin (H&E) will be taken from each sample to calculate % of necrosis / inflammation, % regeneration and %fat. A second section from each sample is stained with Masson's trichrome (MT) to calculate collagen.

Values from the two samples will be averaged. Changes from baseline will then be calculated for these averages.

### 5.3.4 Blood Biomarkers

Blood biomarkers (including creatine kinase and matrix metallopeptidase 9 [MMP9]) will be measured at Baseline and Weeks 4, 8, 12, 24, 36 and 48 during the first 48 weeks and then 6 monthly during the extension phase. Changes from baseline will be calculated. Imputation will not be used for any missing data.

Fibroblast growth factor 19 (FGF19) and 7α-hydroxy-4-cholesten-3-one (C4) will be measured at screening, Day 1, end of study and Weeks 24 and 48. At Weeks 24 and 48 measurements will be taken pre-AM dose, 3h post-AM dose, pre-PM dose and 4h post-PM dose. On Day 1 only the pre and post- AM measurements will be taken.

## 5.4 Safety Assessments

### 5.4.1 Adverse Events (AE)

A treatment emergent AE (TEAE) includes any condition that: 1) was not present prior to study treatment, but appeared or reappeared following initiation of study treatment, or 2) was present prior to study treatment, but worsened during study treatment.

The duration of AEs will be derived as the AE end date (imputed date for incomplete AE end date) – AE onset date (imputed date for incomplete AE onset date) +1.

AEs leading to discontinuation of IMP are those with an action taken with study treatment on the AE eCRF page of "Drug Withdrawn'.

Treatment-related TEAEs are defined as those TEAEs where relationship to study treatment is either considered as 'Possibly Related' or 'Probably Related' by the Investigator. A missing value for relationship to treatment will be considered as 'Related' in summaries.

A missing assessment of severity will be considered as 'severe' in summaries.

### 5.4.2 Laboratory Data

Laboratory parameters will be reported in International System of Units (SI).

Coagulation parameters will only be assessed in Cohorts 2 and 3.

The table below details the times when laboratory measurements will be taken:

| Visit | Cohort | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Screening | H, CC, U, LFT | H, CC, U, LFT,Coag | H, CC, U, LFT,Coag |
| Baseline Phase | H, CC, U, LFT | H, CC, U, LFT, Coag | |
| Day 1 | LFT | LFT | H, CC, U, Coag |
| Day 7 | | LFT, Coag | H, CC, U, LFT,Coag |
| Week 4 | LFT | LFT | LFT |
| Week 8 | LFT | LFT | |
| Week 12 | H, CC, U, LFT | H, CC, U, LF, Coag | H, CC, U, LFT,Coag |
| Week 24 | H, CC, U, LFT | H, CC, U, LF, Coag | H, CC, U, LFT,Coag |
| Week 36 | H, CC, U, LFT | H, CC, U, LFT, Coag | H, CC, U, LFT,Coag |
| Week 48 | H, CC, U, LFT | H, CC, U, LFT, Coag | H, CC, U, LFT,Coag |
| Extension Visits | H, CC, U, LFT | H, CC, U, LFT, Coag | H, CC, U, LFT,Coag |

H: Haematology, CC: Clinical Chemistry, U: Urinalysis, LFT: Liver Function Tests, Coag: Coagulation parameters

Changes from baseline will be calculated.

Some laboratory parameters will be categorized to assist identifying values of potential concern. Details are provided in Section 9.8.3.

The following parameters will be assessed relative to the upper limit of normal, e.g. value/ULN:

- Alkaline Phosphatase
- ALT
- AST
- Creatine kinase
- GLDH
- Total Bilirubin

For those parameters recorded as >x or <x a small value (0.01) will be added or subtracted from the value x respectively prior to performing analyses. Listings will present the original value.

### 5.4.3 Vital Signs

Vital sign measurements will be taken at screening, baseline, end of study, Day 1 and Weeks 12, 24, 36 and 48 during the first 48 weeks and then 3 monthly during the extension phase. If a subject withdraws from the study prematurely they will also be assessed at the termination visit.

Pulse, respiratory rate, oral temperature, and systolic and diastolic blood pressures will be measured.

Changes from baseline will be calculated.

### 5.4.4 Twelve-Lead Electrocardiogram (ECG)

Triplicate ECG measurements will be taken at screening, baseline, end of study, Day 1 and Weeks 12, 24, 36 and 48 during the first 48 weeks and then 6 monthly during the extension phase. If a subject withdraws from the study prematurely they will also be assessed at the termination visit.

Cohorts 1 and 2

On Day 1 and at Weeks 24 and 48 the measurements will be taken at either pre-AM dose and 0.5, 2, 4 and 6h post-AM dose OR pre-PM dose and 0.5, 2 and 4h post-PM dose. At Weeks 12 and 36 the measurements will be taken at 4h post-AM dose.

Cohort 3

At Weeks 12, 24, 36 and 48 the measurements will be taken at pre-AM dose and 0.5, 2, 4 and 6h post-AM dose.

Extension Phase

At Week 48 (start of extension phase) the measurements will be taken at 0.5, 2, 4 and 6h post-AM dose. Then measurements will be taken at 4h after dosing at each 6 monthly visit.

Heart rate, PR interval, RR interval, QRS complex and QT interval will be recorded. Heart rate corrected QTc will be determined using Fridericia (QTcF) and Bazett (QTcB) formulae.

The average of the triplicate measurements will be used in the summaries of data by visit, however individual replicates and unscheduled data will be used in categorical analyses (e.g. determining number

of subjects with a QTcF ≥ 60ms). A categorical analysis will also be conducted based on the averages of the triplicate measurements.

Changes from baseline will be calculated for averaged triplicate data and for individual replicate data.

### 5.4.5 Echocardiogram (Cohorts 1 and 2)

Echocardiograms will be taken at screening, end of study and Weeks 24 and 48 during the first 48 weeks, and then 6 monthly during the extension phase. If a subject withdraws from the study prematurely they will also have it taken at the termination visit if not performed in the last 12 weeks.

The left ventricular ejection faction (LVEF), and the fractional shortening (FS) will be recorded. Changes from baseline will be calculated.

Additionally, the site will record if the echocardiogram is normal, abnormal–not clinically significant or abnormal-clinically significant. If abnormal-clinically significant the reason should also be recorded.

### 5.4.6 Physical Examination

Physical examinations will be conducted at various times during the study. Any clinically significant findings post-dose will be reported as adverse events.

Body weight and height will be measured when physical examinations are conducted. BMI will be derived.

Changes from baseline in weight, height and BMI will be calculated.

### 5.4.7 Pulmonary Assessment

Pulmonary assessments will be made at screening, end of study and Weeks 12, 24, 36 and 48 during the first 48 weeks and then 6 monthly during the extension phase. If a subject withdraws from the study prematurely they will also be assessed at the termination visit.

The predicted spirometry assessments will be adjusted for age and sex. Assessments will be adjusted for race as shown in the Table 1 of section 6.4.5 in the protocol. These adjustments are made at the site by the spirometry software.

$FEV_1$, FVC, MIP, MEP and PEF will be measured. Changes from baseline will be calculated.

## 5.5 Pharmacokinetics (PK)

Samples will be taken for the determination of SMT C1100, DHDI (SMT022346) and DHDIII (SMT022389) concentrations. The table below details the times when PK samples will be taken:

| Visit | Cohort | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Day 1 | Pre-AM and 3 and 6h post-AM | Pre-AM and 3 and 6h post-AM | Pre-AM and 3 and 6h post-AM |
| Day 7 | | 4h post-AM | 4h post-AM |
| Week 4 | Pre-PM and 4 and 10 h post-PM | Pre-PM and 4 and 10 h post-PM | Pre-AM and 3 and 6h post-AM |
| Week 8 | Pre-AM and 3 and 6h post-AM | Pre-AM and 3 and 6h post-AM | |
| Week 12 | Pre-AM and 3 and 6h post-AM | Pre-AM and 3 and 6h post-AM | Pre-AM and 3 and 6h post-AM |
| Week 24 | Pre-PM and 4 and 10 h post-PM | Pre-PM and 4 and 10 h post-PM | Pre-AM and 3 and 6h post-AM |
| Week 36 | Pre-AM and 3 and 6h post-AM | Pre-AM and 3 and 6h post-AM | Pre-AM and 3 and 6h post-AM |
| Week 48 | Pre-PM and 4 and 10 h post-PM | Pre-PM and 4 and 10 h post-PM | Pre-AM and 3 and 6h post-AM |
| Extension Visits | 4h post-AM | 4h post-AM | 4h post-AM |

These concentrations will be used in a population PK (pop-PK) model through which exposure parameters ($C_{max}$, $Ct_{rough}$, and $C_{av}$) will be predicted for each subject. The pop-PK model may be reported separately.

Concentrations below the lower limit of quantification (BLQ) will be taken as zero for the calculation of summary statistics for the concentration data.

# 6.0 Analysis Sets

## 6.1 Screened Population

The screened population will consist of all subjects who have written informed consent/assent. This population will only be used for summarizing disposition information.

## 6.2 Intention-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all subjects who received at least one dose of study medication.

## 6.3 Safety Population

The safety population is also defined as all subjects who received at least one dose of study medication.

### 6.4 Endpoint Populations

Separate populations will be identified for different sets of endpoints, based upon their baseline ability to be assessed for the relevant endpoints. These populations will be:

- Leg MRI/MRS Population *(Cohorts 1 and 2)*
- Cardiac MRI Population *(Cohort 3)*
- Biopsy Population
- Functional measures Population
- Blood Biomarker Population
- PK Population

All subjects in the ITT population will be included in each set if they also have at least one assessment of an endpoint in the set (which could be their baseline assessment).

Justification for exclusions from populations will be documented prior to reporting.

## 7.0 Interim Analyses

While the study is in progress, a Data Monitoring Committee (DMC) will conduct planned reviews of the study data to evaluate the safety, tolerability and activity of the study drug treatment. Detailed information can be found in the DMC Charter and Data Monitoring Analysis Plan.

An interim analysis will also be conducted when all subjects in Cohorts 1 and 2 have completed their Week 24 visit. This interim analysis will only include Cohort 1 and 2 efficacy and pharmacodynamic data till Week 24. All safety data from Cohorts 1 and 2 will be presented, though the key data for the interim analysis will be data reported till Week 24. The tables generated for the interim analysis are identified in the list of TFLs.

The main clinical study report (CSR) will be written when all subjects in Cohorts 1 and 2 have completed their Week 48 visit. This CSR will include all available data from these two cohorts (including extension data) and serious adverse event data from Cohort 3.

Further analyses will be conducted when all subjects in Cohort 3 have completed their Week 48 visit and prior to submission. The final reporting of data from this study will be conducted at the end of the study (when SMT C1100 is either approved in the relevant countries or development of SMT C1100 is discontinued).

## 8.0 Data Review

### 8.1 Data Handling and Transfer

Data will be entered into a Medidata Rave database and exported as SAS® version 9.4 datasets. Converted datasets will be created using SAS and following standard Clinical Data Interchange Standards Consortium Standard Data Tabulation Model (CDISC SDTM, version 1.3, Implementation Guide version v3.1.3) conventions. Analysis datasets will be created using SAS and following CDISC Analysis Data Model (ADaM, version 2.1, Implementation Guide 1.0) standards.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 on an ongoing basis to assign a system organ class (SOC) and preferred term (PT) to each event. Prior and concomitant medications and steroids will be coded using the World Health Organization Drug Dictionary WHO DDE B2 Dec_2015 (Enhanced) on an ongoing basis.

Additional details can be found in the PRA Coding Conventions and the Data Management Plan for this study.

## 8.2 Data Screening

In addition to the data cleaning described in the Data Management Plan, the programming of analysis datasets, tables, figures, and listings (TFLs) will include additional data reviews when data are extracted for reporting (e.g. DMC meetings and preparation of patient profiles). Presumed data issues will be extracted into SAS logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to Data Management.

Review of a pre-freeze TFL run and a post-freeze TFL run on the frozen database will allow for further data reviews prior to database lock. The post-freeze TFLs will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and the sponsor must approve the database lock.

A similar process will be followed for the different analyses described in Section 7, except on these occasions the database will only be frozen and not locked.

# 9.0 Statistical Methods

## 9.1 General

All statistical analyses will be performed using SAS (Version 9.4).

Unless otherwise specified, descriptive data summaries will be tabulated for all endpoints. Categorical data will be summarized using number of subjects (n), frequency and percentages of subjects falling into each category, with the denominator for percentages being the number of subjects in the study population, unless otherwise noted. Percentages will be rounded to one decimal place except for 100%, which will have no decimal place. Counts of zero will not display a percentage.

All continuous variables will be summarized using mean, standard deviation, median, Q1, Q3, minimum, maximum, and number of subjects with observations. The mean, median will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

For both categorical and continuous variables the number of missing values will be presented in summary tables and will be split by the number of missing values due to discontinuation of treatment and due to missing. Subjects will only be counted if they had the potential to reach the visit (e.g. a subject who has been in the study 48 weeks will not be considered as having a missing Week 60 visit). Their potential to reach a visit is based on the duration of time they could have been in the study, from their first dosing date till the datacut date. If a subject does not have a record for a visit and did not discontinue treatment, then the record will be counted as due to missing. For subjects who discontinue treatment then the date of discontinuation will be considered as the date of the last dose of study medication plus 1 day, any missing records prior to this date will be classed as missing and any missing records after this date will be

classed as discontinued. The target study day for a visit will be used to assess whether a subject could have had a visit prior to discontinuation of treatment.

Section 5 provides details of where efficacy data is imputed if the reason given for not performing or completing an assessment is related to the subject's medical condition (e.g. if a subject is physically unable to do the 6MWD then their distance will be imputed as 0). For such efficacy endpoints the number of imputed values will also be tabulated along with other descriptive statistics in summary tables.

Listings will present cohort as a sub-header. Unless otherwise specified, tabulations will present data for each cohort separately as well as all subjects.

In by-time summary tables the baseline will be summarized using all available data, but also for each visit using only the baseline data from subjects with available data at the visit; hence the mean change from baseline will equal the mean visit value – mean baseline value.

All data will be listed and will present study days in addition to dates. Dates will be presented in DDMMMYYYY format (e.g. 28Jul2017).

Listings will be sorted by cohort (used as sub-header), subject and, where appropriate, time.

### 9.1.1 Methods for Handling Dropouts and Missing Data

Imputation details concerning missing efficacy data where a subject has attended the relevant visit are discussed in Section 5. Where missing data is due to a missed visit values will not be imputed.

The imputation approaches for handling partial or missing start and/or end dates of AEs and concomitant medications are summarized in Appendix 2. Partial and missing AE or concomitant medication dates will be imputed with conservatism. Unless an AE is proven to occur prior to the first dose of the study drug, it will be considered to be a treatment-emergent adverse event (TEAE). Similarly, a medication with a missing stop date will be considered as concomitant medication unless there is obvious evidence that the stop date is prior to the first date of IMP treatment. If the day, or month and day, of the start date are not obviously before the date of first IMP treatment, then the start date will be imputed as the first day of the available month and or year, or the start date of IMP, whichever is later.

The imputed dates will be used to assess whether AEs should be considered to be treatment emergent, medications should be included in the safety summaries as prior and/or concomitant, and for the calculation of AE durations; however, the original partial/missing dates will be included in data listings.

Partial dates for age at diagnosis will also have the missing information imputed for the purposes of calculating the duration since diagnosis. The earliest date consistent with the information provided will be used.

### 9.1.2 Multiplicity

There will be no multiplicity adjustments for this study.

### 9.1.3 Pooling of Sites

All sites will be pooled together for the analyses.

## 9.2 Subject Disposition

The following disposition information will be tabulated:

- Number of subjects screened
- Number (%) of subjects who failed screening, along with reasons for failure
- Number (%) of subjects treated with study drug

- Number (%) of subjects who discontinued study treatment permanently before Weeks 24 and 48, along with reasons for discontinuing
- Number (%) of subjects who completed study treatment *(i.e. not identified as discontinuing study treatment).* This information will be split into two categories, those who complete the study treatment till the study itself closes and those who complete the study treatment till their Week 48 visit and decide not to enter the extension phase.
- Number (%) of subjects who withdrew from the study before Weeks 24 and 48, along with reasons for withdrawal
- Number (%) of subjects who completed the study *(including the end of study visit or approval/discontinuation visit).* This information will be split into two categories, those who complete the study till the study itself closes and those who complete the study till their Week 48 visit, decide not to enter the extension phase and have their follow-up visit (Week 52).
- Number (%) of subjects in each analysis population

Where percentages are presented the number of subjects treated will be used as the denominator, except for the number of subjects who failed screening, where the number screened will be used for the denominator.

If the study isn't terminated prior to Week 48 the study will continue until either SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued. For this reason the discontinuation reason 'study terminated by sponsor' will no longer be suitable as this will be the natural closure for the study.

The following will be presented for each scheduled visit:

- Number (%) of subjects who had the potential to reach the visit
- Number (%) of subjects who attended the visit
- Number (%) of subjects who discontinued treatment permanently prior to the visit
- Number (%) of subjects who withdrew from the study permanently prior to the visit
- Number (%) of subjects who missed the visit
- Number (%) of subjects who did not enter extension phase (only applicable for extension visits)

The potential for a subject to have reached a visit will be determined by calculating the duration between the data cut date and the subject's first dose date (i.e. data cut date – first dose date + 1), regardless of whether they withdraw from the study. If this duration is longer than the target study day for a visit, then the subject will be deemed to have had the potential to reach the visit. A check will also be made for subject's attending a visit earlier than the visit target day; if this is the case the subject will be included in the count of potential subjects.

For example, consider a data cut date of 1st December 2016

Subject X: has their first dose on 15th June 2016: the data cut date would be the subject's Study Day 170. Hence the subject could have reached the Week 24 visit (168 days).

Subject Y: has their first dose on 25th June 2016: the data cut date would be the subject's Study Day 160. Hence the subject was not scheduled to have reached the Week 24 visit. However, if they attended their Week 24 visit early (e.g. Day 158) they would be counted.

For percentages the number of subjects in the ITT/Safety populations will be used as the denominator.

## 9.3 Protocol Deviations and Violations

Protocol deviation data will be entered into the Clinical Trials Management System (CTMS). The study team will conduct on-going reviews of the protocol deviation data from CTMS.

Important protocol deviations (IPD) are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

The protocol deviation/violation (PDV) list will be finalized prior to the database freeze, and based on the PDV data entered into CTMS, the IPD will be listed and tabulated using incidence by deviation type.

## 9.4 Treatments

### 9.4.1 Drug Exposure

Summary statistics will be provided for total duration (days) of study drug exposure and treatment compliance for the safety population.

Total duration of study exposure in days is defined as (last dose date - first dose date+1).

The total duration of study exposure will also be summarized categorically by 4 week intervals; less than 4 weeks, 4(inclusive) to 8 (exclusive) weeks, and so on. The number of weeks will be derived as (total duration of study exposure/7).

For all 3 cohorts study medication compliance with the protocol will be calculated as (100*total number of days subject took their study medication/total duration of study exposure).

The total number of days the subject took their study medication will be determined by subtracting the days the subject didn't take their medication (as reported by the dose diary or CRF pages for clinic visits) from the duration of study exposure. Days where a subject was instructed not to take their dose, recorded in the eCRF (patient dose regimen), should be excluded from the calculation of compliance; if a subject is instructed by the site to not take their dose it isn't a compliance issue.

Additionally, for Cohorts 1 and 3, compliance will also be assessed from the planned weights of IMP used. Compliance will be calculated as 100*weight used (added across bottles dispensed)/( total duration of study exposure*weight per day)

Weight of bottles is recorded in g. Each day the subject should be taking 5g (if they haven't had a dose reduction) – i.e. 2 doses of 2500mg.

As every 1g of IMP contains 200mg of SMT C1100 the planned weight of medication is calculated as follows:

Planned weight of medication = (1000/200) x Number of days x Daily dose

If the subject changes their dose, then appropriate adjustments are required for their duration on each dose level. Similarly, an adjustment should be made if a subject is instructed not to take their dose.

If bottles are not returned the subject's compliance should be provided as a range – the lower value assuming they took none of the material from these bottles and the higher value assuming they used all of it.

Subjects will be considered compliant with the protocol if they take ≥ 80% of their medication as scheduled. The compliance values derived by the above two approaches will also be summarized categorically by groups of 'less than 80%', 'greater or equal to 80% but less than 95%' and 'greater than or equal to 95%'.

A subject listing of study drug accountability, dosing diary, in-clinical visit dosing and study medication compliance will be provided.

Dose regimens will be detailed in a listing. The listing will detail the dosing regimen start/stop study days and duration. The number of subjects with a dose reduction, dosing regimen change, temporary cessation of treatment or permanent cessation of treatment will be tabulated.

### 9.4.2 Prior and Concomitant Medications/Procedures

Prior/concomitant medications will be summarized by Anatomic Therapeutic Classification (ATC) class and preferred name. The analysis will be performed using the Safety population. Summaries will be presented for all medications and also specifically for steroids taken for DMD. The summaries will include the steroids taken for DMD by boys participating in the FOR-DMD study (recorded in DMD history page of eCRF); their data will be presented in a separate listing.

The numbers (%) of subjects using each medication will be displayed. Subjects taking more than one medication in the same ATC class or preferred name will be counted once for the number of subjects taking that preferred name.

Medications will be split into two groups, by clinical review; those taken specifically for the anaesthetics related to the biopsy procedure and all others. Separate listings will be generated for each group.

Separate concomitant medication summaries (all medications and steroid medications) will be generated for the first 24 weeks, first 48 weeks and for the whole study.

## 9.5 Demographic and Baseline Characteristics

Demographics, baseline disease characteristics, baseline measurements will be summarized using descriptive statistics for continuous variables and frequency distributions for discrete variables, using the Safety population.

Demographics will include:

- Age (Age at screening is recorded, but age on Day 1 of dosing will be derived* and summarized in the demography summary table. The subject's age on Day 1 will also presented, as an integer, in subject listings).
- Race
- Country
- Ethnicity
- Weight
- Height
- BMI
- Lean body mass (using Peter's formula = 3.8 × eECV, where estimated Extracellular Fluid Volume (eECV) = 0.0215 × [weight(kg)]$^{0.6469}$ × [height(cm)]$^{0.7236}$)

* Subject's age on Day 1 will be derived as (date of first dose – date of birth)/365.25.

The baseline disease characteristics will include:

- Duration of DMD in years (derived as, date of first dose – date of diagnosis +1)
- Age at Diagnosis (derived as, date of diagnosis – date of birth +1)

- Whether the subject has participated in any other DMD studies in 12 months prior to enrollment
- Participation in the FOR-DMD study

For the calculation of duration of DMD and age at diagnosis partial dates will be imputed using the earliest date that is consistent with the information available.

The baseline measurements will include:

- 6MWD (last measurement before dosing)
- NSAA total score
- NSAA linearized score
- 10 metre run/walk
- Time to stand
- PUL dimension and total scores
- PODCI sub-scales and global scores
- MRI parameters (the Vastus Lateralis and Soleus MRS fat fractions [MRS_FF_VL & MRS_FF_SOL] and water transverse relaxation times [MRS_T2_VL & MRS_T2_SOL)
- %MHCd positive (biopsy)
- Fibre diameter – mean
- Utrophin intensity – mean
- Utrophin heterogeneity score
- $FEV_1$ and FVC

The correlation between these baseline characteristics will also be tabulated. Age will be included.

In addition to summarizing the 6MWD as a continuous variable the number (%) of subjects in the following categories will be tabulated for the 6MWD and %-predicted 6MWD:

- 6MWD: < 300m, ≥300m and < 350m, ≥350m and < 400m, ≥400m
- <50% predicted, ≥50% and <70% predicted, ≥70 and <80% predicted, and ≥80% predicted

Similarly, in addition to summarizing the Vastus Lateralis and Soleus MRS fat fractions as a continuous variable the number (%) of subjects in the following categories will be tabulated:

- < 10%, ≥10% and < 20%, ≥ 20% and < 30%,≥ 30% and < 40%, ≥40% and < 50%, ≥50% and < 60%, ≥60%.

Medical history data will be summarized by SOC and PT.

## 9.6 Efficacy Analyses

### 9.6.1 General

All analyses will be performed on the functional measures population.

Tabulations will be over all Cohorts 1 and 2 subjects and will not provide separate information for the two cohorts. Cohort 3 data will be summarized separately. In addition to the standard set of descriptive statistics summaries will also tabulate the number of subjects where their value has been imputed (see Section 9.1). The 95% confidence interval will also be included for the mean changes from baseline.

Box and whisker plots will display the Baseline, Weeks 12, 24, 36 and Week 48 data.

Mean changes from baseline, with associated 95% confidence intervals, will be plotted against visit. As visits in the extension phase will be included the plot will also include the n contributing to the visit.

The velocity of change per month will be assessed for specific endpoints. Velocities will be estimated using mixed effect models of the absolute values, including baseline. The model will include visit as a fixed effect term and subject as a random effect term. The following will be estimated along with 95% confidence intervals:

Velocity (12-B): (Week 12 – Baseline)/3

Velocity (24-12): (Week 24 – Week 12)/3

Velocity (36-24): (Week 36 – Week 24)/3

Velocity (48-36): (Week 48 – Week 36)/3

And

Velocity (24-B): (Week 24 – Baseline)/6

Velocity (48-24): (Week 48 – Week 24)/6

…

The following differences between velocities will also be estimated along with 95% confidence intervals:

Velocity (24-12) – Velocity (12-B)

Velocity (36-24) – Velocity (12-B)

Velocity (48-36) – Velocity (12-B)

And

Velocity (48-24) – Velocity (24-B)

..

### 9.6.2 Six-Minute Walk Distance

Screening and baseline data will be plotted using a Bland-Altman plot to assess their agreement for both the 6MWD and the %-predicted 6MWD. If there is agreement between the two measurements the average will be used as baseline for other analyses; otherwise the last measurement prior to dosing will be used. Note: These data have been reviewed and the decision was taken to use the last measurement before dosing.

Observed values and changes from baseline will be summarized by visit using descriptive statistics for both the 6MWD and the %-predicted 6MWD.

The number and percentage of subjects using orthoses or aids will be summarized by visit using a shift table from baseline. Marginal totals will be included. Similarly, the number and percentage of subjects having falls or having the follower providing support will be summarized using a shift table.

The velocities of change will be summarized using descriptive statistics. Velocities of change will also be analyzed using the methods described in Section 9.6.1.

Individual subject data will be plotted against age as individual line plots (spaghetti plots).

Week 12, 24, 36 and 48 changes from baseline will also be plotted against age on Day 1 and baseline, using different symbols to identify the Week. The Pearson correlation coefficient (for each week) will be footnoted on the plots.

The time till a 10% reduction in 6MWD will be plotted using a Kaplan-Meier curve and estimated proportions will be tabulated over time.

### 9.6.3 North Star Ambulatory Assessment

Scores and changes from baseline will be summarized by visit using descriptive statistics for both the total score and the linearized score.

The individual activity scores will be summarized by visit using a shift table from baseline. Marginal totals will be included.

The number (percentage) of subjects who have lost 0, 1, 2…activities will be tabulated by visit.

The velocities of change for the total score will be summarized using descriptive statistics. Velocities of change will also be analyzed using the methods described in Section 9.6.1.

The 6MWD and NSAA total score changes from baseline will be plotted together against visit in trellis plots with one subject per plot. The two parameters will have different y-axes and a legend will be provided to distinguish 6MWD and NSAA lines on the plot.

Individual subject total scores will be plotted against age as individual line plots (spaghetti plots).

Week 12, 24, 36 and 48 changes from baseline for the total scores will also be plotted against age on Day 1 and baseline, using different symbols to identify the Week. The Pearson correlation coefficient (for each week) will be footnoted on the plots.

The box and whisker and mean change from baseline plots will only be presented for the total scores.

The number and percentage of subjects who lose ambulation will be summarized by visit.

### 9.6.4 10-Metre Run/Walk

Scores and changes from baseline will be summarized by visit using descriptive statistics.

The velocities of change will be summarized using descriptive statistics. Velocities of change will also be analyzed using the methods described in Section 9.6.1.

Individual subject data will be plotted against age as individual line plots (spaghetti plots).

Week 12, 24, 36 and Week 48 changes from baseline will also be plotted against age on Day 1 and baseline, using different symbols to identify the Week. The Pearson correlation coefficient (for each week) will be footnoted on the plots.

### 9.6.5 Time to Stand

Scores and changes from baseline will be summarized by visit using descriptive statistics.

The velocities of change will be summarized using descriptive statistics. Velocities of change will also be analyzed using the methods described in Section 9.6.1.

Individual subject data will be plotted against age as individual line plots (spaghetti plots).

Week 12, 24, 36 and Week 48 changes from baseline will also be plotted against age on Day 1 and baseline, using different symbols to identify the Week. The Pearson correlation coefficient (for each week) will be footnoted on the plots.

### 9.6.6 PODCI

Scores and changes from baseline will be summarized by visit using descriptive statistics for each scale's standardized score and the global functioning scale score.

Individual subject global function scale score data will be plotted against age as individual line plots (spaghetti plots).

The box and whisker and mean change from baseline plots will only be presented for the global functioning scale score.

### 9.6.7 PUL

Scores and changes from baseline will be summarized by visit using descriptive statistics for each dimension and the total score.

Individual subject total score data will be plotted against age as individual line plots (spaghetti plots).

Week 12, 24, 36 and Week 48 changes from baseline in the total score will also be plotted against age on Day 1 and baseline, using different symbols to identify the Week. The Pearson correlation coefficient (for each week) will be footnoted on the plots.

## 9.7 Pharmacodynamics Analyses

### 9.7.1 Leg MRI/MRS (Cohorts 1 and 2)

All analyses will be performed using the Leg MRI/MRS population.

Tabulations will be over all subjects and will not provide separate information for the different cohorts.

Absolute values and changes from baseline will be summarized by visit for each of the 10 parameters. The 95% confidence interval will also be included for the mean changes from baseline.

The MRS fat fractions for the Vastus Lateralis and Soleus will be summarized by visit using a shift table from baseline. Marginal totals will be included. The categories used will be < 10%, ≥10% and < 20%, ≥ 20% and < 30%,≥ 30% and < 40%, ≥40% and < 50%, ≥50% and < 60%, ≥60%.

Vastus Lateralis and Soleus MRS fat fraction and T2 parameters

The following outputs will only be presented for the Vastus Lateralis and Soleus MRS fat fraction and T2 parameters.

The velocities of change will be summarized using descriptive statistics. Velocities of change will also be analyzed using the methods described in Section 9.6.1.

Individual subject data will be plotted against age as individual line plots (spaghetti plots) for each parameter.

Box and whisker plots will display the Baseline, Week 12, Week 24, Week 36 and Week 48 data.

Mean changes from baseline, with associated 95% confidence intervals, will be plotted against visit. As visits in the extension phase will be included the plot will also include the n contributing to the visit.

Week 12, 24, 36 and 48 changes from baseline will also be plotted against age on Day 1 and baseline, using different symbols to identify the Week. The Pearson correlation coefficient (for each week) will be footnoted on the plots.

The changes from baseline for parameters will be plotted against one another for Weeks 12, 24, 36 and 48 data. The week will be identifiable using different symbols. The Pearson correlation coefficients (for each week) will also be presented in the footnote of the plots.

The MRS fat fractions will be plotted against the corresponding MRI fat fractions and the MRS T2 values will be plotted against the corresponding MRI T2 values for the Vastus Lateralis and Soleus muscles. Absolute values will be plotted with different symbols used for each visit. The plot will be repeated for changes from baseline.

### 9.7.2 Cardiac MRI (Cohort 3)

All analyses will be performed using the Cardiac MRI population.

Details concerning the analyses of the cardiac MRI parameters will be added in a later version of the SAP.

### 9.7.3 Fibre Regeneration (via Biopsy) (Cohorts 1 and 2)

All analyses will be performed on the Biopsy population.

Tabulations will be over all subjects and will not provide separate information for the different cohorts.

Imputation will not be used for missing data with summaries and plots, and so subjects with missing baseline or Week 24/48 data will be excluded from presentations for the relevant time-point and change from baseline presentations. However, mixed effect models will be used to make comparisons to baseline; these analyses will use all available data and adjusts the results for missing data under the assumption of missing at random.

Summary tables will acknowledge the number of subjects who have their biopsy performed at Week 24 and Week 48 (e.g. if a subject isn't supposed to have a Week 24 measurement it will not be counted as missing).

The total number of fibres assessed with each assay will be summarized using descriptive statistics (n, median, Q1, Q3, minimum and maximum) by visit. These variables won't be included in any other analyses.

The percentage of fibres (%fibre) with 0, 1, 2 and 3 MHCd/Utrophin intensity will be excluded from analyses unless specifically mentioned.

For each assay (Myosin and Utrophin) the number of subjects contributing 1 or 2 samples worth of data will be tabulated for each visit for each of the two groups (Week 24 and Week 48). Where there is 1 sample with data the number of subjects with 1, 2 and 3 sections will be tabulated and where there are 2 samples with data the number of subjects with 2, 3, 4, 5 and 6 sections will be tabulated.

#### 9.7.3.1 Developmental Heavy Chain Myosin (MHCd), Utrophin Expression and Fibre Diameter

Absolute values and changes from baseline in parameters (including % fibre parameters) will be summarized for the Week 24 and Week 48 visits separately.

The change in parameters at Week 24 and Week 48 will also be estimated using a mixed effects model that acknowledges the random effects of subject, samples within subjects and sections for each sample. Visit (Baseline and the relevant Week) will be fitted as a fixed effect and the change from baseline estimated along with its 95% confidence interval. Week 24 and Week 48 data will be analyzed separately.

The mean percentage of fibres with intensity scores of 1, 2 and 3 (i.e. excluding 0), for Myosin and Utrophin, will be plotted as stacked bar charts by visit – with the baselines for the two groups (Week 24 or Week 48) presented separately.

%MHCd, Fibre Diameter (mean), Utrophin Intensity (mean) and Utrophin Heterogeneity Score

The following plots will be presented for %MHCd, fibre diameter (mean), Utrophin intensity (mean) and Utrophin heterogeneity score.

Individual subject data will be plotted against visit as individual line plots (spaghetti plots).

Week 24 and Week 48 changes from baseline will also be plotted against age on Day 1 and baseline, using different symbols to identify the Week. The Pearson correlation coefficient (for each week) will be footnoted on the plots.

Plots will also be produced for each subject against visit showing each section result within each sample. The sample will be identifiable by the symbol used.

Waterfall plots will be presented for Week 48 changes from baseline and box and whisker plots will display the Baseline, Week 24 and Week 48 data. As subjects only have data collected at either Week 24 or Week 48 the baseline data will be presented separately for these two groups.

Mean changes from baseline, with associated 95% confidence intervals, will be plotted against visit.

#### 9.7.3.2 % Necrosis/Inflammation, % Regeneration, % Fat and % Collagen

Absolute values and changes from baseline in each parameter will be summarized for the Week 24 and Week 48 visits separately.

The change in each parameter will also be estimated using a mixed effects model, fitting a fixed effect for visit (Baseline and the relevant Week) and random effects for subject and sample within subjects for each visit. The change from baseline will be estimated along with its 95% confidence interval.

#### 9.7.3.3 Relationship Between Parameters

The changes from baseline for parameters (will be plotted against one another for Week 24 and Week 48 data. Week 24 and Week 48 data will be identifiable using different symbols. The Pearson correlation coefficients (for each week) will also be presented in the footnote of the plots.

### 9.7.4 Blood Biomarkers

All analyses will be performed on the Blood Biomarker population.

Biomarkers will be summarized by visit, along with their changes from baseline.

A decision was made to cease collecting MMP9, FGF19 and C4 after Week 48. Consequently, these data will only be summarized up to the Week 48 visit. Any data collected from subjects after Week 48 will be included in the listing.

## 9.8 Safety Analyses

### 9.8.1 Adverse Events

All safety analyses will be performed on the Safety population.

The listing of AEs will include the duration of the AE. It will be flagged if this is derived using imputed dates.

An overall summary will present the number (%) of subjects with:

- any TEAE

- any TEAE considered as related to study drug
- any serious TEAE
- Maximum intensity TEAE of none, mild, moderate, severe ; i.e. a subject with TEAEs at different intensities will be summarized at the most severe intensity
- any TEAE leading to study drug discontinuation
- any TEAE leading to death

The table will also include the total number of TEAEs reported and the total number of unique terms. For unique terms a preferred term will only be counted once within a subject.

Subject incidence of the following AEs will be tabulated by SOC (descending order of frequency) and PT (descending order of frequency):

- TEAEs
- treatment-related TEAEs
- maximum severity of TEAEs

Subject incidence of the following AEs will be tabulated by PT in descending order of frequency:

- TEAEs
- treatment-related AEs

Separate summaries will be generated for the first 24 weeks, first 48 weeks and for the whole study.

Serious TEAEs and TEAEs leading to discontinuation of study drug will be provided in by-subject listings.

Subjects will be counted only once within each SOC or PT. For tables categorized by severity, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event for that SOC or PT.

### 9.8.2 Deaths and Serious Adverse Events

Subject listings of serious TEAEs, including treatment-emergent fatal AEs, will be provided.

### 9.8.3 Laboratory Data

Descriptive summaries of absolute values and changes from baseline will be provided for numerical laboratory parameters for each visit. At each visit the number of subjects with ‘High’, ‘Low’ or ‘Normal’ with respect to their reference range will be tabulated.

The categorical lab results will only be listed.

The number (%) of subjects who fulfill the following liver function test criteria at any time after the start of dosing will be tabulated:

- ALT ≥ ULN, ≥ 2 x ULN, ≥3 x ULN
- AST ≥ ULN, ≥ 2 x ULN, ≥3 x ULN
- Total Bilirubin ≥ ULN, ≥ 2 x ULN
- alkaline phosphatase ≥1.5x ULN
- GLDH ≥ ULN

The number (%) of subjects who fulfill Hy’s Law (ALT or AST > 3x ULN + bilirubin > 2x ULN, Alkaline Phosphatase must also be ≤ULN) will also be tabulated.

Separate summaries will be generated for the first 24 weeks, first 48 weeks and for the whole study.

These parameters will be listed, along with the value related to ULN (i.e. value/ULN) for subjects who fulfill one of the following criteria:

- ALT ≥ 2 x ULN
- AST ≥ 2 x ULN
- Total Bilirubin ≥ 2 x ULN
- alkaline phosphatase ≥1.5x ULN
- GLDH ≥ ULN

For each liver function test (ALT, AST, total bilirubin, alkaline phosphatase, GLDH) and creatine kinase, the value related to ULN (i.e. value/ULN) will be plotted against time in trellis plots, where each subject will have their own plot and the legend distinguishing the laboratory parameter. The plot will use a log10 scale with the axis labels reflecting the actual value (e.g. 1, 10, 100…).

For Cohort 2 the number (%) of subjects who fulfill the following coagulation test criteria at any time after the start of dosing will be tabulated:

- International Normalised Ratio ≥ 1.5x ULN
- Activate Partial Thromboplastin > ULN

Separate summaries will be generated for the first 24 weeks, first 48 weeks and for the whole study.

A listing will also present all data that meet these criteria along with the value related to ULN (i.e. value/ULN).

### 9.8.4 Vital Signs

Observed values, baseline and changes from baseline will be summarized by visit for each vital sign parameter.

The number (%) of subjects meeting the following criteria at any time after the start of dosing will also be tabulated for systolic BP, diastolic BP and pulse:

- All values within 20% of change from baseline
- At least one value ≥ 20% reduction from baseline, but no increases ≥ 20% from baseline
- At least one value ≥ 20% increase from baseline, but no reductions ≥ 20% from baseline
- At least one value ≥ 20% reduction from baseline and at least one value ≥ 20% increase from baseline

This summary will present data for the first 24 weeks, first 48 weeks and the whole study.

Values displaying a ≥ 20% change from baseline will be flagged in the listings, with the flag identifying if it is a reduction or increase from baseline.

### 9.8.5 Twelve-Lead Electrocardiogram

Observed values, baseline and changes from baseline will be summarized by visit for each ECG parameter.

The number (%) of subjects meeting the following criteria at any time after the start of dosing will also be tabulated:

Maximum PR interval

- < 170ms
- ≥ 170ms

Also

- All values within 20% of change from baseline
- At least one value ≥ 20% reduction from baseline, but no increases ≥ 20% from baseline
- At least one value ≥ 20% increase from baseline, but no reductions ≥ 20% from baseline
- At least one value ≥ 20% reduction from baseline and at least one value ≥ 20% increase from baseline

Heart Rate

- All values within 20% of change from baseline
- At least one value ≥ 20% reduction from baseline, but no increases ≥ 20% from baseline
- At least one value ≥ 20% increase from baseline, but no reductions ≥ 20% from baseline
- At least one value ≥ 20% reduction from baseline and at least one value ≥ 20% increase from baseline

Maximum QTcF

- < 450ms
- ≥ 450ms

Maximum increase from baseline in QTcF

- < 30ms
- 30ms - < 60ms
- ≥ 60ms

This summary will present data for the first 24 weeks, first 48 weeks and the whole study.

The number (%) of subjects with ECG results in the following categories (per the investigator's interpretation) will be presented by visit/time point:

- normal
- abnormal - not clinically significant
- abnormal - clinically significant

The listing of ECG data will present the replicate data separately from the 'mean of replicate' data.

Values meeting the criteria of potential concern above will be flagged in listings.

Further analyses of QT, QTcF and Heart Rate, and PK:PD modelling investigating any relationship with exposure will be detailed in a separate QT analysis plan for the project and reported in a separate ECG report.

### 9.8.6 Echocardiogram (Cohorts 1 and 2)

The observed values and changes from baseline will be summarized for each parameter (LVEF and SF) by visit.

The number (%) of subjects with normal and abnormal assessments will be tabulated by visit.

### 9.8.7 Physical Examination

Weight and BMI values and changes from baseline in weight and BMI will be summarized by visit.

The number (%) of subjects with physical examination results in the following categories will be presented by body system and visit:

- normal
- abnormal - not clinically significant
- abnormal - clinically significant

### 9.8.8 Pulmonary Assessment

The predicted spirometry assessments will be adjusted for age and sex by the site. Assessments will be adjusted for race as shown in the Table 1 of Section 6.4.5 in the protocol. The observed values and changes from baseline will be summarized for each parameter by visit.

Individuals data will be plotted over time for each parameter and box and whisker plots will be presented for the changes from baseline against visit.

## 9.9 Pharmacokinetic Analyses

Plasma concentrations of SMT C1100, DHDI and DHDIII will be summarized (n, median, minimum and maximum) by cohort, visit and time-point. The summaries will also present the median and the number of subjects who have plasma concentrations below the lower limit of quantification (LLOQ). The SMT C1100 summary will also include the number of subjects achieving SMT C1100 concentrations of ≥30 ng/mL and ≥ 70 ng/mL.

The concentration listings will present the data as <LLOQ with the actual limit of quantification value presented.

Individual concentration-time plots will be presented in trellis plots for SMT C1100 and metabolites separately. A log10 scale will be used for the concentration axis. The plots will identify the subject's cohort.

The metabolite ratios (DHDI/SMT C1100 and DHDIII/SMT C1100) will also be plotted over time and will be summarized by cohort, visit and time-point.

Pop-PK analyses are described in a separate Pop-PK analysis plan and may be reported separately.

Observed Week 12 $C_{trough}$ and simulated $C_{max}$ and $C_{av}$ parameters will be summarized. The number of subjects achieving SMT C1100 levels ≥30 ng/mL, ≥ 70 ng/mL will also be reported for each parameter.

## 9.10 Relationship Analyses (Cohorts 1 and 2)

### 9.10.1 Relationship with SMT C1100 and Metabolite Exposures

The following Week 12, 24, 36 and 48 data will be plotted against SMT C1100 concentrations:

- MRI parameter changes from baseline (MRS fat fractions for the Vastus Lateralis and Soleus, and MRS T2 for Vastus Lateralis and Soleus)
- %MHCd change from baseline * (Weeks 24 and 48 only)

- Fibre diameter (mean) change from baseline * (Weeks 24 and 48 only)
- Utrophin intensity (mean) change from baseline * (Weeks 24 and 48 only)
- Utrophin heterogeneity score change from baseline * (Weeks 24 and 48 only)
- 6MWD change from baseline
- NSAA (total) change from baseline
- 10 metre walk/run duration change from baseline
- Time to stand change from baseline
- PUL total score change from baseline
- PODCI global function scale change from baseline

* based on average values across samples/sections (Section 5.3.2).

For a visit, the above response will be plotted separately with relevant observed Week 12 $C_{trough}$ and the simulated parameters $C_{max}$ and $C_{av}$.

The Pearson correlation coefficients (for each week) will also be presented in the footnote of the plots.

These plots will also be produced for the metabolites DHDI and DHDIII.

Any other exposure response modeling conducted will be reported separately.

### 9.10.2 Relationship with MRS parameters

The following Week 12, 24, 36 and 48 data will also be plotted against the MRS parameter changes from baseline (MRS fat fractions and T2s for the Vastus Lateralis and Soleus) for Weeks 12, 24, 36 and 48:

- %MHCd change from baseline * (Weeks 24 and 48 only)
- Fibre diameter (mean) change from baseline * (Weeks 24 and 48 only)
- Utrophin intensity (mean) change from baseline * (Weeks 24 and 48 only)
- Utrophin heterogeneity score change from baseline * (Weeks 24 and 48 only)
- 6MWD change from baseline
- NSAA (total) change from baseline
- 10 metre walk/run duration change from baseline
- Time to stand change from baseline
- PUL total score change from baseline
- PODCI global function scale change from baseline

* based on average values across samples/sections (Section 5.3.2).

Week 12, 24, 36 and 48 data will be identifiable using different symbols.

The Pearson correlation coefficients (for each week) will also be presented in the footnote of the plots.

### 9.10.3 Relationship with Biopsy Parameters

The following Week 24 and 48 data will also be plotted against the %MHCd, Fibre diameter (mean), Utrophin intensity (mean), Utrophin heterogeneity score, (changes from baseline (based on average values across samples/sections [Section 5.3.2]):

- 6MWD change from baseline
- NSAA (total) change from baseline
- 10 metre walk/run duration change from baseline

- Time to stand change from baseline
- PUL total score change from baseline
- PODCI global function scale change from baseline

Week 24 and Week 48 data will be identifiable using different symbols.

The Pearson correlation coefficients (for each week) will also be presented in the footnote of the plots.

### 9.10.4 Relationship with Functional Measures of Activity

The following Week 12, 24, 36 and 48 data will also be plotted against each other:

- 6MWD change from baseline
- NSAA (total) change from baseline
- 10 metre walk/run duration change from baseline
- Time to stand change from baseline
- PUL total score change from baseline
- PODCI global function scale change from baseline

Week 12, 24, 36 and 48 data will be identifiable using different symbols.

The Pearson correlation coefficients (for each week) will also be presented in the footnote of the plots.

## 10.0 Changes from Planned Analyses

This analysis plan provides further information to that provided in the study protocol.

Changes from the planned analyses in the protocol include:

- Protocol Section 12.1.3 states that, as the study is open-label, the data will be explored on a regular basis by the sponsor. A data access plan has been written that provides details concerning data accessibility to the study data by company individuals whilst the study is ongoing.
- Protocol Section 12.1.4.2 mentions that PK parameters will be used as the exposure parameters when investigating the relationship with other data. Instead the maximum concentration recorded at the relevant visit will be used in these analyses.
- Cohort 3 efficacy data will not be combined with Cohort 1 and 2 data in any analyses.
- The SAP doesn't currently provide details concerning cardiac MRI parameters or the investigation of the relationship of exposure with changes in pulmonary function parameters and blood biomarkers. This detail will be added in a later version.

Important changes from Version 1.0 of the SAP:

- Inclusion of Week 12 and Week 36 data in plots looking at the relationships between efficacy and pharmacodynamic endpoints and also their relationships with pharmacokinetic endpoints and demographics.
- Inclusion of all safety data for the first interim analysis.

- Exclusion of Dystrophin mutation type from the baseline disease characteristic summary.
- Inclusion of FOR-DMD subject's steroid data in steroid use summaries.
- Adjustment of windows to allow a wider window for Weeks 4 and 8, and to allow all available post baseline biopsy data to be included.
- Imputation method for missing activity scores from the NSAA which is only partially completed.

Important changes from Version 2.0 of the SAP:

- Inclusion of fibre diameter and utrophin expression parameters.
- Functional endpoint data from Cohort 3 will not be combined with data from Cohorts 1 and 2.
- Clarification concerning the CSR when Cohorts 1 and 2 have completed their Week 48 visit.
- Inclusion of NSAA total score plots, sometimes replacing those for the NSAA linearized scores.
- Inclusion of waterfall plots, box and whisker plots and mean change from baseline plots for specified endpoints.
- Inclusion of PK parameters (observed [Week 12 $C_{trough}$] and simulated [$C_{max}$ and $C_{av}$])
- Reduction in the number of relationship plots – focusing on most important endpoints.
- Clarification concerning the reporting of blood biomarker data.

# 11.0 Validation

The programming (including quality control) of the analysis datasets and TFLs will be conducted under PRA's standard processes PRS 050 and documented accordingly. The entire set of TFLs will be checked for completeness and consistency prior to its delivery to the client by the lead statistician and a senior level statistician, or above, who is not a member of the project team.

The PRA validation process will be repeated any time the TFLs are redelivered using different data. Execution of this validation process will be documented through the study Table of Programs.

# 12.0 References

Geiger R, Strasak A, Treml B, Gasser K, Kleinsasser A, Fischer V, et al. Six-minute walk test in children and adolescents. Journal of Pediatrics, Volume 150, Number 4, April 2007, Pages 395-399.

Marika Panea, Elena S. Mazzonea, Lavinia Fanellia, etc. Reliability of the Performance of Upper Limb assessment in Duchenne muscular dystrophy, Neuromuscular Disorders, Volume 24, Issue 3, March 2014, Pages 201–206

Mayhew A, Cano S, Scott E, Eagle M, Bushby K, Manzur A & Muntoni F, on behalf of the North Star Network for Neuromuscular Disease. Detecting meaningful change using the North Star Ambulatory Assessment in Duchenne muscular dystrophy. Developmental Medicine & Child Neurology, Volume 55, Issue 11, November 2013 Pages 1046–1052

# Appendix 1 Glossary of Abbreviations

| Glossary of Abbreviations: | |
|---|---|
| **6MWD** | six-minute walk distance |
| **AE** | adverse event |
| **ALT** | alanine aminotransferase |
| **AST** | aspartate aminotransferase |
| **ATC** | Anatomic Therapeutic Classification |
| **AUC** | area under the curve |
| **BMI** | body mass index |
| **BP** | blood pressure |
| **C4** | 7α-hydroxy-4-cholesten-3-one |
| **CRF** | case report form |
| **CTMS** | Clinical Trials Management System |
| **DMC** | Data Monitoring Committee |
| **DMD** | duchenne muscular dystrophy |
| **ECHO** | echocardiogram |
| **ECG** | electrocardiogram |
| **$FEV_1$** | forced expiratory volume in 1 second |
| **FGF19** | fibroblast growth factor 19 |
| **FS** | fractional shortening |
| **FVC** | forced vital capacity |
| **GLDH** | glutamate dehydrogenase |
| **IMP** | investigational medicinal product |
| **ITT** | Intention-to-Treat |
| **LLOQ** | lower limit of quantification |
| **LVEF** | left ventricular ejection fraction |
| **MEP** | maximum expiratory pressure |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MHCd** | developmental heavy chain myosin |
| **MIP** | maximum inspiratory pressure |
| **MRI** | magnetic resonance imaging |
| **MRS** | magnetic resonance spectroscopy |
| **NSAA** | North Star Ambulatory Assessment |

| | |
|---|---|
| **PCF** | peak cough flow |
| **PEF** | peak expiratory flow |
| **PK** | pharmacokinetic |
| **PODCI** | Paediatric Outcomes Data Collection Instrument |
| **PT** | preferred term |
| **PUL** | Performance of Upper Limbs |
| **QTcB** | QT interval, heart rate corrected using Bazett's formula |
| **QTcF** | QT interval, heart rate corrected using Fridericia's formula |
| **SI** | international system of units |
| **SNIP** | sniff nasal inspiratory pressure |
| **SOC** | system organ class |
| **TEAE** | treatment-emergent adverse event |
| **TFLs** | tables, figures and listings |
| **ULN** | upper limit of normal |

# Appendix 2: NSAA Score Sheet

| Activity | 2 | 1 | 0 |
|---|---|---|---|
| **1. Stand** | Stands upright, still and symmetrically, without compensation (with heels flat and legs in neutral) for minimum count of 3 seconds | Stands still but with some degree of compensation (e.g. on toes or with legs abducted or with bottom stuck out) for minimum count of 3 seconds | Cannot stand still or independently, needs support (even minimal) |
| **2. Walk** | Walks with heel-toe or flat-footed gait pattern | Persistent or habitual toe walker, unable to heel-toe consistently | Loss of independent ambulation – may use KAFOs or walk short distances with assistance |
| **3. Stand up from chair** | Keeping arms folded<br>Starting position 90º hips and knees, feet on floor/supported on a box step. | With help from thighs or push on chair or prone turn | Unable |
| **4. Stand on one leg - right** | Able to stand in a relaxed manner (no fixation) for count of 3 seconds | Stands but either momentarily or needs a lot of fixation e.g. by knees tightly adducted or other trick | Unable |
| **5. Stand on one leg - left** | Able to stand in a relaxed manner (no fixation) for count of 3 seconds | Stands but either momentarily or needs a lot of fixation e.g. by knees tightly adducted or other trick | Unable |
| **6. Climb box step - right** | Faces step – no support needed | Goes up sideways or needs support | Unable |
| **7. Climb box step - left** | Faces step – no support needed | Goes up sideways or needs support | Unable |
| **8. Descend box step - right** | Faces forward, climbs down controlling weight bearing leg. No support needed | Sideways, skips down or needs support | Unable |
| **9. Descend box step -left** | Faces forward, climbs down controlling weight bearing leg. No support needed | Sideways, skips down or needs support | Unable |
| **10. Gets to sitting** | Starts in supine – may use one hand to assist | Self assistance e.g. – pulls on legs or uses head-on-hands or head flexed to floor | Unable |
| **11. Rise from floor** | From supine – no evidence of Gowers' manoeuvre* | Gowers' evident | (a) NEEDS to use external support object e.g. chair OR (b) Unable |
| **12. Lifts head** | In supine, head must be lifted in mid-line. Chin moves towards chest | Head is lifted but through side flexion or with no neck flexion | Unable |
| **13. Stands on heels** | Both feet at the same time, clearly standing on heels only (acceptable to move a few steps to keep balance) for count of 3 | Flexes hip and only raises forefoot | Unable |
| **14. Jump** | Both feet at the same time, clear the ground simultaneously | One foot after the other (skip) | Unable |
| **15. Hop right leg** | Clears forefoot and heel off floor | Able bend knee and raise heel, no floor clearance | Unable |
| **16. Hop left leg** | Clears forefoot and heel off floor | Able bend knee and raise heel, no floor clearance | Unable |
| **17. Run (10m)** | Both feet off the ground (no double stance phase during running) | 'Duchenne jog' | Walk |

# Appendix 3 The Scoring Algorithms for the Paediatric Outcomes Data Collection Instrument

| The algorithm for the upper extremity and physical function core scale is as follows: | | |
|---|---|---|
| **Component** | **Value** | **Result** |
| **Notes:**<br>• Any item rated "5" (Too young for this activity) is considered missing and is not added into the scale.<br>• A minimum of 4 items must have valid answers to score this scale (including those marked "too young" as missing). | | |
| **Raw Score:** | Sum of items Q1, Q2, Q3, Q4, Q5, Q6, Q8, Q32 | Value ranging:<br>8 to 32 (if all 8 questions are answered) |
| **Mean of Items:** | (sum of items Q1, Q2, Q3, Q4, Q5, Q6, Q8, Q32/ (number of non-missing items) | Value ranging:<br>1 to 4 |
| **Standardized Score:** | [ (4 - mean of items) / 3 ] * 100 | Value ranging:<br>0 to 100 |
| **The algorithm for the transfer and basic mobility core scale is as follows:** | | |
| **Component** | **Value** | **Result** |
| **Note:**<br>• Any item rated "5" (Too young for this activity) is considered missing and is not added into the scale.<br>• A minimum of 7 items must have valid answers to score this scale (including those marked "too young" as missing). | | |
| | Q34 is RESCALED as follows: Q34rescaled = [ (Q34 - 1)* 3/4 ] + 1 | Value ranging:<br>1 to 4 |
| | Q35 is RESCALED as follows: Q35rescaled = [ (Q35 - 1)* 3/4 ] + 1 | Value ranging:<br>1 to 4 |
| **Raw Score:** | Sum of items Q7, Q21, Q24, Q25, Q28, Q29, Q30, Q31, Q33, Q34Rescaled, Q35Rescaled | Value ranging:<br>11 to 44 (if all 11 questions are answered) |
| **Mean of Items:** | (sum of items Q7, Q21, Q24, Q25, Q28, Q29, Q30, Q31, Q33, Q34Rescaled, Q35Rescaled) / (number of non-missing items) | Value ranging:<br>1 to 4 |
| **Standardized Score:** | [ (4 - mean of items) / 3 ] * 100 | Value ranging:<br>0 to 100 |
| | | |

| The algorithm for the sports and physical functioning core scale is as follows: | | |
|---|---|---|
| **Component** | **Value** | **Result** |
| **Note:**<br>• Any item rated "5" (Too young for this activity) is considered missing and is not added into the scale.<br>• A minimum of 6 items must have valid answers to score this scale (including those marked "too young" as missing). | | |
| | Q26 is RESCALED as follows:<br>Q26rescaled = [ (Q26 -1) * 3/4 ] + 1 | Value ranging:<br>1 to 4 |
| | Q27 is RESCALED as follows:<br>Q27rescaled = [ (Q27 -1) * 3/4 ] + 1 | Value ranging:<br>1 to 4 |
| | Q36 is RECODED to MISSING if (Q36 = 4 and EITHER [Q42 = 1] or [Q43 = 1] ) | Value ranging:<br>1 to 4 |
| | Q44 is RECODED to MISSING if (Q44 = 4 and EITHER [Q50 = 1] or [Q51 = 1] ) | Value ranging:<br>1 to 4 |
| | Q52 is RECODED to MISSING if (Q52 = 4 and EITHER [Q58 = 1] or [Q59 = 1] ) | Value ranging:<br>1 to 4 |
| | Q60 is RECODED and RESCALED as follows: | |
| | Step #1: Q60 is RECODED to MISSING if (Q60 = 3 and Q65 = 1 ) | |
| | Step #2: If Q60 is not missing, Q60rescaled = [ (Q60 -1) * 3/2 ] + 1 | Value ranging:<br>1 to 4 |
| | Q66 is RECODED and RESCALED as follows: | |
| | Step #1: Q66 is RECODED to MISSING if (Q66 = 4 ) | |
| | Step #2: Q66 is RECODED to MISSING if (Q66 = 3 and EITHER [Q72 = 1] or [Q73 = 1] ) | |
| | Step #3: If Q66 is not missing, Q66rescaled = [ (Q66 - 1) * 3/2] + 1 | Value ranging:<br>1 to 4 |
| **Raw Score:** | Sum of items Q18, Q19, Q20, Q22, Q23, Q26rescaled, Q27rescaled, Q36, Q44, Q52, Q60rescaled, Q66rescaled | Value ranging:<br>12 to 48 (if all 12 questions are answered) |
| **Mean of Items:** | (sum of items Q18, Q19, Q20, Q22, Q23, Q26rescaled, Q27rescaled, Q36, Q44, Q52, Q60rescaled, Q66rescaled) / (number of non-missing items) | Value ranging:<br>1 to 4 |
| **Standardized Score:** | [ (4 - mean of items) / 3 ] * 100 | Value ranging:<br>0 to 100 |
| | | |

| The algorithm for the pain/comfort core scale is as follows: | | |
|---|---|---|
| **Component** | **Value** | **Result** |
| **Notes:** A minimum of 2 items must have valid answers to score this scale. | | |
| | Q17 is RESCALED as follows:<br>Q17rescaled = [ (4 - Q17) * 4/3 ] + 1 | Value ranging:<br>1 to 5 |
| | Q75 is RESCALED as follows:<br>Q75rescaled = [ (Q75 - 1) * 4/5 ] + 1 | Value ranging:<br>1 to 5 |
| **Raw Score:** | Sum of items Q17rescaled, Q75rescaled, Q76 | Value ranging:<br>3 to 15 (if all 3 questions are answered) |
| **Mean of Items:** | (sum of items Q17rescaled, Q75rescaled, Q76) / (number of non-missing items) | Value ranging:<br>1 to 5 |
| **Standardized Score:** | [ (4 - {mean of items - 1} ) / 4 ] * 100 | Value ranging:<br>0 to 100 |
| **The algorithm for the happiness core scale is as follows:** | | |
| **Component** | **Value** | **Result** |
| **Notes:**<br>• Any item rated "5" (Too young for this activity) is considered missing and is not added into the scale.<br>• A minimum of 3 items must have valid answers to score this scale (including those marked "too young" as missing). | | |
| **Raw Score:** | Sum of items Q10, Q11, Q12, Q13, Q14 | Value ranging:<br>5 to 25 (if all 5 questions are answered) |
| **Mean of Items:** | (sum of items Q10, Q11, Q12, Q13, Q14) / (number of non-missing items) | Value ranging:<br>1 to 5 |
| **Standardized Score:** | [ (5 - mean of items) / 4 ] * 100 | Value ranging:<br>0 to 100 |
| **The algorithm for the Global Function scale is as follows:** | | |
| **Component** | **Value** | **Result** |
| **Notes:**<br>• If ANY of the four relevant scales are missing, this is not calculated. | | |
| **Mean of Items:** | (sum of "Standardized Score" values for scales: 'Upper extremity and physical function' + 'Transfer and basic mobility' + Sports and physical function' and 'Pain/comfort' ) /4 | Value ranging:<br>0 to 100 |

# Appendix 4 PUL Assessment

**1.4 Performance of the Upper Limb Module for DMD 2.0 (PUL for DMD) Worksheet**

**Preferred arm (used for all tests):** ☐ **Right** ☐ **Left**

**Elbow extension ROM: Right:** **Left:** **e.g. full = 0° 10° contracture = -10°**

**Supination ROM: Right:** ☐ Full ☐ ¾ ☐ ½ ☐¼ **Left:** ☐ Full ☐ ¾ ☐ ½ ☐¼

**Entry item A. – start with A to identify starting point for subsequent tests. Circle score for each item. DO NOT INCLUDE IN TOTAL SCORE**

| Item | Description | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|
| **A.** | **Entry item** | No useful function of hands. | Can use hands to hold pen or pick up a coin or drive a powered chair | Can raise 1 or 2 hands to mouth but cannot raise a cup with a 200g weight in it to mouth | Can raise plastic cup with 200g weight in it to mouth using 1 or 2 hands | Can simultaneously raise both arms (to shoulder height with or without compensation) .i.e. elbow bent or in extension | Can raise both arms simultaneously above head only by flexing the elbow (shortening circumference of the movement /using accessory muscles) | Can abduct both arms simultaneously elbows in extension in a full circle until they touch above the head. |

**For item A:** A score of 3, 4, 5, 6 on item A, start with item 1 – on this page
A score of, 1, 2 start with item 7 on page 2

**High level shoulder Dimension**

| Item | Description | 0 | 1 | 2 | Score |
|---|---|---|---|---|---|
| **1 Score from Entry item above** | **Shoulder abduction both arms above head** "Raise your arms out to the side and above your head– try and keep straight elbows" | Unable | Can raise both arms simultaneously **above head** only by flexing the elbow - **with** compensation | Can abduct both arms simultaneously elbows in extension in a full circle until they touch above the head | |
| **2** | **Raise both arms to shoulder height (elbows at shoulder height)** "Raise your arms to shoulder level" | Unable | Can raise both arms to shoulder height either one at a time or with elbows flexed (**with compensation**) | Can raise both elbows to shoulder height **without** compensation e.g. simultaneously with elbows straight | |
| **3** | **Shoulder flexion to shoulder height (no weights)** "Reach out and touch my hand" – | Unable | Able **with** compensation | Able **without** compensation | |
| **4** | **Shoulder flexion to shoulder height with 500g weight** "Reach out and touch my hand" – | Unable | Able to lift 500g weight **with compensation** | Able to lift 500g weight **without compensation** | |

| High level shoulder Dimension (continued) | | | | | |
|---|---|---|---|---|---|
| **Item** | **Description** | **0** | **1** | **2** | **Score** |
| **5** | **Shoulder flexion above shoulder height with 500 g weight**<br>Hand on lap – "give me the weight" | Unable | Able to lift 500g weight **with compensation** | Able to lift 500g weight **without compensation** | |
| **6** | **Shoulder flexion above shoulder with 1 kg weight**<br>Hand on lap – "give me the weight" | Unable | Able to lift 1 kg weight **with compensation** | Able to lift 1 kg weight **without compensation** | |

| Mid level elbow Dimension | | | | | |
|---|---|---|---|---|---|
| **Do these tests on all individuals** | | | | | |
| **Item** | **Description** | **0** | **1** | **2** | **Score** |
| **7** | **Hand(s) to mouth**<br>"Bring the cup to your mouth with one hand" | Unable | Able to bring 200g in cup with any compensation to mouth (can use more than one hand and / or bring head to hands) | Able to bring 200g in cup to mouth with one hand no elbow support (without compensation) | |
| **8** | **Hands to table from lap**<br><br>"Bring both hands from lap to table" | Unable | Able to bring two hands completely (to wrist crease) to table but **NOT simultaneously or in one action** | Two hands completely on table simultaneously | |
| **9** | **Move weight on table 100g**<br><br>"Move the weight from outside circle to centre circle" | Unable | Can move **100g** weight from outer to centre circle using compensation<br><br>(slide forearm or elbow make contact with table) | Can lift **100g** weight from outer to centre circle without compensation | |
| **10** | **Move weight on table 500g**<br><br>"Move the weight from outside circle to centre circle" | Unable | Can move **500g** weight from outer to centre circle using compensation<br><br>(slide forearm or elbow make contact with table) | Can lift **500g** weight from outer to centre circle without compensation | |
| **11** | **Move weight on table 1kg**<br><br>"Move the weight from outside circle to centre circle" | Unable | Can move **1kg** weight from outer to centre circle using compensation<br><br>(slide forearm or elbow make contact with table) | Can lift **1kg** weight from outer to centre circle without compensation | |
| **12** | **Lift heavy can diagonally**<br>"Lift can from this circle nearest your hand to this circle furthest away and across your body" | Unable | Can move heavy can from nearest circle across body with compensation<br><br>(slide forearm or elbow make contact with table) | Can lift heavy can from nearest circle across body without compensation | |

| Mid level elbow Dimension (continued) | | | | | |
|---|---|---|---|---|---|
| **Item** | **Description** | **0** | **1** | **2** | **Score** |
| **13** | **Stack of three cans** "Stack these two cans, one at a time on the middle can using one hand" | Unable to stack third can even with compensation | Able to stack third can with compensation | Able to stack third can without compensation | |
| **14** | **Stack of five cans** "Stack these two additional cans, one at a time on top of this can using one hand" | Unable to stack fifth can even with compensation | Able to stack fifth can with compensation | Able to stack fifth can without compensation | |
| **15** | **Remove lid from container** **"**Use your hands to open this container" | Unable | Opens completely | | |

| Distal wrist and hand Dimension | | | | | |
|---|---|---|---|---|---|
| **Do these tests on all individuals** | | | | | |
| | | **0** | **1** | **2** | **Score** |
| **16** | **Tearing paper** "Tear the sheet of paper beginning from here" | Unable | Tears the sheet of paper folded in half from the folded edge | Tears the sheet of paper folded in 4,beginning from the folded edge | |
| **17** | **Tracing path** "Use your pencil to complete the path in one smooth movement" | Unable | Completes the path with compensation - needs to raise pencil from paper or pivot arm | Able to complete the path **without stops** or raising hand from paper | |
| **18** | **Push on light** "Push on the light with the fingers of one hand" | Unable | Able to turn the light on momentarily with fingers of one hand | Able to turn the light on permanently with fingers of one hand | |
| **19** | **Supination** "Pick up the light and turn your hand over" | Unable | Picks up the light but either turns hands over incompletely or uses compensation to turn it over | Picks up the light, and turns the hand over completely with no compensatory movements | |
| **20** | **Picking up coins** **"**Using one hand, Pick up 6 coins, one at a time" | Cannot pick up one coin | Can pick up **one** coin/ token | Can pick up six coins in one hand | |
| **21** | **Placing finger on number diagram** (precision not essential) **"**Using one finger to touch each number on the diagram" | Cannot raise the finger or slide it on the diagram | Able to place finger (slide or lift) between at least two squares | Able to place finger successively on the numbers of the diagram (with or without compensation) | |
| **22** | **Pick up 10g weight finger pinch** "Pick up this small weight like this (by body of weight)" | Unable | Able to grip and lift weight off surface | | |

# Appendix 5 Imputation Rules for Partial or Missing Start Dates

If dates are missing or incomplete for an AE (including deaths) or concomitant medication, the following algorithm will be used for imputation:

| Start Date | | Stop Date | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Complete: yyyymmdd | | Partial: yyyymm | | Partial: yyyy | | Missing |
| | | <1st dose | ≥1st dose | <1st dose yyyymm | ≥1st dose yyyymm | <1st dose yyyy | ≥1st dose yyyy | |
| Partial: yyyymm | = 1st dose yyyymm | 2 | 1 | n/a | 1 | n/a | 1 | 1 |
| | ≠ 1st dose yyyymm | | 2 | 2 | 2 | 2 | 2 | 2 |
| Partial: yyyy | = 1st dose yyyy | 3 | 1 | 3 | 1 | n/a | 1 | 1 |
| | ≠ 1st dose yyyy | | 3 | | 3 | 3 | 3 | 3 |
| Missing | | 4 | 1 | 4 | 1 | 4 | 1 | 1 |

1 = Impute as the date of first dose
2 = Impute as the first of the month
3 = Impute as January 1 of the year
4 = Impute as January 1 of the stop year
Note: If the start date imputation leads to a start date that is after the stop date, then there is a data error and do not impute the start date.

Imputation rules for partial or missing stop dates:

1. Initial imputation
    a. For partial stop date “mmyyyy”, impute the last of the month.
    b. For partial stop date “yyyy”, impute December 31 of the year.
    c. For completely missing stop date, impute the last visit date.
2. If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date.

Imputation rules for partial or missing death dates:

1. If death year and month are available but day is missing:
    d. If “mmyyyy” for last contact date = “mmyyyy” for death date, set death date to the day after the last contact date.
    e. If “mmyyyy” for last contact date < “mmyyyy” for death date, set death date to the first day of the death month.
    f. If “mmyyyy” for last contact date > “mmyyyy” for death date, data error and do not impute.
2. If both month and day are missing for death date or a death date is totally missing, set death date to the day after the last contact date.