16.1.9 Documentation of Statistical Methods

The document listed below is provided in this section.

Statistical Analysis Plan (DSC/14/2357/48) dated 13-April-2022

Statistical Analysis Plan (DSC/14/2357/48) Addendum 1 dated 14-July-2022

Randomised, Double Blind, Placebo Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Givinostat in Ambulant Patients with Duchenne Muscular Dystrophy

Italfarmaco Study No: DSC/14/2357/48
Veristat Study No: ICO16001

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Statistical Analysis Plan

Version: Final 6.0

Date: 13th April 2022

For Veristat
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Contents

LIST OF ABBREVIATIONS

4SC	4-stairs climb
6MWT	6-minute walking test
AE	Adverse Event
ANCOVA	Analysis of covariance
BDRM	Blinded Data Review Meeting
BMI	Body mass index
CI	Confidence interval
DMD	Duchenne muscular dystrophy
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HHM	Hand-held myometry
IDMC	Independent data monitoring committee
IMP	Investigational Medicinal Product
ITT	Intent-to-treat analysis set
LLOQ	Lower Limit of Quantification
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MFF	Muscle fat fraction
MR	Magnetic Resonance
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NSAA	North Star Ambulatory Assessment
PD	Pharmacodynamic
PK	Pharmacokinetic
PODCI	Paediatric Outcomes Data Collection Instrument
PT	Preferred Term
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan

SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
US	United States
VL MFF	Vastus lateralis muscle fat fraction

1 INTRODUCTION

This statistical analysis plan (SAP) is based on protocol version 8.0 (and 8.1 for France use only) dated 8th April 2020 and Version 8.1 for Germany use only dated 25th June 2020 and will be finalised prior to full study unblinding. Any additional details or amendments will be discussed with Italfarmaco and included in a revised version of the SAP.

The table, figure and listing shells will be supplied in a separate document.

The analysis and statistical reporting will be conducted at Veristat using SAS version 9.2 or higher.

Summary statistics will consist of number of subjects (n), mean, standard deviation (SD), minimum, first quartile, median, third quartile and maximum, unless specified otherwise. The precision of these variables is defined in the table, figure and listing shells document.

Unless stated otherwise, for example in Section 4.4.4, missing data will be considered missing at random and there will be no imputation of missing data.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

The primary objective of the study is to establish the effects of givinostat versus placebo administered chronically over 18 months to slow disease progression in ambulant Duchenne muscular dystrophy (DMD) subjects.

The secondary objectives of this study are:

i. To assess the safety and tolerability of givinostat versus placebo administered chronically in DMD subjects

ii. To evaluate the pharmacokinetic (PK) profile of givinostat administered chronically in DMD subjects

iii. To evaluate the impact on quality of life and activities of daily living of givinostat versus placebo administered chronically.

The secondary exploratory objectives of this study are:

iv. To evaluate the correlation between PK profile of givinostat and pharmacodynamics (PD) data

v. To explore whether the effects of givinostat versus placebo administered chronically may be related to the type of DMD mutation or to the biomarkers.

2.2 Study Endpoints

The study endpoints are detailed in Section 5.2 of the protocol.

2.3 Study Design

This is a Phase 3, randomised, double blind, placebo controlled, multicentre study to evaluate the efficacy and safety of givinostat in ambulant subjects with DMD. This

study will include ambulant male paediatric subjects aged ≥ 6 years at baseline affected by DMD.

A target population (Group A) will consist of subjects with a baseline vastus lateralis muscle fat fraction (VL MFF) assessed by Magnetic Resonance Spectroscopy (MRS) in the range > 5% and ≤ 30%. An off-target population (Group B) will consist of subjects with a baseline VL MFF assessed by MRS in the range ≤ 5% or > 30%. The target and off-target population assignments will be derived from the actual VL MFF values entered onto the electronic Case Report Form (eCRF) at baseline. If for any reason this information is missing or it is not possible to determine the assignment from the VL MFF results recorded, the subject will be classified as off-target. Following collection of MRS VL MFF data, a blinded central review of the data will be conducted by University of Florida Imaging DMD network, which may lead to adjustment of some VL MFF results. The final VL MFF results following blinded review (external to the eCRF) will be used for analyses of MRS data (see Section 4.2.2). However, the assignment to target and off-target populations based on the initial values entered onto the eCRF will not be adjusted for any changes in baseline MRS VL MFF results from blinded review.

All subjects in the target population will undergo the magnetic resonance assessment at baseline, 12 and 18 months and will be eligible for inclusion in the Magnetic Resonance (MR) Cohort defined in Section 3.1.1.

A total of 110 male ambulant subjects in the target population are planned to be randomised (Group A). In addition, it is planned that up to 50 subjects (about 35% of the overall population) outside of the target population may also be recruited into the study (Group B). The overall subject population (Group A + Group B) will provide supportive data.

At the randomisation visit, in addition to the continued standard of care corticosteroids regimen, DMD subjects will be randomised in a 2:1 ratio to receive givinostat oral suspension 10mg/mL or placebo oral suspension b.i.d. in a fed state.

At randomisation, subjects will be stratified for their concomitant use of steroids in 4 strata:

1. Deflazacort daily regimen
2. Deflazacort intermittent regimen
3. Other steroids daily regimen
4. Other steroids intermittent regimen

Details regarding concomitant steroid use at randomisation will be collected on the diagnosis page of the eCRF and these data will be used to derive the appropriate stratum for each subject for the purposes of summary and analyses.

The study is planned for 19 months and comprises 2 phases:

1. Screening period: starting 4 weeks (± 2 weeks) before randomisation
2. Treatment period: 18 months of treatment

There will be a total of 15 visits, including the screening and randomisation visits and excluding the follow up visit. Subjects may be evaluated more often if necessary for safety reasons.

A final follow up visit will be performed 4 weeks after the last administration of givinostat or placebo. However, in order to guarantee continuation of treatment with

givinostat, the Sponsor has planned a long-term study which will start when the first subject randomised in this study has attended his last visit. Therefore, the final follow up visit will only be performed if the subject does not assent/consent and/or the parent/legal guardian does not consent to participation in the long-term study.

A single interim analysis has been planned and will be conducted by the independent data monitoring committee (IDMC) in order to ensure study integrity. The interim analysis will be performed when the first 50 subjects randomised in the target population have reached the 12-month visit, where the effects of givinostat versus placebo on the mean VL MFF will be assessed in terms of futility. If the IDMC recommends that the study should proceed as planned, a blinded sample size re-estimation will be conducted for VL MFF and the time taken to climb 4 stairs (4SC) in the target population.

Further details regarding the interim analysis are given in Section 2.6.

2.4 Visit Structure

The visit structure and scheduled assessments are detailed in Section 9.1 of the protocol.

2.5 Sample Size

The sample size was originally calculated to provide 90% power and a 1-sided alpha of 2.5% to detect a true difference of 3 seconds between givinostat and placebo in the target population 4SC change from baseline to 18 months, assuming a common standard deviation (SD) of 6 seconds. The estimated SD was based on publicly available Phase 3 study data on ataluren and drisapersen in subjects with DMD in addition to internal Italfarmaco data. This gave rise to an estimated sample size of N=192 subjects in the target population.

Based on internal Italfarmaco data, a total of N=99 subjects was originally calculated as sufficient to provide 80% power to detect a 55% reduction in the annual mean increase in VL MFF (of 6.6%) with givinostat as compared to placebo with a 1-sided alpha of 2.5% and assuming an SD for the change from baseline in VL MFF of 6%.

The pre-planned interim analysis took place in January 2020 based upon the first 50 randomised subjects reaching 12 months of treatment. It was concluded by the IDMC that futility on VL MFF was not met and the trial should continue. Therefore, the pre-planned blinded sample size re-assessment was performed. This provided a revised, blinded within treatment SD estimate for the change in 4CS from baseline to 18 months of 3.094 seconds, approximately half of that assumed in the original power calculation. Based on this revised SD estimate, the revised sample size (utilising a 2:1 randomisation scheme) is N=102. This provides 90% power and a 1-sided alpha of 2.5% to detect a true difference of 2 seconds between givinostat and placebo in the target population, for the change from baseline in 4SC at 18 months.

With an estimated drop-out rate of 8%, a total of 110 male ambulant subjects will be randomized in the target population (Group A). Up to 50 subjects (about 35% of the overall population) outside of the target population may also be recruited into the study (Group B). The overall subjects population (Group A + Group B) will provide supportive data.

For the MR cohort, the blinded SD estimate was 5.941%, being in line with the 6% SD assumed in the original power calculation, hence all the subjects in the target population will be included in the MR cohort.

2.6 Interim Analyses

An IDMC will review and oversee one planned formal interim analysis in the target population. Full details regarding the role, function and operations of the IDMC and the rules to be used when reviewing interim data are given in the IDMC charter.

The interim analysis will be a performed when the first 50 subjects randomised in the target population have reached the 12-month visit. In this interim analysis, the IDMC will evaluate the effects of givinostat versus placebo on the VL MFF in terms of futility, via a review of the treatment difference on the mean change in VL MFF as assessed by MRS before and after 12 months of treatment. Note that the primary endpoint data will not be unblinded at this interim and no subject level unblinding will occur except for the VL MFF endpoint only if required. Futility will be mandated if the mean change from baseline to month 12 in VL MFF as assessed by MRS in the givinostat group is equal to or worse than that seen in the placebo group since the biologic plausibility of a subsequent treatment effect on 4SC would be greatly diminished. The IDMC will only communicate to the Sponsor whether the study should proceed or it should be stopped having met the futility criteria.

If the IDMC indicates that the study should proceed, a blinded sample size re-estimation will be conducted for VL MFF and 4SC in the target population as follows:

i. To maintain the blind on the primary endpoint, the within treatment SD for the change from baseline will be estimated as $\hat{\sigma}_{within} = \sqrt{\hat{\sigma}^2_{overall} - \left(\frac{\Delta}{2}\right)^2}$ where $\hat{\sigma}_{overall}$ is the overall SD for the change from baseline in 4SC based on the n=50 subjects in the interim and Δ is the originally hypothesized treatment effect, i.e., $\Delta = 3$ seconds. Dependent upon the blinded SD estimate, the sample size may be decreased or increased to maintain 90% power. Any increase in sample size for 4SC will be limited to 1.5 times maximum of the initial target population sample size, i.e., to a maximum of $1.5 \times 192 = 288$ subjects. For a 20% increase in the SD, this degree of increase in sample size will maintain 90% power, and for a 40% increase in SD power will be maintained at 80%.
ii. With respect to VL MFF, a similar approach will be applied; the within treatment SD for the change from baseline will be estimated as $\hat{\sigma}_{within} = \sqrt{\hat{\sigma}^2_{overall} - \left(\frac{\Delta}{2}\right)^2}$ where $\hat{\sigma}_{overall}$ is the overall SD for the change from baseline in VL MFF and Δ is the originally hypothesized treatment effect, i.e. $\Delta = 3.63\%$ (i.e., 55% of 6.6%). Dependent upon the blinded SD estimate, the sample size may be decreased or increased to maintain 90% power. Any increase in sample size required to assess VL MFF will also be limited to 1.5 times the required target population sample size stated in the preceding power calculation, to a maximum of $1.5 \times 99 \approx 150$ subjects.

To ensure that the blind is maintained for the sample size re-estimation, this will be completed by a blinded statistician at Veristat. The IDMC will then formally communicate the outcome of the sample size re-estimation.

At this interim futility analysis, there will be no efficacy assessment and no unblinded analysis of the primary endpoint and, hence, no alpha spend nor early stopping of the study for efficacy.

Details of the outputs to be produced at the interim analysis are given in Appendix 7.7. Shells for the outputs to be produced at this interim analysis are included in a separate 'Interim Analysis 1 Table, Figure and Listing Shells' document.

As noted above in Section 2.5, the interim analysis took place in January 2020; futility was passed and the blinded sample size reassessment followed. The estimated SD for 4SC was approximately half of that assumed in the original power calculation. Consequently, it was determined that a total of N=102 patients would be sufficient to test the hypothesis that 4SC was improved by at least 2 seconds with givinostat compared with placebo after 18 months of treatment. With allowance for a small dropout rate, a total of 110 male ambulant subjects will be randomised in the target population (Group A). Up to 50 subjects (about 35% of the overall population) outside of the target may also be recruited into the study (Group B). The overall subjects population (Group A + Group B) will provide supportive data.

For the MR cohort, the blinded SD estimate was 5.941%, being in line with the SD assumed in the original power calculation for VL MFF. Therefore, all the subjects in the target population will be included in the analysis of the MR cohort.

Following this interim analysis, the study will continue subject follow-up and recruitment and a final analysis will be performed once all randomised subjects have achieved 18 months of follow-up. The p-value applicable to the final analysis of 4SC in the target population will be $p \leq 0.025$ 1-sided. See Section 4.4.5 for further details regarding all adjustments for multiple comparisons where analyses are formal, and the presentation of nominal p-values for supportive analyses. Note that references to 1-sided p-values are to indicate significance in either direction (i.e. a 2-sided test) per Section 4.4.1.

In addition to the formal interim analysis described above, the IDMC will review, evaluate and categorise unblinded safety findings every three months during the study.

An unblinded team at Veristat will be responsible for the ongoing safety summaries that are to be produced every 3 months as well as any unblinded aspects of the formal interim analysis.

The outputs to be produced for the safety reviews are listed in Appendix 7.6.

All details regarding reviews performed by the IDMC at the interim analysis and safety reviews are documented in the IDMC charter.

2.7 Changes from the Protocol Planned Analysis

The pharmacokinetic analysis set has been introduced.

The exploratory endpoint "Time to loss of standing (Baseline through end of study)" has been updated to clarify that this is the time to *persistent* loss of standing in order to allow time for recovery due to trauma. Additional clarity has also been added regarding how this endpoint is derived.

The exploratory endpoint "Proportion of subjects with ≥10% worsening in 6MWT at the end of the study" has been updated to clarify that this is the proportion of subjects with

≥10% *persistent* worsening in 6MWT at the end of the study. Additional clarity has also been added regarding the definition for inclusion of subjects in this proportion.

In addition, exploratory subgroup and supplementary analyses have been included in this SAP.

Summary and analysis of results of the DMD serum biomarker assessment and any relationship with treatment effect will not be included as part of this SAP but in a separate dedicated SAP.

The presentation of data on the target and/or overall subject populations has been streamlined to ensure the most appropriate population is used for each data type, with the option to include additional repeats post hoc if required.

Additional criteria have been added to the definition of the Intent-To-Treat (ITT) analysis set to ensure that subjects included in this population have received at least one dose of study drug and have at least one post-baseline 4SC measure, or alternatively a missing 4SC measure due to being either non-ambulatory or otherwise physically unable to perform the assessment (as this still provides useful information regarding disease progression). This was felt appropriate to ensure a suitable population for the primary analysis.

The text for the analysis set definitions has been updated slightly to clarify the difference between the analysis sets themselves (defined by the analysis set criteria) and the subdivision into target/overall populations (defined by baseline MRS VL MFF results).

The definition for the MR cohort has been updated to clarify that subjects must complete at least one post-baseline MRI/MRS assessment to be included as this cohort is to be used for presentation of MRI and MRS data.

2.8 Data presentations

The data will be summarised in tabular form by treatment group apart from disposition of subjects, protocol deviations, background and demographic data, administration of investigational medicinal product (IMP), plasma concentrations of givinostat and its major metabolites, prior and concomitant medications, which will be summarised by treatment group and overall subjects.

Only scheduled post-baseline laboratory, vital signs and electrocardiogram (ECG) values will be tabulated, post-baseline repeat/unscheduled assessments will be listed.

Listings will be sorted by treatment group, subject number and date/time of assessment.

Treatment groups will be presented in the following order: Givinostat, Placebo.

Graphical presentations of the data will also be provided where appropriate.

All efficacy analyses and data summaries will be presented for the target population only. Safety data will only be summarised for the overall subject population. Data summaries for disposition of subjects, protocol deviations, background and demographic data, administration of IMP, ankle range of motion, modified MRC grade and genotype data will be presented for both the target and overall subject populations. Presentation of analyses and summaries of PK data will be discussed in a separate Population PK data analysis plan (see Section 4.5).

Listings will be presented for the overall subject population. Inclusion of each subject in the target or off-target population will be indicated in the listing of analysis set assignments for reference. Listings for efficacy and PK data will also present patients sorted by target or off-target population for each treatment group.

The target population will serve as the basis for any formal analysis of efficacy.

Any further repeats of the data summaries and analyses for target, off-target or overall subject populations may be considered at a later date and included post hoc. Details of any such repeats will be included in a SAP addendum as appropriate.

Where data are imputed according to the rules defined in Section 4.4.4, the imputed data will be used in all data presentations and analyses. Imputed values for efficacy data will be flagged in the listings with an indication of the missing data classification as applicable.

Data collected at the 'EOS/Early Withdrawal' visit (Week 72) will be mapped to either 'EOS' for subjects who complete the study, or 'Early Withdrawal' for subjects who withdraw early. The mapped visits will be used for all data presentations and analyses. Data presentations by visit will present 'EOS' followed by 'Early Withdrawal'. Data collected for the 'Follow Up Visit' (Week 76) will be presented and analysed without any mapping for completers versus early withdrawal subjects.

2.9 COVID-19

It is noted that particular attention may need to be given to the impact on key efficacy or safety assessments as a result of the COVID-19 pandemic. Consideration of the different areas of impact has been made as described below.

Protocol deviations related to COVID-19 will be recorded under separate categories indicating the type of deviation and that this was due to COVID-19. The assigned categories will be presented in the protocol deviation listing and table summary of major deviations as described in Section 3.2.

Subjects who prematurely discontinue the study due to COVID-19 will record this as their reason for withdrawal and this will be included in the summary of reasons for withdrawal as described in Section 3.1.

Subjects with a modification, interruption or who permanently stop IMP due to COVID-19 will record this as the reason for modification and this will be presented in the summary and listing of IMP modifications as described in Section 3.5.

Missing efficacy data will be subject to the imputation and analysis methods described in Sections 4.4.4.1 and 4.4.4.2. Missing data due to COVID-19 will be assumed to be Class 1 missing data (due to reasons other than being non-ambulatory or physically unable to perform the test / assessment) and handled accordingly. The tipping point analysis described in Section 4.4.4.3 will assess the impact of the missing data on the primary analysis.

In order to provide supportive information for interpretation of the key efficacy and safety analyses, a summary of the number and percentage of subjects with missing assessments at each scheduled visit will be presented by treatment group and overall for the following selected data on the ITT analysis set in the target population (efficacy data) or safety analysis set in the overall population (safety data) as appropriate:

- All primary and key secondary efficacy assessments

- Clinical laboratory
- Vital signs
- Electrocardiogram
- Echocardiography
- Pulmonary function test

In addition, these summaries will be repeated to present the number and percentage of subjects with assessments completed outside of the expected protocol defined assessment window, at each scheduled visit by treatment group and overall. This summary will also include the number and percentage of subjects with assessments completed outside of the extended window for the 18 month assessment (+/-60 days) which was applied due to impact of the COVID-19 pandemic.

The COVID-19 pandemic has resulted in some subjects completing the EOS (18 month) assessment outside of the expected protocol defined assessment window or, additionally, outside of the extended +/-60 day window, which may have an impact in progressive disease. Therefore, a sensitivity analysis will be conducted on the ITT analysis set in the target population. The analysis described in Section 4.4.2 for each of the primary and key secondary endpoints will be repeated, excluding any subjects whose respective 18 month assessment was completed outside of the expected assessment window. In each case, the analysis will first exclude subjects where the 18 month assessment was outside of the protocol defined window and then will be repeated only excluding subjects where the 18 month assessment was outside of the +/-60 day window.

If these summaries and analyses suggest that further investigation is beneficial, additional summaries and/or analyses may be added post hoc to address missing data or assessments outside of protocol defined windows. This may include but is not limited to: additional sensitivity analyses of the efficacy endpoints, additional summaries of selected safety data for overall worst case post-baseline values, application of visit windows to group post-baseline data across multiple visits as appropriate.

2.10 Blinded Data Review Meeting

Italfarmaco will convene a blinded data review meeting (BDRM) after the data have been cleaned and before the study is locked and unblinded.

The BDRM will make decisions that will include, but not be limited to, the determination of whether protocol deviations are 'major' or 'minor', or not a protocol deviation at all. The definitions used to classify deviations as ‘major’ will be documented in the BDRM minutes.

3 STUDY SUBJECTS

All study subject data summaries and listings will be based on all enrolled subjects unless specified otherwise. Additionally, see Section 2.8 regarding use of the target versus overall population. Baseline is defined as the last non-missing value recorded prior to or on the date of first study treatment. Where the value is recorded on the same date as first study treatment and there is no further information to confirm whether this was prior to start of treatment, the value will be considered prior to

treatment if this was a screening or randomisation assessment and otherwise will be considered post treatment.

3.1 Disposition of Subjects

The number and percentage of all subjects enrolled, included in the intent-to-treat analysis set, safety analysis set, PK analysis set and MR cohort who completed the study and prematurely discontinued the study will be presented by treatment group and overall. The number and percentage of subjects will be summarised by their reasons for withdrawal. In addition, the summary of subjects included in analysis sets, completed, discontinued and reasons for withdrawal will be repeated by country. Individual reasons for withdrawal will be presented in a listing.

A table will also present the number and percentage of subjects screened, randomised and who failed screening overall for all subjects screened. The number and percentage of subjects who passed screening but were not randomised will also be presented. This table will also present the number and percentage of screen failed subjects by inclusion/exclusion criteria failed.

Details of eligibility, including whether all eligibility criteria were met and the criteria that were failed (screen failures) or reason for withdrawal (subjects who passed screening but were not randomised), will be listed for all screened subjects, including the protocol version that the subjects were screened under.

3.1.1 Analysis Sets

The **All enrolled subjects** set for the target population will include all subjects in the target population who were randomised to study treatment. The all enrolled subjects overall set will include all subjects in both the target and off-target populations (Group A + Group B) who were randomised to study treatment.

The **Intent-To-Treat** (ITT) analysis set for the target population will include all subjects in the target population who are randomised, who receive at least one dose of study drug and who have at least one non-missing post-baseline 4SC measure or missing post-baseline 4SC measure due to being either non-ambulatory or otherwise physically unable to perform the assessment, irrespective of any deviation from the protocol or premature discontinuation. The treatment group assignment will be designated according to initial randomisation. The ITT analysis set in the target population will serve as the basis for the formal analysis of efficacy. The ITT analysis set for the overall population will include all subjects in both the target and off-target populations who are randomised, who receive at least one dose of study drug and who have at least one post-baseline 4SC measure or missing post-baseline 4SC measure due to being either non-ambulatory or otherwise physically unable to perform the assessment, irrespective of any deviation from the protocol or premature discontinuation. The ITT analysis set in the overall population may be used for any supportive efficacy analyses.

The **Safety** (SAF) analysis set for the target population will include all randomised subjects in the target population who receive at least one dose of the study drug. The treatment group assignment in this analysis set will be defined by the treatment actually received. This will be used for any evaluation of safety in the target population. The SAF analysis set for the overall population will include all randomised subjects in both the target and off-target populations who receive at least one dose of study drug. This will be used for evaluation of safety in the overall population.

The **Pharmacokinetic** (PK) analysis set for the target population will include all subjects in the target population who have received at least one dose of treatment with givinostat and who have at least one post-dose concentration of study drug. The PK analysis set in the target population will be used for all formal PK summaries and analyses. The PK analysis set for the overall population will include all subjects in both the target and off-target population who have received at least one dose of treatment with givinostat and who have at least one post-dose concentration of study drug. The PK analysis set in the overall population may be used for any supportive PK evaluations. Final membership of the PK analysis set in both the target and overall populations will be confirmed after unblinding.

The **Magnetic resonance** (MR) cohort includes all subjects in the target population who were randomised to study treatment and completed at least one post-baseline MRI/MRS assessment. These subjects will be expected to perform the magnetic resonance assessment at baseline, 12 and 18 months. Therefore, this cohort will form the basis for analysis of all MRI/MRS parameters.

The definitions for all the above analysis sets are sufficient to determine the subjects included and there will be no requirement for formal review and approval of population membership by Italfarmaco.

Membership to each of the above analysis sets will be determined programmatically based on the data collected and in line with the defined criteria above. The assignment of subjects to each of the analysis sets, except for the PK analysis set, will be determined prior to unblinding, once all study data are available for the respective analysis. For the PK analysis set, final membership to this set will be confirmed following unblinding and will again use programmatic derivations without the requirement for manual review.

All enrolled subjects will be listed indicating their membership to each analysis set along with the reason for exclusion. A listing will also present details of any randomisation code breaks.

3.2 Protocol Deviations

Subject level protocol deviations will be recorded in the eCRF. Prior to database lock (interim and final analyses) or data extract for safety reviews, Italfarmaco will review the individual deviations recorded in the eCRF and classify them as major or minor. The review prior to the final analyses will be conducted at the BDRM and documented as described in Section 2.10.

All protocol deviations will be listed and major protocol deviations will be summarised by treatment group and deviation category.

In addition, site level deviations will be captured and provided to Veristat as a separate report for provision to the IDMC members at safety reviews. This report will not otherwise be included in the formal data presentations covered by this SAP.

3.3 Background and Demographic Characteristics

Demographic characteristics and other baseline characteristics will be listed based on all enrolled subjects and analysed based on the safety analysis set unless specified

otherwise. Additionally, see Section 2.8 regarding use of the target versus overall population.

3.3.1 Demography

Summary statistics will be calculated for continuous variables and the number and percentage of subjects in each category will be presented for categorical variables for each treatment group and overall. Individual subject demographic and baseline data will be listed.

Demographic characteristics (age, ethnic origin and race) and body measurements (height, weight and body mass index) collected at baseline will be summarised by treatment group and overall.

Age at first dose with study treatment will be collected in years and months. However, this will be re-derived in years and months from the subject date of birth and date of first IMP intake. The re-derived age will be used for presentation of demography data and any further data presentations or calculations using age at first dose throughout. Note that the date of birth used in the age calculation will, in all cases, be subject to the rules given in Section 4.4.4.4 prior to the calculation.

BMI will be calculated as follows:

BMI = weight at baseline (kg) / [height at baseline* height at baseline (m^2)]

Individual subject demographic and body measurement data recorded at baseline will be listed.

3.3.2 Diagnosis

A table summarising the time since diagnosis (years) and DMD mutation (deletion, duplication, point mutation) will be presented. This table will also include a summary of the time since steroid initiation (years), type of steroid (Prednisone, Deflazacort, other) and schedule of steroid use.

Time since diagnosis will be calculated in years as the date of informed consent - date of diagnosis + 1.

Time since steroid initiation will be calculated in years as the date of informed consent - start date of initial steroid usage + 1.

Where only a partial date of diagnosis or date of initial steroid usage is available, this will be imputed to the first of the month or 1st January as needed.

All details of DMD diagnosis will be listed in full.

3.3.3 Medical History

Medical history events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1. The number and percentage of subjects will be presented for ongoing conditions and previous conditions separately by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

All events will be listed.

3.4 Administration of Investigational Medicinal Products

The duration (days) of exposure to the study treatment will be calculated as date of last exposure to study drug – date of first dose + 1. Where these data are analysed

prior to study completion, the duration of exposure will be calculated as follows for subjects who have not yet completed the study: date of data cut for analysis – date of first dose + 1. The actual duration of treatment will be calculated as the exposure period – number of days on which treatment was temporarily withdrawn (calculated from the start and end dates of any modification recorded as 'Dose temporarily stopped' or 'Dose skipped'). Where only the morning or evening dose is recorded as skipped, this will be counted as 0.5 days of withdrawn treatment.

At each visit, the 'Subject Compliance' page of the eCRF will be completed with details of the last IMP dose taken, any doses missed and the date and timing of the first IMP dose at the visit. For subjects who were enrolled after the introduction of this eCRF page, total percent compliance for the study will be calculated as follows:

Total number of expected doses = Duration of exposure (days) x 2

Total number of missed doses = Sum of number of missed doses at all visits

Total number of doses taken = Total expected doses – Total missed doses

Total percent compliance = Total doses taken / Total expected doses x 100

For subjects who were enrolled prior to the introduction of the 'Subject Compliance' eCRF page, total percent compliance will be calculated using the information collected on the 'Investigational Medicinal Product Administration' page as follows:

Total number of expected doses = Duration of exposure (days) x 2

Total number of missed doses = Number of days on which treatment was temporarily withdrawn or skipped x 2*

Total number of doses taken = Total expected doses – Total missed doses

Total percent compliance = Total doses taken / Total expected doses x 100

* Number of days on which treatment was temporarily withdrawn will be calculated from the start and end dates of any modification recorded as 'Dose temporarily stopped' or 'Dose skipped'. Where only the morning or evening dose is recorded as skipped, this will be counted as 0.5 days of withdrawn treatment equating to one dose missed for the respective day.

Subjects will be categorised as 'compliant' or 'not compliant', where compliant subjects are those who achieve >80% overall compliance according to the above calculation.

A table will be presented to summarise the duration of exposure to study treatment, actual duration, percent compliance and number and percentage of subjects categorised as compliant, by treatment group and overall for the safety analysis set. This table will also summarise the total daily dose of treatment administered by visit, allowing for any dose modifications. This will be presented both for total daily dose measured in mg, as well as for total daily dose measured in mg per kg. Total daily dose (mg per kg) will be calculated as: total daily dose (mg) at the time of the visit / most recent non-missing subject weight (kg) at the time of the visit. In addition, the table will summarise total weight adjusted exposure (mg/kg), calculated as:

$$\sum(\text{duration of dosing period (days)} * \text{total daily dose for dosing period (mg per kg)})$$

where the duration of dosing period refers to the duration each different dose was taken, excluding interruptions and skipped doses.

Details about medication bottles dispensed and returned, study drug administration and modifications, compliance and derived variables will be listed for the safety analysis set.

3.5 Investigational Medicinal Product Modifications

The number and percentage of subjects in the safety analysis set with and without any IMP modification, as well as the number and percentage of subjects with each type of IMP modification (dose increased, dose reduced, dose permanently stopped, dose temporarily stopped or dose skipped) and the reason for the modification (adverse event or other) will be summarised by treatment group and overall for each visit and overall for the study. For each visit in this table, the summaries will be presented both in relation to the number of subjects recording modifications in the time from the previous visit up to and including the time of the respective visit and also the cumulative number of subjects who have recorded a modification at any visit up to and including the respective visit. The overall cumulative summary will additionally include the number and percentage of subjects who recorded more than one occurrence of each type of IMP modification during the study. A separate table will summarise the duration of first temporary dose interruption (for subjects with temporary dose interruption) and time from first IMP administration to the first dose modification of each type, presented by treatment and overall for the safety analysis set. Finally, a further table will present descriptive statistics for the number of times dose was temporarily stopped for each patient both in total and by visit.

All details about IMP modifications will be listed for the safety analysis set, including flags to indicate any subject who recorded more than one occurrence of a dose reduction and those who recorded more than one occurrence of a temporary stop (with an indication of the number of temporary stops where this is the case).

3.6 Ankle Range of Motion

Summary statistics of ankle dorsiflexion flexed (left and right) and ankle dorsiflexion straight (left and right) will be presented by treatment group and overall for the all enrolled subjects set.

All ankle range of motion data will be listed in full for the all enrolled subjects set.

3.7 Muscle Strength Test Modified MRC Grade

Muscle strength test modified MRC grade will be evaluated for each knee at baseline. The number and percentage of subjects with each modified MRC grade will be presented by treatment group and overall for each knee for the safety analysis set. All baseline data for muscle strength test modified MRC grade will be listed for the all enrolled subjects set.

3.8 Blood Collection for Genotypes

Haplotypes of LTBP4 (VTTT, IAAM and other), SPP1 (TT, GT and GG) and the number of samples collected will be summarised by treatment group and overall for the all enrolled subjects set.

All genotype data will be listed in full for the all enrolled subjects set.

Only overall haplotype results will be summarised and listed. Any further results for sub-parameters (e.g. relating to different positions on the gene and nucleotide substitutions) will not be presented but will be kept within the data for reference.

4 EFFICACY EVALUATION

Unless specified otherwise, all listings will be based on the all enrolled subjects set. All efficacy analyses and summaries will be performed on the ITT analysis set with the exception of analyses and summaries presenting MRI/MRS data which will be on the MR cohort. Additionally, see Section 2.8 regarding use of the target versus overall population.

Baseline is defined as the last non-missing value recorded prior to or on the date of first study treatment. Where the value is recorded on the same date as first study treatment and there is no further information to confirm whether this was prior to start of treatment, the value will be considered prior to treatment if this was a screening or randomisation assessment and will be considered post treatment otherwise.

4.1 Primary Efficacy Variable

The primary efficacy assessment for this study is based on the time to climb 4 standard stairs (4SC) at 18 months. The primary endpoint is the mean change in time to climb 4 standard stairs before and after 18 months of treatment of givinostat versus placebo. Baseline 4SC will be the measurement taken at the randomisation assessment unless this is missing in which case baseline will be taken as the last non-missing value recorded prior to or on the date of first study treatment.

In addition to the 4SC recorded in seconds, functional adaptation employed by the subject during the test will be evaluated and graded by functional evaluators according to standardised scales (See Appendix 7.1).

Summary statistics of 4SC observed values and change from baseline will be presented by visit and treatment. In addition, a plot of the average 4SC at each visit will be produced by treatment group.

A shift table showing the movement of subjects with respect to functional adaptation options for the 4SC from baseline to 18 months after treatment will be presented by treatment.

Furthermore, in order to additionally assess the 4SC data in terms of velocity rather than time, a reciprocal transformation will be applied to convert the timed results to appropriate units of velocity, according to the following conversion:

$$\text{Velocity (stairs/second)} = 4 / \text{Completion time (seconds)}$$

where this conversion is applied following any imputation of missing data as described in Section 4.4.4. The summary statistics and plot described above will be repeated for these transformed values. Analysis of this endpoint (described in Section 4.4.2) will also be repeated on the transformed scale.

All 4SC and functional adaptation data will be listed.

4.2 Key Secondary Efficacy Variables

All key secondary efficacy data will be listed. All key secondary efficacy variables will be formally assessed after 18 months of treatment.

4.2.1 Functional Key Secondary Efficacy Variables

4.2.1.1 Time to Rise from Floor

The mean change from baseline in time to rise from the floor after 18 months of treatment with givinostat versus placebo will be assessed. Time to rise from the floor will also be graded by functional evaluators according to standardised scales (see Appendix 7.2).

Summary statistics of time to rise from floor observed values and change from baseline will be presented by visit and treatment group. A plot of the average time to rise from the floor over time by treatment group will be produced.

A shift table showing the movement of subjects with respect to functional adaptation options employed for rising from the floor from baseline to 18 months after treatment will be presented by treatment group.

Note that where subjects have stopped the test prematurely, this is equivalent to not completing the test and therefore the missing time to rise from floor will be imputed according to the rules in Section 4.4.4 for summaries, plots and analyses.

Furthermore, in order to additionally assess the time to rise from floor data in terms of velocity rather than time, a reciprocal transformation will be applied to convert the timed results to appropriate units of velocity, according to the following conversion:

Velocity (1/second) = 1 / Completion time (seconds)

where this conversion is applied following any imputation of missing data as described in Section 4.4.4. The summary statistics and plot described above will be repeated for these transformed values. Analysis of this endpoint (described in Section 4.4.2) will also be repeated on the transformed scale.

4.2.1.2 Distance Walked in 6 Minutes

The mean change from baseline in 6MWT after 18 months of treatment with givinostat versus placebo will be assessed.

The number and percentage of subjects who completed the assessment and who stopped the assessment prematurely will be presented by visit and treatment group. Summary statistics of 6MWT observed values and change from baseline will be presented by treatment group. In addition, a plot of the mean 6MWT over time will be produced by treatment group. Summary statistics of observed values and change from baseline in the number of falls will also be presented. Note that subjects who stopped the test prematurely will still be included in the summaries, plots and analyses of the total distance walked by the end of the test and the number of falls.

4.2.1.3 Physical Function as Measured by NSAA

The 17 items of the NSAA, ranging from ability to stand to ability to run 10 metres, will be graded using a standard score card with each assessment rated as 0 – unable to achieve independently, 1 – modified method but achieves goal independent of physical assistance from another, or 2 – normal with no obvious

modification of activity. The total NSAA score will be calculated as the sum of the scores for each of the items. Where one or more scores for the 17 items are missing at a visit, the relevant rules described in Section 4.4.4 and Appendix 7.5.4 will be followed.

The first key secondary endpoint associated with NSAA is the change from baseline in the total NSAA score to after 18 months of treatment with givinostat or placebo.

The second key secondary endpoint associated with NSAA is the cumulative loss of function on the NSAA over 18 months of treatment with givinostat or placebo. For each subject at each post-baseline visit, failure to perform each of the 17 items of the NSAA will be assessed, where 'failure' is defined as a score transition from 2 or 1 at baseline to 0 at the respective visit. The total number of failed items for the visit will be calculated (maximum of 17 failed items per visit per subject). The subject's cumulative number of failures across all visits will be the sum of the total failures at each post-baseline visit. Subject cumulative number of failures across all post-baseline visits will be the endpoint of interest for analysis. In addition, total failed items at baseline will be calculated for each subject as the number of items with a score of 0 at the baseline NSAA assessment. Where one or more scores for the 17 items are missing, the relevant rules described in Section 4.4.4 and Appendix 7.5.4 will be followed. Note that as a result of the rule to impute any scheduled visits after early withdrawal, early withdrawal subjects will be included in the analysis using both collected and imputed assessments to calculate the cumulative number of failures post-baseline. The early withdrawal visit itself will be excluded from the cumulative number of failures across all post-baseline visits since this is an additional visit for these subjects outside of the expected scheduled post-baseline visits and would result in an inflated cumulative count. Where a subject scores zero at baseline on all items of the test, they will be excluded from the summaries and analyses of cumulative loss of function.

Summary statistics for the observed responses and change from baseline for each item included in the NSAA assessment, as well as for the total NSAA score will be presented by visit and treatment group.

Summary statistics will also be presented for baseline total items failed and for subject cumulative number of failed items across all post-baseline visits by treatment group. In addition the number and percentage of subjects meeting the above criteria for failure will be presented by visit for each of the NSAA items.

4.2.1.4 Muscle Strength Evaluated by Knee Extension and Elbow Flexion as Measured by Hand-held Myometry

The key secondary efficacy endpoint related to muscle strength is the mean change from baseline to 18 months after treatment with givinostat versus placebo in muscle strength evaluated by knee extension and elbow flexion. These muscle strength variables will be measured by hand-held myometry (HHM).

Summary statistics of the observed muscle strength measured in N (left knee extension, right knee extension, left elbow flexion and right elbow flexion) and change from baseline will be presented by visit and treatment group. If more than one measurement is taken, the arithmetic mean of the measurements will be used for that visit for that particular subject. These summaries will be repeated for muscle strength assessments normalised by subject weight (i.e. measured in N/Kg). A plot of the mean muscle strength (measured in N/Kg) over time will be produced by treatment group.

The endpoint values of interest for analysis will be the normalised muscle strength values (N/Kg).

4.2.2 Imaging Key Secondary Efficacy Variable (MR Cohort)

4.2.2.1 Fat Fraction of Vastus Lateralis Muscles assessed by MRS

The key secondary efficacy endpoint relating to imaging data will be the mean change in VL MFF as assessed by MRS before and after 18 months of treatment with givinostat versus placebo. Analysis of this endpoint will only apply to the MR cohort (who will complete magnetic resonance assessment at baseline, 12 and 18 months).

Observed values and change from baseline in VL MFF will be summarised by visit and treatment group for the MR cohort. The listing of MRS data for the final analysis will include the baseline data for all subjects, as well as the post-baseline data for the MR cohort, with a flag to indicate subjects in the MR cohort.

For all analyses of MRS VL MFF, the final results from the blinded review of these data by University of Florida Imaging DMD network (see Section 2.3) will be used (external to the eCRF). The baseline VL MFF value initially entered onto the eCRF, prior to any adjustment from blinded review, will not be used in the analyses and will only be used for the purposes of assignment to target or off-target populations. It is acknowledged that there may be differences between the initial eCRF baseline result and the final baseline result following blinded review. This could mean that the adjusted result indicates the subject is in a different target/off-target population to that assigned from the initial eCRF result. Population assignment will not be adjusted for this. However, the listing of MRS data will include the baseline results from both the eCRF and final blinded data with an indication of the target/off-target outcome in each case.

4.3 Exploratory Efficacy Variables for All Subjects

All exploratory efficacy endpoint data will be listed. The exploratory efficacy variables will be analysed at the final analysis after 18 months of treatment and will be supportive only and not subject to alpha control. Therefore, nominal p-values will be presented with no adjustment.

4.3.1 Time to Run/Walk 10 Metres

Mean change before and after 18 months of treatment with givinostat and placebo in the time to run or walk 10 metres will be assessed. Summary statistics of observed values and change from baseline in the time to run or walk 10 metres will be presented by visit and treatment group. A plot of the average time to run/walk 10 metres at each visit will also be produced by treatment group. A shift table showing the movement of subjects with respect to functional adaptation options (see Appendix 7.3) from baseline to 18 months after treatment will also be presented by treatment group.

Note that where subjects have stopped the test prematurely, this is equivalent to not completing the test and therefore the missing time to run or walk 10 metres will be imputed according to the rules in Section 4.4.4 for summaries, plots and analyses.

Furthermore, in order to additionally assess the time to run or walk 10 metres data in terms of velocity rather than time, a reciprocal transformation will be applied to

convert the timed results to appropriate units of velocity, according to the following conversion:

Velocity (metres/second) = 10 / Completion time (seconds)

where this conversion is applied following any imputation of missing data as described in Section 4.4.4. The summary statistics and plot described above will be repeated for these transformed values. Analysis of this endpoint (described in Section 4.4.2) will also be repeated on the transformed scale.

4.3.2 Paediatric Outcomes Data Collection Instrument (PODCI) Scores

The PODCI quality of life questionnaire can either be completed by the subject's parent or the subject themselves. A total of five subscales (upper extremity function; transfer and basic mobility; sports and physical functioning; pain/comfort and happiness) and one global function scale can be calculated from the questionnaire.

Summary statistics for the raw scores and standardised scores, together with the change from baseline over time for each subscale included in the PODCI assessment, as well as for the standardised scores of the global function scale will be presented by treatment group. These tables will be produced separately for assessments completed by parents and for assessments completed by the subjects themselves. The endpoints of interest will be the change from baseline to 18 months in the standardised scores for each subscale and the global function scale, as completed by the parent and the subject.

Details of the items included in each of the subscales, as well as the calculations to be applied in order to derive the raw and standardised scores, are included in Appendix 7.4.

4.3.3 Percent Predicted 6MWT

The endpoint associated with the % predicted 6MWT is the mean change from baseline to after 18 months of treatment with givinostat or placebo in % predicted 6MWT. The predicted 6MWT at baseline is against healthy male subjects and is calculated using the Geiger formula (Geiger R, 2007) which is given as:

♂: $6MWT = 196.72 + (39.81*age) - (1.36*age^2) + (132.28*height)$

where age is the re-derived age in years and months at first study drug intake and height is in metres at baseline. The % predicted 6MWT at each visit for a subject is then found as: measurement for 6MWT at the visit / predicted 6MWT at baseline * 100.

Summary statistics of the % predicted 6MWT observed values and change from baseline will be presented by visit and treatment group. In addition, subjects will be assigned to one of two subgroups based on their baseline % predicted 6MWT value (<80% versus ≥80%). A summary table will present the observed values and changes from baseline over time for actual 6MWT values by treatment group and baseline % predicted 6MWT subgroup.

4.3.4 MRI Parameters (MR Cohort Only)

The quantitative analysis of the acquired MRI imaging and QC reviewing will be performed by blinded personnel from University of Florida Imaging DMD. Two QC reviewers will cross-reference the event; in case of disagreement in grading, a third reader will provide independent grading as a tiebreaker.

The following MRI observed values and change from baseline will be summarised by visit and treatment group for the MR cohort. The endpoints of interest will be the mean change from baseline to 18 months in:

- Fat fraction in 5 thigh muscles or muscle groups
    - Vastus lateralis
    - Biceps femoris long head
    - Semitendinosus
    - Quadriceps, encompassing the vastus lateralis, vastus intermedius, vastus medialis, rectus femoris
    - Hamstrings, encompassing the biceps femoris, semitendinosus, semimembranosus.
- Cross-sectional area of 5 thigh muscles or muscle groups
    - Vastus lateralis
    - Biceps femoris long head
    - Semitendinosus
    - Quadriceps, encompassing the vastus lateralis, vastus intermedius, vastus medialis, rectus femoris.
    - Hamstrings, encompassing the biceps femoris, semitendinosus, semimembranosus.
- Fat-corrected cross-sectional area (i.e. contractile CSA) of 5 thigh muscles or muscle groups
    - Vastus lateralis
    - Biceps femoris long head
    - Semitendinosus
    - Quadriceps, encompassing the vastus lateralis, vastus intermedius, vastus medialis, rectus femoris.
    - Hamstrings, encompassing the biceps femoris, semitendinosus, semimembranosus.

The listing of MRI data for the final analysis will include the baseline data for all subjects, as well as the post-baseline data for the MR cohort, with a flag to indicate subjects in the MR cohort.

4.3.5 Time to 10% Persistent Worsening in 6MWT

Time to 10% persistent worsening in 6MWT will be defined as the time from the date of first study treatment to the last time the 6MWT was not ≥10% worse than the baseline 6MWT (McDonald, et al., 2013). If a subject has not achieved ≥10% persistent worsening in 6MWT, then time to 10% persistent worsening in 6MWT will be censored at the date of the last 6MWT assessment (including imputed assessments per Section 4.4.4.1), i.e. the 18 month assessment.

The number and percentage of subjects who achieved ≥10% persistent worsening in 6MWT and of those censored will be summarised by treatment group. The Kaplan-

Meier estimates of the median, 25th percentile and 75th percentile for time to ≥10% persistent worsening in 6MWT, together with the associated 2-sided 95% confidence intervals (CI) will also be presented by treatment group. Time to 10% persistent worsening in 6MWT will also be presented graphically by treatment group using a Kaplan-Meier plot.

4.3.6 Proportion of Subjects with ≥10% Persistent Worsening in 6MWT

The proportion of subjects with ≥10% persistent worsening in 6MWT at the end of the study (compared to baseline) will be summarised by treatment group. Subjects with ≥10% persistent worsening in 6MWT at the end of the study will be defined as those who record a 6MWT value which is ≥10% worse than the baseline 6MWT at any visit before or at the end of the study and this remains ≥10% worse than baseline until the end of the study.

4.3.7 Time to Persistent Loss of Standing (Baseline Through End of Study)

Functional assessments are scheduled to take place every 3 months. In order to allow time for recovery due to trauma, a subject will be considered to have persistent loss of standing if they are unable to stand for at least 2 consecutive assessments (i.e. at least 6 months). Start of a persistent loss of standing will be the first assessment where this is observed. A subject is unable to stand if their score for "Rise from floor" on the NSAA assessment is 0b ("Unable") and if their rising from floor grading is 1 on the Rise from floor assessment. If a subject has not met the criteria for persistent loss of standing by the end of the study, the time to persistent loss of standing will be censored at the date of the last NSAA or Rise from floor assessment (including imputed assessments per Section 4.4.4.1), i.e. the 18 month assessment.

The number and percentage of subjects who have persistent loss of standing at any point post-baseline, as well as those censored, will be summarised by treatment group. Time to persistent loss of standing will be calculated as the time from the date of first study treatment to the start of the first occurrence of persistent loss of standing. The Kaplan-Meier estimates of the median, 25th percentile and 75th percentile for time to persistent loss of standing, together with the associated 2-sided 95% CIs will also be presented by treatment group. Time to persistent loss of standing will also be presented graphically by treatment group using a Kaplan-Meier plot.

4.3.8 Proportion of Subjects Who Lose Ambulation

The proportion of subjects who lose ambulation during the study will be summarised by treatment group. Loss of ambulation is defined as any subject who satisfies both of the following criteria at the same visit at any point prior to or at the end of the study and continues to satisfy the criteria at all subsequent visits to the end of the study:

- Subject is unable to perform the 6MWT due to physical inability
- Subject is unable to complete the 10-metre walk/run test in 30 seconds or less without any support or devices (10-metre walk/run test grading ≤2).

4.3.9 Correlation between the effect of Givinostat on disease progression and the type of DMD mutation, LTBP4 and Osteopontin genotype

The exploratory endpoint of interest here is to evaluate any correlation between the effect of givinostat on disease progression and separately: the type of DMD mutation (Deletion, Duplication, Point Mutation); LTBP4 genotype (VTTT, IAAM, Other); Osteopontin (SPP1) genotype (TT, GT, GG). This will be evaluated via summaries, plots and analyses for these subgroups of subjects, as described in Section 4.4.6. If deemed of interest, additional investigation into correlation between these subgroups and the effect of givinostat on disease progression may be included at a later date as post hoc analyses.

4.3.10 DMD serum biomarker

A listing will present details regarding sample collection for evaluation of any possible DMD serum biomarker. Summary and analysis of results of the DMD serum biomarker assessment will not be included as part of this SAP but in a separate dedicated SAP.

4.4 Statistical Analysis

4.4.1 Hypothesis to be Tested

The null hypothesis being tested for the primary endpoint is that there is no difference in mean change in 4SC from baseline to 18 months between the givinostat and placebo treatment groups:

$$H_0: 4SC_{givinostat} = 4SC_{placebo}$$

The alternative hypothesis is that there is a difference in either direction in the mean change in 4SC from baseline to 18 months between the givinostat and placebo treatment groups:

$$H_0: 4SC_{givinostat} \neq 4SC_{placebo}$$

All tests will be two directional and thus references to 1-sided p-values throughout this SAP refer to significance in either direction. For all analyses, 2-sided p-values will be presented and will be subject to the relevant significance level in either direction, as stated in Section 4.4.5. Similarly, 2-sided CIs will be presented.

4.4.2 Modelling Methods

All efficacy analyses will be conducted in the target population. Formal analysis will be conducted as described in this Section for the following in the target population: the primary efficacy endpoint at 18 months, all key secondary efficacy endpoints at 18 months. All other analyses (i.e. for different endpoints or timepoints in the target population, sensitivity or supplementary analyses, or any efficacy analyses later added for the overall population) will be supportive only and will not be subject to alpha control. Therefore, nominal p-values will be presented.

The change from baseline to 18 months after treatment with givinostat or placebo for the continuous efficacy variables described in Sections 4.1, 4.2 and 4.3 will be analysed using an analysis of covariance (ANCOVA). Note that the ANCOVA analysis of muscle strength will be performed on the normalised muscle strength variable (measured in N/Kg) only. In addition, the ANCOVA analysis of NSAA will be performed on the total NSAA score only, ANCOVA analysis of PODCI scores will be performed

on the standardised scores only (for each subscale and the global function scale as completed by subject and parent), and ANCOVA analysis of MRI parameters will be performed for the fat fraction results only. In each instance, the dependent variable will be the outcome being modelled and terms for the corresponding baseline value and re-derived age at first dose (in years and months) will be included as independent covariates in the model, with randomised treatment group and concomitant steroid use (according to the 4 possible strata) included as independent classification factors. Where the dependent variable is not the muscle strength test, MRS VL MFF, PODCI score or MRI parameters, additional covariates will also be included in the model for the following baseline values (where not already included): 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes (for the analysis of percent predicted 6MWT, this will be replaced with baseline percent predicted distance walked in 6 minutes).

Least squares means and associated 2-sided CIs will be estimated for givinostat and placebo. The treatment effect, being the difference in least squares means (givinostat-placebo), will be presented along with the associated 2-sided CI and p-value.

The need for a possible log transformation of these variables will be investigated prior to unblinding by assessing the ANCOVA model residuals without a treatment term. Where data are transformed for analysis, back transformation will be applied for the presentation of results. Presentation of the tables will be amended as needed for this, for example with the addition of an explanatory footnote.

Analysis of cumulative loss of function on the NSAA over 18 months of treatment with givinostat or placebo will be performed using negative binomial regression. The dependent variable will be the subject cumulative number of failures across all post-baseline visits. Total failed items at baseline, baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose (in years and months) will be included as independent covariates in the model, with randomised treatment group and concomitant steroid use included as independent classification factors. The estimated cumulative number of failures across 18 months and associated 2-sided CIs from the model will be presented for each treatment group. The treatment effect will be presented as the ratio of cumulative failures for givinostat relative to placebo along with the associated 2-sided CI and p-value, where a lower ratio indicates a greater reduction in cumulative number of failures across 18 months for givinostat compared with placebo.

The binary efficacy variables (proportion of subjects with $\geq$ 10% persistent worsening in 6MWT, proportion of subjects losing ambulation during the study) will be analysed using logistic regression. In each instance baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose (in years and months), will be included as independent covariates. Randomised treatment group and concomitant steroid use will be included as independent classification factors. The odds ratio comparing the treatment groups will be presented, together with its associated 2-sided CI and p-value.

The time to event variables (time to 10% persistent worsening in 6MWT, time to persistent loss of standing) will be analysed using Cox proportional hazards modelling, including baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose (in years and months) as independent covariates and randomised treatment group and concomitant steroid

use as independent classification factors. The hazard ratio will be presented, together with its associated 2-sided CI and p-value.

Where adjustment of alpha is applied to any of the above analyses per the methods described in Section 4.4.5, the 2-sided CIs will be subject to the corresponding adjustment. Thus the adjusted 2-sided CIs will be as indicated in the following table:

Analysis Time Point	Endpoint	Applicable p-value (1-sided)	Applicable p-value (2-sided)	CI (2-sided)
Final analysis	4SC at 18 months in the target population	$p \leq 0.025$	$p \leq 0.05$	95%
Final analysis	Key secondary efficacy endpoints at 18 months in the target population	$p \leq 0.025/i$ (i = rank according to Hochberg procedure)	$p \leq 0.05/i$ (i = rank according to Hochberg procedure)	100(1-0.05/i)% (i = rank according to Hochberg procedure)
General	All other analysis (supportive only)	$p \leq 0.025$ (nominal p-values presented)	$p \leq 0.05$ (nominal p-values presented)	95%

For the final analysis of key secondary efficacy endpoints at 18 months in the target population, unadjusted 95% CIs will be presented in the individual analysis tables. However, the applicable adjusted CIs following the Hochberg procedure will be given in an overall summary of these endpoints per Section 4.4.5.

Further, as a reflection of the overall totality of evidence for a treatment effect on functional outcomes, the primary endpoint and the functional key secondary endpoints (as detailed in Section 4.2.1) will be subject to assessment by Hochberg. This is equivalent to considering the primary and functional key secondary endpoints as equally important facets of the disease such that an improvement in any one, or more than one, of these endpoints can be considered to reflect a clinically meaningful benefit to the patient.

4.4.3 Adjustment for Covariates

All efficacy analyses will be adjusted for covariates as described in Section 4.4.2. These will include the corresponding baseline value and re-derived age at first dose (in years and months) as covariates, and concomitant steroid use as a factor. Additional covariates will also be included for the following baseline values where appropriate (see Section 4.4.2): 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes (for the analysis of percent predicted 6MWT, this will be replaced with baseline percent predicted distance walked in 6 minutes).

4.4.4 Handling of Missing Data

4.4.4.1 Classification and Imputation

For the efficacy analyses, any missing data for continuous values for a subject will be classified as follows:

1. the subject has missing data due to reasons other than being non-ambulatory or physically unable to perform the test / assessment
2. the subject has missing data due to being either non-ambulatory or otherwise physically unable to perform the test / assessment.

Any missing values classified as 1 will be imputed using the mean of all non-missing values for the respective measurement and timepoint across all subjects randomised to the respective treatment and in the respective concomitant steroid stratum and Group (i.e. Group A, target population or Group B, off-target population).

Any missing values classified as 2 will be imputed by setting the value to zero or to twice the maximum non-missing value recorded across all subjects depending on the directionally of the test.

In all cases, imputation of any data classified as 1 will be completed first, followed by imputation of any data classified as 2.

Classification and imputation of missing data will be completed prior to any transformation of the data for analysis. For example transformation of the timed function test results for presentation of velocity or any log transformation applied as needed (per Section 4.4.2).

For binary or time to event variables where missing data means that the binary response or time to event cannot be determined, the missing data from which the variable is derived (e.g. 6MWT values) will first be classified and imputed, as described above, in order to then derive the binary response or the time to event. Exceptions to this are where the criteria for deriving the binary response themselves refer to presence of missing data, for example loss of ambulation. The classification described above will be used for the relevant missing data in these cases in order to confirm physical inability to complete the respective test. Further details are given below regarding the rules for derivation of the binary endpoints in the presence of missing data.

For the NSAA assessment, where the total score is a sum of ordinal item scores, imputation of Class 1 and Class 2 data will follow a different approach as defined in Appendix 7.5.4.

The rules for classifying missing data from the responses on the eCRF and any additional considerations for imputation are given in Appendix 7.5 for each respective endpoint. Unless otherwise stated, only the value of interest for analysis will be classified and imputed. For example, the ‘duration’ for the 4SC assessment will be imputed but not the 4-stair ascent grading.

Note that missing data at any scheduled timepoint should be imputed according to the above rules. This includes any scheduled timepoints after a subject withdraws early. In these cases, where the final assessment prior to withdrawal was missing and determined to be Class 2 missing data, all missing assessments post withdrawal will also be considered Class 2. Otherwise, these will be considered Class 1. Note that where this applies to an NSAA assessment, ‘Class 1’ will refer to the scenario where

'Was assessment attempted?' = 'No'. Where a date of assessment is required, the predicted date for imputed timepoints post withdrawal will be used. The same approach will be followed for any completely missing visits prior to withdrawal or completing the study, where no information has been entered into the respective CRF assessment page indicating whether or not it was performed.

Where data entered into the CRF for an assessment are ambiguous such that they do not reflect any of the expected responses outlined in Appendix 7.5 and therefore missing data cannot be classified, a worst case approach will be followed and the missing data will be assumed Class 2.

A review will be performed at the BDRM to confirm correct classification of missing data. This may identify data entered into the CRF assessment page which comply with Appendix 7.5 but additional information is available to contradict the classification (for example in comments). Any such cases will be assessed on a case by case basis to determine the appropriate classification to be applied.

4.4.4.2 Analysis

Once classified and imputed, the following procedures will be applied for the analysis of endpoints where there are missing data with imputation. The approach will be dependent on the class(es) of missing data present and also the directionality of the test where Class 2 missing data are present. Any analysis of binary or time to event variables with missing data, or the cumulative loss of function on the NSAA, will use the appropriate procedure described in Section 4.4.2, following any classification and imputation per the methods above. Thus, the below procedures apply only to the continuous variables.

Note that where the endpoint to be analysed is a change from baseline, any imputation (per the following procedures) will be applied to the observed values prior to finding the corresponding change from baseline.

Variables with only Class 1 missing data

For the following variables, only Class 1 missing data will be applicable:

- VL MFF determined by MRS
- PODCI standardised scores for each subscale and the global function scale, as completed by the parent and the subject
- Fat fraction in 5 thigh muscles as determined by MRI
- Cross-sectional area of 5 thigh muscles as determined by MRI
- Any other variable where all missing values have been classified as 1 and no Class 2 missing values have been identified.

Any missing values will be imputed as per the rules for Class 1 missing data and the applicable analysis will be performed as described in Section 4.4.2 and Sections 4.1 to 4.3.10 as relevant to the respective variable.

Variables with any Class 2 missing data where higher values are worse

For the following variables, the directionality is such that higher values represent a worse outcome:

- 4SC
- Time to rise from the floor
- Time to run/walk 10 metres

If any Class 2 missing data are identified for these variables, the analysis of the variable will be performed as follows:

If x_{ijk} represents the value of the variable to be analysed for subject i randomised to treatment j at time k, then missing data will be imputed as

Class 1: $x_{ijk} = \bar{x}_{jk}$ where $\bar{x}_{jk}$ is the mean of all non-missing values for the respective measurement at time k across all subjects randomised to treatment j and in the respective concomitant steroid stratum and Group (i.e. Group A, target population or Group B, off-target population).

Class 2: $x_{ijk} = 2 \times Max(x)$ where $Max(x)$ is the maximum non-missing value recorded for the variable across all subjects, regardless of treatment, stratum or Group.

Following the assignment of imputed values, the data x_{ijk} will be analysed as described in Section 4.4.2 and Sections 4.1 to 4.3.10, as relevant to the respective variable using PROC MIXED, ensuring that reference levels are stated for all class variables so that difference in LSmeans is calculated as givinostat-placebo. F-tests from PROC MIXED will be based on Kenward-Roger's adjusted degrees of freedom.

LSmeans for drug and placebo from this model, denoted $\bar{x}_D$ and $\bar{x}_P$ respectively, the difference in the LSmeans, $\bar{x}_D - \bar{x}_P$, and the associated 2-sided CI and p-value will be taken from the LSmeans statement in PROC MIXED.

Note that for the analysis of these variables on the transformed scale representing velocity rather than time, transformation will be applied to the imputed data x_{ijk} to give the velocity values u_{ijk} used in the analysis model described above. The results from the model will be presented on the transformed scale without back transformation and will be interpreted as estimates of velocity.

Variables with any Class 2 missing data where lower values are worse

For the following variables, the directionality is such that lower values represent a worse outcome:

- 6MWT
- Percent predicted 6MWT
- NSAA
- Muscle strength evaluated by knee extension and elbow flexion as measured by HHM.

If any Class 2 missing data are identified for these variables, the analysis of the variable will be performed as follows:

If x_{ijk} represents the value of the variable to be analysed for subject i randomised to treatment j at time k, then subjects with missing data will be imputed as

Class 1: $x_{ijk} = \bar{x}_{jk}$ where $\bar{x}_{jk}$ is the mean of all non-missing values for the respective measurement at time k across all subjects randomised to treatment j and in the respective concomitant steroid stratum and Group (i.e. Group A, target population or Group B, off-target population).

Class 2: $x_{ijk} = 0$

The exception to this is the NSAA total score which will be derived from imputed item scores as described in Appendix 7.5.4.

Following the assignment of imputed values, these variables will be analysed as described in Section 4.4.2 and Sections 4.1 to 4.3.10, as relevant to the respective variable, using the same PROC MIXED approach as detailed above.

4.4.4.3 Tipping Point Sensitivity Analysis

In addition to the above methods for handling missing data, if the treatment effect on the primary analysis is significant, a 'tipping point' sensitivity analysis of the primary outcome will be performed. This analysis assesses the impact of missingness across a continuum of assumptions until the 'tipping point' is identified. This is the point at which the assumption regarding the effect of the treatment in subjects with missing data nullifies or reverses the treatment effect obtained in the primary analysis. Implementation of this sensitivity analysis mimics standard multiple imputation and is described below:

1. For any Class 1 missing 4SC values, use the mean and SD of all non-missing values for the respective treatment group to generate the imputed values from a normal distribution. Note that any Class 2 missing 4SC values should continue to be imputed with twice the maximum non-missing value recorded across all subjects as applicable per the above rules.
2. Implement Step 1 10 times so that 10 complete datasets are produced. For each of these datasets, find the change from baseline to 18 months in 4SC values for each subject.
3. Analyse the 10 complete datasets; this should be performed as described in Section 4.4.2 using the PROC MIXED approach described in Section 4.4.4.2.
4. Combine the results from the 10 data sets using Rubins methods via PROC MIANALYZE for inference.
5. Repeat Steps 1 to 4 but now with an appropriate small shift (+δ) applied to the individual subject values for the change from baseline in 4SC in the givinostat treatment group (but not to the placebo group). This shift is applied after step 2, i.e. after the generation of the datasets including any imputation, and after finding the change from baseline values but prior to the analysis of these. The directionality of the shift will be such that this reduces the treatment difference between givinostat and placebo.
6. Display the estimated treatment effect and associated 2-sided CIs vs degree of shift.
7. Repeat Steps 5 and 6, increasing the shift each time as +2δ, +3δ,…,+(treatment effect seen in the primary analysis).
8. Identify the tipping point where p>0.025.

4.4.4.4 Imputation of Date of Birth

For the purpose of any data presentation and calculations requiring date of birth, any partially collected date of birth, or date of birth collected according to quarterly periods, will be imputed according to the following rules.

For all subjects enrolled prior to protocol version 6.0 who did not enrol with the updated CRF page to collect quarterly date of birth, any partial date of birth with a non-missing month and year was imputed to the first of the month at data entry. Any partial date of birth with a non-missing year was imputed to 1st January at data entry. Therefore, date of birth will be used as collected in the analyses and data presentations.

For all subjects enrolled under protocol version 6.0 or above, or who enrolled prior to protocol version 6.0 but with the updated CRF page to collect quarterly date of birth, the collected quarterly date of birth will be imputed to the middle of each quarter as follows:

Collected date of birth = 01JANXXXX, imputed to 14FEBXXXX

Collected date of birth = 01APRXXXX, imputed to 16MAYXXXX

Collected date of birth = 01JULXXXX, imputed to 15AUGXXXX

Collected date of birth = 01OCTXXXX, imputed to 15NOVXXXX

where XXXX is the collected year of birth.

4.4.4.5 Imputation of Dates for Calculations or Classification

Note that where calculations or classification of data relies on the use of partial collected dates, imputation of the partial dates may be performed for the purposes of the derivation. Where this is the case, specific details are provided in the relevant sections of this SAP.

4.4.5 Adjustment for Multiple Comparisons

The p-value applicable to the final analysis of 4SC at 18 months in the target population will be $p \leq 0.025$ 1-sided. For final analysis of the key secondary efficacy endpoints at 18 months in the target population, adjustment for multiple comparisons will be applied as described below. For all other analyses (i.e. for different endpoints or timepoints in the target population, or analyses in the overall population), analysis will be considered supportive only. Therefore, nominal p-values will be presented and the significance level applicable will be $p \leq 0.025$ 1-sided.

In accordance with EMA (European Medicines Agency, 2002) and FDA guidelines (U.S. Food and Drug Administration, 2017), the assessment of multiple key secondary efficacy endpoints at 18 months in the target population at the final analysis will be accounted for using the Hochberg procedure (Hochberg, 1988).

The key secondary efficacy endpoints are given in Section 4.2 (time to rise from the floor, 6MWT, muscle strength evaluated by knee extension, muscle strength evaluated by elbow flexion, physical function as measured by total NSAA score, physical function as measured by cumulative loss of function on the NSAA, VL MFF as assessed by MRS). Each of these endpoints will be analysed and the resulting 1-sided p-values will be ordered in descending order, from least to most significant. The highest p-value will then be compared with 0.025, the specified level of significance for the primary endpoint at the final analysis for this study, and if it is >0.025, the subsequent p-value will be considered in relation to 0.025/2=0.0125. As

soon as the ith endpoint has a corresponding p-value <0.025/i, the treatment effects for that endpoint and all of the endpoints following it are considered to be significant. A table will be presented summarising the p-values and associated adjusted 2-sided CIs from each of the key secondary efficacy endpoints with significance indicated according to the above approach.

4.4.6 Examination of Subgroups

Summaries, plots or analyses of efficacy or safety data presented by subgroup will only be produced in each case if there are at least 5 subjects per treatment arm in at least 2 of the respective subgroup levels.

4.4.6.1 Presentation of Efficacy Data by Subgroup

All repeat summaries and analyses of efficacy data by subgroups will be performed on the target population only and will be considered supportive and not subject to alpha control. Therefore, only nominal p-values will be presented.

In order to determine whether dose interruptions, modifications or starting dose have an impact on the efficacy of givinostat, the following subgroups of subjects will be defined:

- Subjects who maintained treatment for greater than 80% of the time versus those who did not. This will be equivalent to total percent compliance calculated as described in Section 3.4.
- Subjects whose total weight adjusted exposure (mg/kg) was < versus >= the median total weight adjusted exposure (mg/kg). For each subject the total weight adjusted exposure (mg/kg) will be calculated as:

$$\sum(\text{duration of dosing period (days)} * \text{total daily dose for dosing period (mg per kg)})$$

  The median total weight adjusted exposure (mg/kg) will be calculated and used to determine the subgroups.
- Subjects who started on the higher dose specified in Protocol Versions =< 4.0 versus those who started on the lower dose specified in Protocol Versions > 4.0.

The following endpoints will be summarised, plotted and analysed in the same way as described in Sections 4.1, 4.2, 4.3 and 4.4.2 for these subgroups:

- Change from baseline to 18 months of treatment with givinostat or placebo in 4SC
- Change from baseline to 18 months of treatment with givinostat or placebo in MRS VL MFF
- Change from baseline to 18 months of treatment with givinostat or placebo in time to rise from the floor
- Change from baseline to 18 months of treatment with givinostat or placebo in 6MWT
- Change from baseline to 18 months of treatment with givinostat or placebo in muscle strength evaluated by knee extension and elbow flexion

- Change from baseline to 18 months of treatment with givinostat or placebo in NSAA score
- Time to persistent loss of standing
- Proportion of subjects who lose ambulation

In order to determine whether the effects of givinostat versus placebo are related to the type of DMD mutation or the LTBP4 and SPP1 genotypes, three further subgroups of subjects will be defined: DMD mutation (Deletion, Duplication, Point Mutation), LTBP4 (IAMM, VTTT, Other) and SPP1 (TT, GT, GG). The following endpoints will be summarised and plotted for these three subgroups in the same way as described in Sections 4.1 and 4.2:

- Change from baseline to 18 months of treatment with givinostat or placebo in 4SC
- Change from baseline to 18 months of treatment with givinostat or placebo in MRS VL MFF
- Change from baseline to 18 months of treatment with givinostat or placebo in time to rise from the floor
- Change from baseline to 18 months of treatment with givinostat or placebo in 6MWT
- Change from baseline to 18 months of treatment with givinostat or placebo in muscle strength evaluated by knee extension and elbow flexion
- Change from baseline to 18 months of treatment with givinostat or placebo in NSAA score

In addition, the following endpoints will be summarised and analysed for the DMD mutation, LTPB4 and SPP1 subgroups in the same way as described in Sections 4.3.7, 4.3.8 and 4.4.2):

- Time to persistent loss of standing
- Proportion of subjects who lose ambulation

Finally, the following endpoints will be summarised, plotted and analysed as described in Sections 4.1, 4.2, 4.3 and 4.4.2 by baseline age category based on the re-derived age at first dose in years and months (6 – 7 years versus > 7 years). Note that subjects will be assigned to these subgroups so that any age from 6 to 7.9999 years is assigned to the 6-7 years group, any ages from 8 years onwards are assigned to the > 7 years group:

- Change from baseline to 18 months of treatment with givinostat or placebo in 4SC
- Change from baseline to 18 months of treatment with givinostat or placebo in time to rise from the floor
- Change from baseline to 18 months of treatment with givinostat or placebo in 6MWT
- Change from baseline to 18 months of treatment with givinostat or placebo in muscle strength evaluated by knee extension and elbow flexion

- Change from baseline to 18 months of treatment with givinostat or placebo in NSAA score
- Percent predicted 6MWT
- Time to 10% persistent worsening in 6MWT
- Proportion of subjects with ≥10% persistent worsening in 6MWT
- Time to persistent loss of standing
- Proportion of subjects who lose ambulation

4.4.6.2 Impact of Age and Baseline Functional Status on Treatment Effect

Further to the above repeat summaries and analyses by subgroups, an analysis will be conducted to better determine the impact on treatment effect of baseline age and, separately, baseline functional status. This may prompt further post hoc analyses by specific subgroups should this be deemed worthwhile. This analysis will be conducted as described below for each of the following endpoints:

- Change from baseline in 4SC
- Change from baseline in time to rise from the floor
- Change from baseline in 6MWT
- Change from baseline in total NSAA score
- Change from baseline in muscle strength evaluated by knee extension and elbow flexion
- Change from baseline in MRS VL MFF.

Impact of baseline age on treatment effect:

To determine the impact of baseline age, for each of the above endpoints the ANCOVA model described in Section 4.4.2 will be repeated with the addition of the interaction term for treatment by re-derived age at first dose (in years and months). The treatment effect and parameter estimates from the model will be used to plot the treatment effect as a function of age, using:

TrtEffect = B1 + B2*Age, where:

TrtEffect = LS mean difference (givinostat-placebo) for the endpoint

B1 = Parameter estimate for treatment from the model

B2 = Parameter estimate for the treatment by age interaction term from the model

Age = Re-derived age at first dose.

The parameter estimate covariate matrix will be used to compute the variance of the treatment effect as a function of age in order to indicate the confidence interval on the plot.

Impact of baseline functional status on treatment effect:

To determine the impact of baseline functional status for the same endpoints, the ANCOVA model will be repeated again but replacing the treatment by age interaction term with the interaction term for treatment by baseline endpoint value (e.g. treatment by baseline 4SC for the 4SC endpoint). The treatment effect and

parameter estimates from this model will be used to plot the treatment effect as a function of baseline endpoint value, using:

TrtEffect = B1 + B2*Base, where:

TrtEffect = LS mean difference (givinostat-placebo) for the endpoint

B1 = Parameter estimate for treatment from the model

B2 = Parameter estimate for the treatment by baseline endpoint interaction term from the model

Base = Baseline of respective functional endpoint value.

The parameter estimate covariate matrix will be used to compute the variance of the treatment effect as a function of baseline endpoint value in order to indicate the confidence interval on the plot.

4.4.6.3 Presentation of Safety Data by Subgroup

In addition to the above subgroup summaries and analyses of efficacy data, selected summaries of safety data as described in Section 5 will also be repeated by subgroups, for the overall population only.

In order to determine any impact of dose interruptions, modifications or starting dose on safety, the following summaries will be repeated for the subgroups total weight adjusted exposure (mg/kg) < versus >= median total weight adjusted exposure (mg/kg), and higher starting dose (Protocol Versions =< 4.0) versus lower starting dose (Protocol Versions > 4.0):

- All adverse event summaries described in Section 5.1
- All hematology summaries and plots described in Section 5.2.1
- All clinical chemistry summaries and plots described in Section 5.2.2 but restricted to triglycerides only.

4.4.7 Supplementary Analyses

4.4.7.1 Impact of 18 Month Visits Performed Outside of Expected Assessment Windows

As described in Section 2.9, in order to address the impact of the COVID-19 pandemic in terms of 18 month visits performed outside of the expected visit windows, repeated analysis of the primary and key secondary endpoints will be performed using the population of subjects excluding those with visits outside of the window. See Section 2.9 for details.

4.4.7.2 Impact of MRS VL MFF on Functional Treatment Effect Over Time

Further supplemental analyses may be performed if the following criteria are met:

- A significant treatment effect is demonstrated for the imaging key secondary efficacy endpoint (mean change in VL MFF as assessed by MRS before and after 18 months of treatment with givinostat versus placebo),

  AND

- Trends over time are observed for the primary endpoint either with or without a significant treatment effect.

In the case that these criteria are met, the data will be reviewed to determine whether to proceed with further supplementary analyses exploring the extent to which treatment effect on the primary endpoint is influenced by the treatment effect on MRS VL MFF over time, thus suggesting a potential functional benefit over a longer follow-up period. Where this analysis is deemed beneficial, the supplementary analysis of the primary endpoint will be conducted as described below.

A mixed effects model with repeated measures (MMRM) will be fitted to the change from baseline in the primary endpoint to each post-baseline visit at which the endpoint is assessed. The model will include baseline values for: 4SC, time to rise from floor, time to run/walk 10 metres, distance walked in 6 minutes and re-derived age at first dose (in years and months) as covariates, concomitant steroid use (according to the 4 possible strata), treatment and visit as fixed effects and the treatment by visit interaction. F-tests from PROC MIXED will be based on Kenward-Roger's adjusted degrees of freedom. An unstructured variance/covariance matrix will be used for the repeated visits within a subject.

The above model will then be repeated with the addition of the following terms: MRS VL MFF value at each visit, MRS VL MFF by visit interaction, MRS VL MFF by treatment interaction, MRS VL MFF by treatment by visit interaction.

For each of the two models, the following will be presented and used to assess whether the treatment effect is reduced by the addition of MRS VL MFF to the model: for each visit included in the model, adjusted least squares means and associated 2-sided CIs will be estimated and presented for givinostat and placebo. The treatment effect at each visit, being the difference in adjusted least squares means (givinostat-placebo), will also be presented along with the associated 2-sided CIs and p-values.

4.5 Pharmacokinetics

Blood samples for PK analysis of givinostat (ITF2357) and its major metabolites (ITF2374 and ITF2375) will be collected. There are 5 possible visits where the PK samples can be taken: Visits 7, 10, 11, 13 and 15.

All subjects will have a total of 6 PK specimens drawn during the study:

- Two samples drawn pre-dose. These 2 specimens must be drawn at different visits
- One sample drawn between 0 and 2 hours post-dose
- One sample drawn between 2 and 4 hours post-dose
- One sample drawn between 4 and 6 hours post-dose
- One sample drawn between 6 and 10 hours post-dose

PK parameters will be derived, where data allow, from the plasma concentration data for givinostat and its major metabolites. The actual sampling times will be used in the derivation of the PK parameters.

A listing will present details of PK assessments and plasma concentrations for the PK analysis set.

Details regarding population PK procedures, the derivation of PK parameters and further analyses and summaries of PK data will be given in a separate Population PK data analysis plan. Any evaluation of the relationship of givinostat PK exposure to efficacy and safety endpoints will also be documented separately to this SAP.

5 SAFETY EVALUATION

All safety listings will be presented for the all enrolled subjects set and all safety tables and figures will be presented for the safety analysis set unless specified otherwise. Additionally, see Section 2.8 regarding use of the target versus overall population. Baseline is defined as the last non-missing value recorded prior to or on the date of first study treatment. Where the value is recorded on the same date as first study treatment and there is no further information to confirm whether this was prior to start of treatment, the value will be considered prior to treatment if this was a screening or randomisation assessment and otherwise will be considered post treatment.

5.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA Dictionary Version 24.1.

A treatment-emergent adverse event (TEAE) is defined as an AE that started or worsened on or after the date of start of the administration of the IMP.

There will be no imputation of unknown dates for the calculation of duration or study day. However, for sorting and assignation, if the start date is unknown then it will be assumed to be treatment emergent unless the partial start date, or other data (i.e. stop date) indicates differently.

If the relationship to study drug is unknown, the AE will be assumed to be related to the study drug.

The total number of TEAEs and the total number of subjects with TEAEs, the total number of serious TEAEs and the total number of subjects with serious TEAEs, the total number of subjects with TEAEs leading to withdrawal, the total number of subjects with TEAEs leading to permanent discontinuation with IMP, the total number of subjects with TEAEs leading to temporary discontinuation with IMP, the total number of subjects with TEAEs leading to dose reduction, the total number of subjects with TEAEs leading to death, the number of subjects with TEAEs by severity and relationship to study drug will be summarised.

If a subject experienced more than one TEAE, the subject will be counted once at the worst severity and at the most related event.

The following summary tables will be produced for each treatment group by MedDRA system organ class (SOC) and preferred term (PT) within each SOC:

- total number of TEAEs and the total number of subjects with TEAEs
- total number of serious TEAEs and the total number of subjects with serious TEAEs
- total number of subjects with TEAEs leading to withdrawal
- total number of subjects with TEAEs leading to permanent discontinuation with IMP

- total number of subjects with TEAEs leading to temporary discontinuation with IMP
- total number of subjects with TEAEs leading to dose reduction
- total number of subjects with TEAEs leading to death
- total number of subjects with serious TEAEs leading to withdrawal
- total number of subjects with TEAEs by severity (Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe or medically significant but not immediately life-threatening, Grade 4 Severe or life-threatening, Grade 5 Death related to AE)
- total number of subjects with TEAEs by relationship to study drug (related to study drug, not related to study drug)
- total number of subjects with TEAEs by steroid type at baseline (deflazacort, prednisone, other)

For all of the above, SOC and PT will be presented in decreasing frequency of the total number of subjects with TEAEs and then alphabetically.

Further details of the above tables are given below:

1. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT.
2. If a subject experienced more than one TEAE, the subject will be counted once for each PT.
3. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT at the worst severity.
4. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT using the most related event.

A by-subject AE data listing including verbatim term, coded term, treatment group, severity, time of onset and cessation of event, whether the AE was serious, action taken with study drug, other action taken, outcome and relationship to study treatment will be provided. The dose at onset of each AE will also be presented. Where a partial AE start date is recorded and there is more than one dose recorded during the possible period of AE onset, the maximum recorded dose taken during this time is presented.

In addition, the number and percentage of subjects with bronchopulmonary AEs (BAEs) will be presented by treatment group. Events considered to be BAEs will be identified via a medical review conducted prior to database lock (interim and final analyses) or data extract for safety reviews. BAEs will include but are not limited to respiratory tract infections involving the larynx, trachea, bronchi, lower airways or lung. As a conservative approach, more generic conditions, such as AEs recorded as ‘respiratory tract infection’, will be included. Where ‘Influenza’ events have been recorded, the concomitant presence of relevant respiratory symptoms (i.e. cough, laryngitis, bronchitis) will be verified in order to determine whether to count as a BAE. This table will also include the number and percentage of subjects who were given antibiotics for BAEs and a summary of the duration of antibiotic use for BAEs by treatment group. Antibiotics given for BAEs will be identified via medical review prior to database lock for the final analysis and interim analyses as needed. Duration of

antibiotic use for BAEs (months) will be calculated for each subject in relation to these identified antibiotics as:

Total duration of antibiotic use for BAEs – Total interruption in antibiotic use for BAEs

where total duration of antibiotic use for BAEs is calculated as:

Last antibiotic end date – First antibiotic start date + 1

and total interruption in antibiotic use for BAEs is calculated as the sum of any time that antibiotics were not taken for BAEs between the first antibiotic start date and the last antibiotic end date.

Serious AEs, AEs leading to permanent discontinuation of IMP and AEs leading to dose reduction or permanent discontinuation of IMP will be listed separately.

5.2 Clinical Laboratory Evaluation

For each laboratory parameter, the baseline value will be defined as the last non-missing scheduled or unscheduled value available prior to or on the date of first study treatment. Where the value is recorded on the same date as first study treatment and there is no further information to confirm whether this was prior to start of treatment, the value will be considered prior to treatment if this was a screening or randomisation assessment and otherwise will be considered post treatment. If no measurement is recorded prior to first study treatment administration, the baseline value will be considered missing.

5.2.1 Hematology

Hematology parameters will be measured in Système International (SI) units at all EU sites and in US conventional units at all US sites. All results will be converted to SI units for the purposes of summaries, plots and listings. Summary statistics of hematology observed values and change from baseline by parameter and visit will be presented by treatment group for all subjects in the safety analysis set.

In addition, the following summaries in relation to post-baseline platelet counts will be presented by treatment group: minimum values, time to nadir (days) and time to recovery (days). These will be defined as follows:

Minimum value = minimum post-baseline platelet count for the subject.

Time to nadir (days) = time to first minimum value post-baseline regardless if this is within the normal range.

Time to recovery (days) = for subjects whose minimum post-baseline value is below the lower limit of normal, the time to recovery is calculated as the time from the minimum value below lower limit of normal to the first value within the normal range.

Furthermore, a table will be presented for subjects in the safety analysis set who reduced dose due to platelet count decrease which will summarise the following in relation to post-baseline platelet counts by treatment group: minimum values, time to nadir (days), time to recovery (days), time on treatment after recovery (days), additional platelet decrease after recovery, time on treatment without recovery (days), where:

Time on treatment after recovery = for subjects who record recovery from the minimum value below the lower limit of normal, the time on treatment after recovery

is calculated as the time from the date of recovery to the last treatment date or date of data cut-off.

Additional platelet decrease after recovery = number of subjects who record recovery from the minimum value below the lower limit of normal and then record a subsequent value below the lower limit of normal.

Time on treatment without recovery = for subjects who do not record recovery from the minimum value below the lower limit of normal, the time on treatment without recovery is calculated from the date of the minimum value below the lower limit of normal to the last treatment date or date of data cut-off.

A plot of the mean platelet count at each visit will be produced by treatment group.

Shift in hematology values from baseline to each visit for low, normal, high and total results based on reference ranges will be summarised by treatment group.

A box and whisker plot will present the results for the following parameters over time by treatment group: platelets, hemoglobin, neutrophils, leukocytes.

All hematology values will be listed, flagging all abnormal findings.

5.2.2 Clinical Chemistry

Clinical chemistry results will be summarised in the same way as the hematology data. The box and whisker plot will present the results for the following parameters: triglycerides, total cholesterol, total bilirubin, cystatin C and creatinine.

The separate summaries described for presentation of platelets will be presented in relation to triglycerides. However, these summaries will be adjusted to relate to increase in triglycerides. Therefore, time to nadir will be replaced with time to first maximum value post-baseline, and references in the definitions to ‘minimum’, ‘decrease’ or ‘below lower limit of normal’ should be replaced with ‘maximum’, ‘increase’ and ‘above the upper limit of normal’ respectively. The summary of platelet data described for subjects in the safety analysis set who reduced dose due to platelet count decrease will instead be a summary for subjects in the safety analysis set who reduced dose due to triglyceride increase.

A plot of the mean triglyceride count at each visit will be produced by treatment group.

All clinical chemistry values will be listed, flagging all abnormal findings.

Data for the following liver function parameters will also be listed separately: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase (GGT).

5.2.3 Urinalysis

All urinalysis values will be listed, flagging all abnormal findings where reference ranges are available.

5.2.4 Coagulation

Summary statistics of observed coagulation results and change from baseline will be presented in the same way as the hematology data. A shift table of coagulation results will also be presented as described for the hematology data.

All coagulation values will be listed, flagging all abnormal findings.

5.2.5 Serology

All serology data will be listed in full.

5.3 Vital Signs

Summary statistics of vital sign observed values and change from baseline by parameter and visit will be presented by treatment group for all subjects in the safety analysis set.

All vital sign data will be listed in full.

5.4 Physical Exams

Details regarding whether or not a physical examination occurred, as well as the date of assessment, will be listed.

5.5 Electrocardiography

Clinical interpretations of standard 12-lead ECG assessments will be summarised as follows. Shift in ECG interpretation from baseline to each visit for normal, abnormal NCS, abnormal CS, missing and total results will be summarised by treatment group for all subjects in the safety analysis set using the "worst case" scenario for each set of triplicate readings as required. Subjects will only be included in the missing category if they attended the visit but have no data available for the ECG interpretation. Withdrawn subjects will not be included in the missing category. This shift summary will be repeated for the ECG interpretation as recorded on the CRF by the investigator and the interpretation recorded by the laboratory.

Summary statistics of observed values and change from baseline will be presented by visit and treatment group for all subjects in the safety analysis set for the following parameters:

- RR interval (msec)
- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- QTcF interval (msec) [Fridericia's formula for QTcF (Fridericia, 1920)]
- QTcB interval (msec) [Bazett's formula for QTcB (Bazett, 1920)]
- ECG mean ventricular rate (beats/min)

Where triplicate ECG assessments have been performed, the mean of the non-missing values will be used in the analyses.

The mean QTcF values will be plotted over time for each treatment group.

The incidence of outliers in QTcF intervals (>450, >480, and >500 msec), and the change from baseline in QTcF intervals (>30 and >60 msec) will be summarized by visit and overall for each treatment group as defined in ICH E14 guideline (ICH_E14, 2005). As above, where triplicate ECG assessments have been performed, the mean of the non-missing values will be used to determine outliers. A subject will be counted once for each outlier in the overall summary if they experienced at least one occurrence of that outlier.

All ECG interpretations will be listed. Any comments collected with the ECG data will not be presented in the listing but will be retained in the data for reference.

5.6 Echocardiography

Summary statistics of echocardiography (ECHO) observed values and change from baseline by parameter and visit will be presented by treatment group for all subjects in the safety analysis set.

All echocardiography data will be listed in full.

5.7 Pulmonary Function Test

Pulmonary function test data (FEV1 (L), FVC (L), FEV1/FVC (%) and PEF (L/min)) including change from baseline will be summarised by visit and treatment group. Where multiple assessments have been performed at a visit, the best of the repeated assessments will be used for summaries. The best of the repeated assessments is defined for each parameter as the assessment with the maximum absolute value.

In addition, the percent predicted value of FEV1, FVC and PEF will be calculated at baseline and after 12 and 18 months of treatment according to the following rules. Where multiple assessments have been performed at a visit, the best of the repeated assessments will be used in the calculation according to the same approach as above.

- FEV1% = FEV1*100 / ((-0.7453 - (0.04106 * age)) + (0.004477 * (age^2)) + ((0.00014098 * (height^2))*1)) (Hankinson, Odencrantz, & Fedan, 1999)
- FVC% = FVC*100 / ((-0.2584 - (0.20415 * age)) + (0.010133 * (age^2)) + ((0.00018642 * (height^2))*1)) (Hankinson, Odencrantz, & Fedan, 1999)
- PEF% = PEF*100 / (-422.8 + 5.288 * height), (Buyse, et al., 2015).

In each of the above calculations, age refers to the age at the time of the pulmonary function test assessment, calculated in years and months from date of birth and assessment date. Date of birth will be subject to the rules given in Section 4.4.4.4 prior to this calculation. Height refers to the most recent non-missing height measurement in cm at the time of the pulmonary function test assessment.

Summary statistics of observed values and changes from baseline in FVC%, FEV1% and PEF% will be presented by visit and treatment group for all subjects in the safety analysis set.

Plots of the mean PEF, FVC, percent predicted PEF and percent predicted FVC over time will be produced by treatment group.

All pulmonary function test data, including calculated percent predicted values, will be listed. These listings will include the age and height at the time of each assessment, as well as the individual triplicate values and the selected best value where appropriate.

5.8 Concomitant Medications

Concomitant medications will be coded according to the WHO Drug Dictionary Version B3 Sept 21.

Prior medications are defined as those that started and ended prior to the first dose of study treatment. Medications that are ongoing at the first dose of study treatment or that started after the time of the first dose of study treatment will be deemed to be concomitant medications.

There will be no imputation of unknown dates. However, for sorting and assignation, if the start date is unknown then the medication will be assumed to be concomitant unless the partial start date, or other data (i.e. stop date) indicates differently.

The number and percentage of subjects taking prior and concomitant medications will be summarized separately, each by medication class and standardised medication name sorted alphabetically for each treatment group and overall.

All medications will be listed and concomitant medications will be flagged.

5.9 Concomitant Steroid Treatments

Data regarding steroid treatments received by subjects during the course of or prior to the study are recorded on the CRF separately to the information regarding initial steroid usage at diagnosis (see Section 3.3.2 for details of presentation of data regarding initial steroid usage at diagnosis).

Prior steroid medications are defined as any steroid treatments recorded on the prior and concomitant steroid treatments CRF page that started and ended prior to the first dose of study treatment. Steroid treatments that are ongoing at the first dose of study treatment or that started after the time of the first dose of study treatment will be deemed to be concomitant treatments.

There will be no imputation of unknown dates. However, for sorting and assignation, if the start date is unknown then the steroid will be assumed to be concomitant unless the partial start date, or other data (i.e. stop date) indicates differently.

A summary table will present the following for prior steroid treatments in each treatment group:

- Number and percentage of subjects who recorded taking each type of prior steroid (Prednisone, Deflazacort, Other).
- Number and percentage of subjects who change prior steroid type at least once (for example Prednisone to Deflazacort).
- Duration from start of first recorded steroid to start of study treatment, regardless of break in steroid or changes in regimen, dose or type of steroid (note that this may include steroid treatments that continue after first study treatment and are therefore classified as concomitant steroid treatments). Any breaks in steroid treatment will be excluded from the duration.

A further summary table will present the following for concomitant steroid treatments in each treatment group:

- Number and percentage of subjects who changed concomitant steroid type (for example Prednisone to Deflazacort) after the start of study treatment. Note that this is expected to be zero. However, if the number of subjects is >0, this will be reviewed to determine whether any further summary should be added.

- Duration from start of study treatment to change in steroid type (calculated as End date of first concomitant steroid that was changed – Date of first study treatment +1).
- Duration from start of first concomitant steroid to start of study treatment (note that subjects are expected to have been taking steroid treatment for >=6 months at the time of starting study treatment).
- Number and percentage of subjects who stopped steroid treatment between the start of study treatment and end of study.
- Duration from start of study treatment to end of concomitant steroid use for those who stopped steroid treatment prior to end of study.
- Separate summaries by steroid type (Prednisone, Deflazacort, other) for:
    - Number and percentage of subjects who recorded taking the respective concomitant steroid type.
    - Number and percentage of subjects by frequency.
    - Number and percentage of subjects by route of administration.
    - Duration of exposure from start of first concomitant steroid to the end of the last concomitant steroid (excluding any breaks in steroid treatment).
    - Number and percentage of subjects who changed steroid regimen (i.e. frequency) between the start of study treatment and the end of the study.

For calculations of duration, partial dates will be imputed with the first of the month for a missing day and January for a missing month.

All steroid treatment information will be listed and concomitant steroids will be flagged.

5.10 Raven Coloured Progressive Matrices

The Raven coloured progressive matrices test is a general cognitive function assessment which will be performed at screening and at visit 18.

Summary statistics and change from baseline for the number of right answers for Sections A, AB, B and overall, as well as the percentage of right answers for Sections A, AB, B and overall will be presented by treatment group for all subjects in the safety analysis set.

All Raven coloured progressive matrices data will be listed in full with the derived age at time of each assessment included in the listing.

5.11 Acceptability and Palatability of the Oral Suspension

Acceptability and palatability of IMP will be assessed at week 4 and End of Study/Early Withdrawal. Subject perception of the medicine (ranging from dislike very much to like very much), parent's perception of the medicine based on the child's reaction (unpleasant, not sure or pleasant) and whether there were problems administering the medication will be summarised by visit and treatment group.

All acceptability and palatability data will be listed.

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7 APPENDICES

7.1 Functional Evaluation Scale: 4SC

1. Unable to climb up 4 standard stairs
2. Climbs 4 standard stairs “marking time” (climbs one foot at a time, with both feet on a step before moving to next step), using both arms on one or both handrails
3. Climbs 4 standard stairs “marking time” (climbs one foot at a time, with both feet on a step before moving to next step), using one arm on one handrail
4. Climbs 4 standard stairs “marking time” (climbs one foot at a time, with both feet on a step before moving to next step), not needing handrail
5. Climbs 4 standard stairs alternating feet, needs handrail for support
6. Climbs 4 standard stairs alternating feet, not needing handrail support

7.2 Functional Evaluation Scale: Time to Rise from the Floor

1. Unable to stand from supine, even with use of a chair
2. Assisted Gowers’ – requires furniture for assist in arising from supine to full upright position
3. Full Gowers’ – rolls over, stands up with both hands “climbing up” the legs to achieve full upright posture
4. Half Gowers’ – rolls over, stands up with one hand support on leg
5. Rolls to the side and/or stands up with one hand or both hands on the floor to start to rise up but does not touch legs
6. Stands up without rolling over or using hands

7.3 Functional Evaluation Scale: Time to Walk/Run 10 Metres

1. Unable to walk independently
2. Unable to walk independently, but can walk with full leg calipers (KAFOs) or with support from a person
3. Highly adapted wide based lordotic gait. Cannot increase walking speed
4. Moderately adapted gait. Can pick up speed but cannot run
5. Able to pick up speed, but runs with double stance phase i.e. cannot achieve both feet off the ground
6. Runs and gets both feet off the ground (with no double stance phase)

7.4 PODCI Questionnaire Subscales

The PODCI questionnaire can be completed by either the parent or the subject themselves.

7.4.1 PODCI Completed by Parent

7.4.1.1 Upper Extremity Function

The upper extremity function is comprised of the following 8 items of the parent-completed questionnaire.

Question Number	Description
Q1	Lift heavy books?
Q2	Pour half a gallon of milk?
Q3	Open a jar that has been opened before?
Q4	Use a fork and spoon?
Q5	Comb his/her hair?
Q6	Button buttons?
Q8	Write with a pencil?
Q32	Turn door knobs?

Note that any item rated “5” (Too young for this activity) is considered missing and is not added to the scale. A minimum of 4 items must have valid answers in order for this subscale to be calculated. The raw and standardised scores for the upper extremity function subscale are calculated as:

- Raw Score: Sum of the scores of each of the non-missing items in this subscale.
- Standardised Score: [(4 – mean of items)/3] * 100, where the mean of the items is calculated as (sum of the items)/(number of non-missing items).

7.4.1.2 Transfer and Basic Mobility

The following items are included in the transfer and basic mobility subscale:

Question Number	Description
Q7	Put on his/her coat?
Q21	Climb one flight of stairs?
Q24	Walk one block?
Q25	Get on and off a bus?
Q28	Stand while washing his/her hands and face at a sink?
Q29	Sit in a regular chair without holding on?
Q30	Get on and off a toilet or chair?
Q31	Get in and out of bed?
Q33	Bend over from a standing position and pick up something off the floor?
Q34	How often does your child need help form another person for sitting and standing?
Q35	How often does your child use assistive devices (such as braces, crutches or wheelchair) for sitting and standing?

Any item with a score of “5” (Too young for this activity) is considered missing and is not included in the calculations for this subscale. A minimum of 7 items must have

valid responses in order for this subscale to be calculated. In addition, questions 34 and 35 are to be rescaled as follows:

- Q34rescaled = [(Q34 – 1) * 3/4] + 1
- Q35rescaled = [(Q35 – 1) * 3/4] + 1

The raw and standardised scores for this subscale are calculated as:

- Raw score: sum of the items Q7, Q21, Q24, Q25, Q28, Q29, Q30, Q31, Q33, Q34rescaled, Q35rescaled.
- Standardised score: [(4 – mean of items)/3] * 100, where the mean of the items is calculated as (raw score)/(number of non-missing items).

7.4.1.3 Sports and Physical Function

The items included in the sports and physical function subscale are presented below:

Question Number	Description
Q18	Run short distances?
Q19	Bicycle or tricycle?
Q20	Climb three flights of stairs?
Q22	Walk more than a mile?
Q23	Walk three blocks?
Q26	How often does your child need help from another person for walking and climbing?
Q27	How often does your child need assistive devices (such as braces, crutches or wheelchair) for walking and climbing?
Q36	Can your child participate in recreational outdoor activities with other children the same age?
Q44	Can your child participate in pickup games or sports with other children the same age?
Q52	Can your child participate in competitive level sports with other children the same age?
Q60	How often in the last week did your child get together and do things with friends?
Q66	How often in the last week did your child participate in gym/recess?

Any item with a score of “5” (Too young for this activity) is considered missing and is not included in the calculations for this subscale. A minimum of 6 items must have valid responses in order for this subscale to be calculated. In addition, some of the items in this subscale are to be recoded and rescaled as follows:

- Q26 is rescaled as follows: Q26rescaled = [(Q26 -1) * 3/4] + 1
- Q27 is rescaled as follows: Q27rescaled = [(Q27 -1) * 3/4] + 1
- Q36 is recoded to missing if (Q36 = 4 and either [Q42 = 1] or [Q43 = 1])
- Q44 is recoded to missing if (Q44 = 4 and either [Q50 = 1] or [Q51 = 1])
- Q52 is recoded to missing if (Q52 = 4 and either [Q58 = 1] or [Q59 = 1])
- 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 then Q60rescaled = [(Q60 – 1) * 3/2] + 1
- 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 then Q66rescaled = [(Q66 – 1) * 3/2] + 1

The raw and standardised scores for the sports and physical function subscale are then calculated as follows:

- Raw score: Sum of items Q18, Q19, Q20, Q22, Q23, Q26rescaled, Q27rescaled, Q36, Q44, Q52, Q60rescaled, Q66rescaled
- Standardised score: [(4 – mean of items)/3] * 100, where the mean of the items is calculated as (raw score)/(number of non-missing items).

7.4.1.4 Pain/Comfort

The items included in the pain/comfort subscale are presented below:

Question Number	Description
Q17	Did pain or discomfort interfere with your child's activities?
Q75	How much pain has your child had during the last week?
Q76	During the last week, how much did pain interfere with your child's normal activities (including at home, outside of the home, and at school)?

Note that a minimum of 2 items must have valid answers in order for this scale to be scored. Questions 17 and 75 are to be rescaled as follows:

- Q17rescaled = [(4 – Q17) * 4/3] + 1
- Q75rescaled = [(Q75 – 1) * 4/5] + 1

The raw and standardised scores for the pain/comfort scale are then calculated as:

- Raw score: sum of items Q17rescaled, Q75rescaled, Q76
- Standardised score: [(4 – {mean of items – 1})/4] * 100, where the mean of the items is calculated as (raw score)/(number of non-missing items).

7.4.1.5 Happiness

The following items are included in the happiness subscale:

Question Number	Description
Q10	How he/she looks?
Q11	His/her body?
Q12	What clothes or shoes he/she can wear?
Q13	His/her ability to do the same things his/her friends do?
Q14	His/her health in general?

Note that any item rated "5" (Too young for this activity) is considered missing and is not included in the scale. In addition, a minimum of 3 items must have valid answers in order for this subscale to be computed.

The raw and standardised scores for the happiness subscale are then computed as:

- Raw score: Sum of items Q10, Q11, Q12, Q13, Q14

- Standardised score: [(5 – mean of items)/4] * 100, where the mean of the items is calculated as (raw score)/(number of non-missing items).

7.4.1.6 Global Function Scale

The global function scale is comprised of the upper extremity and physical function; transfer and basic mobility; sports and physical functioning and the pain/comfort subscales. The standardised score for the global function scale can only be calculated if none of the four relevant subscales are missing and is computed as the mean of the standardised scores of the 4 subscales included in this scale.

7.4.2 PODCI Completed by Subject

7.4.2.1 Upper Extremity Function

The upper extremity function is comprised of the following 8 items of the subject-completed questionnaire.

Question Number	Description
Q1	Lift heavy books?
Q2	Pour half a gallon of milk?
Q3	Open a jar that has been opened before?
Q4	Use a fork and spoon?
Q5	Comb your hair?
Q6	Button buttons?
Q8	Write with a pencil?
Q32	Turn door knobs?

Note that a minimum of 4 items must have valid answers in order for this subscale to be calculated. The raw and standardised scores for the upper extremity function subscale are calculated as:

- Raw Score: Sum of the scores of each of the non-missing items in this subscale.
- Standardised Score: [(4 – mean of items)/3] * 100, where the mean of the items is calculated as (sum of the items)/(number of non-missing items).

7.4.2.2 Transfer and Basic Mobility

The following items are included in the transfer and basic mobility subscale:

Question Number	Description
Q7	Put on your coat?
Q21	Climb one flight of stairs?
Q24	Walk one block?
Q25	Get on and off a bus?
Q28	Stand while washing your hands and face at a sink?
Q29	Sit in a regular chair without holding on?
Q30	Get on and off a toilet or chair?
Q31	Get in and out of bed?
Q33	Bend over from a standing position and pick up something off the floor?
Q34	How often do you need help form another person for sitting and standing?

Q35	How often do you use assistive devices (such as braces, crutches or wheelchair) for sitting and standing?

A minimum of 7 items must have valid responses in order for this subscale to be calculated. In addition, questions 34 and 35 are to be rescaled as follows:

- Q34rescaled = [(Q34 – 1) * 3/4] + 1
- Q35rescaled = [(Q35 – 1) * 3/4] + 1

The raw and standardised scores for the transfer and basic mobility subscales are then calculated as:

- Raw score: sum of the items Q7, Q21, Q24, Q25, Q28, Q29, Q30, Q31, Q33, Q34rescaled, Q35rescaled.
- Standardised score: [(4 – mean of items)/3] * 100, where the mean of the items is calculated as (raw score)/(number of non-missing items).

7.4.2.3 Sports and Physical Function

The items included in the sports and physical function subscale are presented below:

Question Number	Description
Q18	Run short distances?
Q19	Bicycle or tricycle?
Q20	Climb three flights of stairs?
Q22	Walk more than a mile?
Q23	Walk three blocks?
Q26	How often do you need help from another person for walking and climbing?
Q27	How often do you use assistive devices (such as braces, crutches or wheelchair) for walking and climbing?
Q36	Can you participate in recreational outdoor activities with other children the same age?
Q43	Can you participate in pickup games or sports with other children the same age?
Q50	Can you participate in competitive level sports with other children the same age?
Q57	How often in the last week did you get together and do things with friends?
Q63	How often in the last week did you participate in gym/recess?

A minimum of 6 items must have valid responses in order for this subscale to be calculated. In addition, some of the items in this subscale are to be recoded and rescaled as follows:

- Q26 is rescaled as follows: Q26rescaled = [(Q26 -1) * 3/4] + 1
- Q27 is rescaled as follows: Q27rescaled = [(Q27 -1) * 3/4] + 1
- Q36 is recoded to missing if (Q36 = 4 and Q42 = 1)
- Q43 is recoded to missing if (Q43 = 4 and Q49 = 1)
- Q50 is recoded to missing if (Q50 = 4 and Q59 = 1)
- Q57 is recoded and rescaled as follows:
    - Step 1: Q57 is recoded to missing if (Q57 = 3 and Q62 = 1)
    - Step 2: If Q57 is not missing then Q57rescaled = [(Q57 – 1) * 3/2] + 1

- Q63 is recoded and rescaled as follows:
    - Step 1: Q63 is recoded to missing if (Q63 = 4)
    - Step 2: Q63 is recoded to missing if (Q63 = 3 and either [Q69 = 1] or [Q70 = 1])
    - Step 3: If Q63 is not missing then Q63rescaled = [(Q63 – 1) * 3/2] + 1

The raw and standardised scores for the sports and physical function are then calculated as follows:

- Raw score: Sum of items Q18, Q19, Q20, Q22, Q23, Q26rescaled, Q27rescaled, Q36, Q43, Q50, Q57rescaled, Q63rescaled
- Standardised score: [(4 – mean of items)/3] * 100, where the mean of the items is calculated as (raw score)/(number of non-missing items).

7.4.2.4 Pain/Comfort

The items included in the pain/comfort subscale are presented below:

Question Number	Description
Q17	Did pain or discomfort interfere with your activities?
Q72	How much pain have you had during the last week?
Q73	During the last week, how much did pain interfere with your normal activities (including at home, outside of the home, and at school)?

Note that a minimum of 2 items must have valid answers in order for this scale to be scored. Questions 17 and 72 are to be rescaled as follows:

- Q17rescaled = [(4 – Q17) * 4/3] + 1
- Q72rescaled = [(Q72 – 1) * 4/5] + 1

The raw and standardised scores for the pain/comfort scale are then calculated as:

- Raw score: sum of items Q17rescaled, Q72rescaled, Q73
- Standardised score: [(4 – {mean of items – 1})/4] * 100, where the mean of the items is calculated as (raw score)/(number of non-missing items)

7.4.2.5 Happiness

The following items are included in the happiness subscale:

Question Number	Description
Q10	How you look?
Q11	Your body?
Q12	What clothes or shoes you can wear?
Q13	Your ability to do the same things your friends do?
Q14	Your health in general?

Note that a minimum of 3 items must have valid answers in order for this subscale to be computed.

The raw and standardised scores for the happiness subscale are then computed as:

- Raw score: Sum of items Q10, Q11, Q12, Q13, Q14

- Standardised score: [(5 – mean of items)/4] * 100, where the mean of the items is calculated as (raw score)/(number of non-missing items)

7.4.2.6 Global Function Scale

The global function scale is comprised of the upper extremity and physical function; transfer and basic mobility; sports and physical functioning and the pain/comfort subscales. The standardised score for the global function scale can only be calculated if none of the four relevant subscales are missing and is computed as the mean of the standardised scores of the 4 subscales included in this scale.

7.5 Missing Data Classification and Imputation Rules

7.5.1 Time to Climb 4 Standard Stairs (4SC)

Class 1 – 'Was assessment performed and completed?' = 'No'.

Class 2 – Was assessment performed and completed?' = 'Yes' but 'Duration' is missing and '4-stair ascent grading' response is '1 = Unable to climb 4 standard stairs'. Note that if the grading is >1 but the 'Duration' is genuinely missing, this should be treated as Class 1 missing data.

7.5.2 Time to Rise from Floor

Class 1 – 'Was assessment performed?' = 'No'.
Class 2 - 'Was assessment performed?' = 'Yes' but 'Duration' is missing and 'Rising from floor grading' response is '1= Unable to stand from supine, even with use of a chair' or '2= Assisted Gowers' - requires furniture for assist in arising from supine to full upright posture'. Note that if the grading is >2 but the 'Duration' is genuinely missing, this should be treated as Class 1 missing data.

7.5.3 Distance Walked in 6 Minutes (6MWT)

Class 1 - 'Was assessment performed?' = 'No'.

Class 2 - 'Was assessment performed?' = 'Yes' but 'Was assessment completed?' = 'Stopped prematurely' and 'Duration walked' is left missing and 'Distance walked at end of test' is left missing.

7.5.4 Physical Function as Measured by NSAA

For the purposes of calculating total NSAA score, classification of missing data should be applied as follows:

Class 1 - Either of the following:

- 'Was assessment attempted?' = 'No' and the reason given is 'Declined to perform test' or 'Other'. In this case, each item score will be imputed using the mode of the non-missing scores for the same item and visit across all subjects randomised to the same treatment and in the same concomitant steroid stratum and Group (i.e. Group A, target population or Group B, off-target population). If there are multiple mode values then the lowest modal value will be used. The total score will be re-derived as the sum of the 17 imputed item scores.
- 'Was assessment attempted?' = 'Yes' but one or more of the item scores is missing. In this case one of two possible methods will be followed:

- If ≥ 9 out of 17 items have been completed with ≤ 8 missing, then the missing item scores for that subject at that visit will be imputed using the mode of the non-missing item scores for the subject and visit. If there are multiple mode values then the lowest modal value will be used. The total score will be re-derived as the sum of the 17 non-missing and imputed item scores.
- If ≤ 8 out of 17 items have been completed with ≥ 9 missing, then the missing item scores for that subject at that visit will be imputed as zero. The total score will be re-derived as the sum of the 17 non-missing and imputed item scores.

Class 2 - 'Was assessment attempted?' = 'No' and the reason given is 'Unable to physically perform the test'. In this case all item scores and the total score will be imputed to zero.

For the purposes of calculating cumulative number of failed items, NSAA data will first be classified and imputed according to the above rules and the assessment of item failure will then be determined using the values after imputation.

7.5.5 Muscle Strength Evaluated by Knee Extension and Elbow Flexion as Measured by Hand-held Myometry

Class 1 – Either of the following:

- 'Was assessment attempted?' = 'No' and the reason given is 'Declined to perform test' or 'Other'.
- 'Were all 4 elements of the extension/flexion assessment attempted?' = 'No' and the reason given is 'Declined to perform test' or 'Other'. Any missing elements of the test (left/right knee extension or left/right elbow flexion) will be classified as 1.

Class 2 – Either of the following:

- 'Was assessment attempted?' = 'No' and the reason given is 'Unable to physically perform the test'.
- 'Were all 4 elements of the extension/flexion assessment attempted?' = 'No' and the reason given is 'Unable to physically perform the test'. Any missing elements of the test (left/right knee extension or left/right elbow flexion) will be classified as 2.

7.5.6 Fat Fraction of Vastus Lateralis Muscles as assessed by MRS

All missing data for this endpoint will be Class 1.

7.5.7 Time to Run/Walk 10 Metres

Class 1 – 'Was assessment performed?' = 'No'.

Class 2 – Was assessment performed?' = 'Yes' but 'Was assessment completed?' = 'No' and 'Distance' is missing and 'Duration walked' is missing and '10-Metre Walk/Run test Grading' response is '1 = Unable to walk independently' or '2 = Unable to walk independently, but can walk with full leg calipers (KAFOs) or with support from a person'. Note that if the grading is >2 but the 'Duration walked' is genuinely missing, this should be treated as Class 1 missing data.

7.5.8 Paediatric Outcomes Data Collection Instrument (PODCI) Scores

All missing data for this endpoint will be Class 1.

7.5.9 Percent Predicted 6MWT

Missing values for the 6MWT will be classified and imputed as described above for that endpoint, prior to finding the percent predicted 6MWT values.

7.5.10 Fat Fraction and Cross-Sectional Area of 5 Thigh Muscles as Assessed by MRI

All missing data for this endpoint will be Class 1.

7.5.11 Time to 10% Persistent Worsening in 6MWT

Missing values for the 6MWT will be classified and imputed as described above for that endpoint, prior to finding the time to 10% persistent worsening in 6MWT. Note that any imputed 6MWT values post early withdrawal will also be considered for the purposes of the time to event analysis.

7.5.12 Proportion of Subjects with ≥10% Persistent Worsening in 6MWT

Missing values for the 6MWT will be classified and imputed as described above for that endpoint prior to finding the proportion of subjects with ≥10% persistent worsening in 6MWT.

7.5.13 Time to Persistent Loss of Standing (Baseline Through End of Study)

The following rules will be applied in order to identify subjects who meet the criteria specified in Section 4.3.7 for persistent loss of standing. Note that any imputed values post early withdrawal will also be considered for the purposes of the time to even analysis:

- Classification and imputation of the NSAA data will be applied as described above. Where Class 2 missing data are identified, the score for the 'Rise from floor' item on the NSAA assessment will be assumed to be '0b - Unable' for the purposes of determining loss of standing. Where Class 1 missing data are identified, the score for the 'Rise from floor' item will be carried forward from the last non-missing score for this item for the subject. If the Class 1 missing data are from a baseline assessment, the score for this item will be assumed >0.
- Classification and imputation of the Time to Rise from Floor data will be applied as described above. Where there are Class 1 missing data for the Rise from Floor assessment and therefore the 'Rising from floor grading' is missing, the grade will be carried forward from the last non-missing Rising from floor grading for the subject. If the Class 1 missing data are from a baseline assessment, the Rising from floor grading will be assumed >1.

7.5.14 Proportion of Subjects Who Lose Ambulation

The following steps will be completed in order to identify subjects who meet the criteria specified in Section 4.3.8 for loss of ambulation:

- Missing 6MWT values will be classified in order to identify any Class 2 missing values, i.e. where the subject meets the criterion for being unable to perform the 6MWT due to physical inability.

- Any missing 10-metre walk/run test values will be classified and imputed. The imputed values will be used to identify subjects who meet the criteria for being unable to complete the 10-metre walk/run test in 30 seconds or less without any support or devices. Where Class 1 missing data are identified and the imputed duration walked is ≤30 seconds, the '10-Metre Walk/Run test Grading' will be carried forward from the last non-missing grading for the subject in order to determine whether the subject was able to complete the test without any support or devices. If the Class 1 missing data are from a baseline assessment, the 10-Metre Walk/Run test Grading will be assumed >2 for the purposes of determining loss of ambulation (i.e. able to complete the test without support or devices).

7.5.15 Type of DMD Mutation, LTBP4 and Osteopontin Genotype

No imputation will be applied to this data. Any missing values for these assessments will be excluded from summaries and analyses as applicable. Where a subject has a missing value such that they cannot be assigned to a group for evaluation of subgroups, they will be excluded from the respective subgroup summaries and analyses.

7.5.16 DMD Serum Biomarker

No imputation will be applied to this data. Any missing values for this assessment will be excluded from summaries and analyses as applicable.

7.6 Outputs to be Reviewed at the Safety Review Meetings

The following tables, figures and listings will be reviewed by the IDMC at the 3 monthly safety review meetings. The IDMC will meet every 3 months from the first subject randomised. All tables and listings provided to the IDMC at safety reviews will be presented for the overall subject population.

Table 14.1.1.1.1.1 Subject Disposition

Table 14.1.1.1.2.1 Disposition of Screened Subjects

Listing 16.2.1.1 Subject Completions and Withdrawals

Listing 16.2.2.1 Eligibility - Inclusion and Exclusion Criteria

Listing 16.2.3.1 Analysis Sets

Table 14.1.1.2.1 Major Protocol Deviations

Listing 16.2.3.2 Protocol Deviations

Table 14.1.2.1 Demography

Listing 16.2.4.1 Demography

Table 14.1.3.1 Medical History

Listing 16.2.4.2 Medical History

Table 14.1.3.2 DMD Diagnosis

Listing 16.2.4.3 DMD Diagnosis

Table 14.1.4.1 Administration of Study Treatment

Table 14.1.4.2 Modifications of Study Treatment

Table 14.1.4.3 Duration of Modifications of Study Treatment

Listing 16.2.5.1 Investigational Product Dispensing

Listing 16.2.5.2 Investigational Product Modifications

Table 14.1.5 Ankle Range of Motion

Listing 16.2.5.3 Ankle Range of Motion

Table 14.1.6 Muscle Strength Test Modified MRC Grade

Listing 16.2.5.4 Muscle Strength Test Modified MRC Grade

Table 14.3.1.1.1 Summary of Treatment-Emergent Adverse Events

Table 14.3.1.2.1 Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term

Table 14.3.1.3.1 Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term

Table 14.3.1.4.1 Summary of Treatment-Emergent Adverse Events Leading to Withdrawal by MedDRA System Organ Class and Preferred Term

Table 14.3.1.6.1 Summary of Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class and Preferred Term

Table 14.3.1.7.1 Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of IMP by MedDRA System Organ Class and Preferred Term

Table 14.3.1.8.1 Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Severity

Table 14.3.1.9.1 Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Relationship to Study Treatment

Table 14.3.1.11.1 Treatment-Emergent Bronchopulmonary Adverse Events (BAEs)

Listing 16.2.7.1 Adverse Events

Listing 16.2.7.2 Serious Adverse Events

Listing 16.2.7.3 Adverse Events Leading to Discontinuation of IMP

Listing 16.2.7.4 Adverse Events Leading to Dose Reduction or Discontinuation of IMP

Table 14.3.2.1 Haematology Values and Change from Baseline over Time

Table 14.3.2.2 Haematology Values and Change from Baseline over Time

Table 14.3.2.3 Platelets Count Values over Time

Figure 14.2.7.1 Plot of Mean Platelets Count by Treatment over Time

Table 14.3.2.4 Shift in Haematology Values over Time

Figure 14.2.7.2.1 Box and Whisker Plot of Selected Haematology Results by Treatment over Time

Figure 14.2.7.2.2 Patient Plots of Selected Haematology Results over Time*

Listing 16.2.8.1 All Haematology Values

Table 14.3.3.1 Clinical Chemistry Values and Change from Baseline over Time

Table 14.3.3.2 Shift in Clinical Chemistry Values over Time

Figure 14.2.7.3.1 Box and Whisker Plot of Selected Clinical Chemistry Results by Treatment over Time

Figure 14.2.7.3.2 Patient Plots of Selected Clinical Chemistry Results over Time*

Listing 16.2.8.2 All Clinical Chemistry Values

Table 14.3.4.1 Coagulation Values and Change from Baseline over Time

Listing 16.2.8.4 All Coagulation Values

Listing 16.2.8.6 All Liver Function Values

Table 14.3.5 Summary of Vital Signs and Change from Baseline over Time

Listing 16.2.9.1 Vital Signs

Table 14.3.6.1 Summary of ECG Results and Change from Baseline over Time

Table 14.3.6.2 Shift in ECG Interpretation

Table 14.3.6.3 Incidence of Outliers in ECG Results

Figure 14.2.8 Plot of Mean QTcF Values by Treatment over Time

Listing 16.2.9.3 ECG Results

Table 14.3.7 ECHO Values and Change from Baseline over Time

Listing 16.2.9.4 All Echocardiography (ECHO) Values

Table 14.3.8.1 Pulmonary Function Test and Change from Baseline over Time

Table 14.3.8.2 Percent Predicted Values for Pulmonary Function Test and Change from Baseline over Time

Figure 14.2.9.1 Plot of Mean Peak Expiratory Flow (L/min) Values by Treatment over Time

Figure 14.2.9.2 Plot of Mean Forced Vital Capacity (L) Values by Treatment over Time

Figure 14.2.9.3 Plot of Mean % Predicted Peak Expiratory Flow (%) Values by Treatment over Time

Figure 14.2.9.4 Plot of Mean % Predicted Forced Vital Capacity (%) Values by Treatment over Time

Listing 16.2.9.5 All Pulmonary Function Test Values

Table 14.3.9.1.2 Concomitant Medications

Table 14.3.9.2.2 Concomitant Steroid Treatments

Listing 16.2.9.6.1 Prior and Concomitant Medications

Listing 16.2.9.6.2 Prior and Concomitant Steroid Treatments

Excel listings of selected laboratory parameter results by visit for each subject in the all enrolled subjects analysis set. This will include the dose administered at each visit alongside the results.*

Excel listing of site level deviations.

** Output is only to be produced for safety reviews and not as part of the final analysis.*

In addition to the above list, the following repeat tables presented by country will also be provided once 30 subjects have been randomised:

Table 14.1.1.1.1.2 Subject Disposition by Country

Table 14.1.1.1.2.2 Disposition of Screened Subjects by Country

Table 14.1.1.2.2 Major Protocol Deviations by Country

Table 14.1.2.2 Demography by Country

Table 14.3.1.1.2 Summary of Treatment-Emergent Adverse Events by Country

Table 14.3.1.2.2 Summary of Treatment-Emergent Adverse Events by Country, MedDRA System Organ Class and Preferred Term

Table 14.3.1.3.2 Summary of Serious Treatment-Emergent Adverse Events by Country, MedDRA System Organ Class and Preferred Term

Table 14.3.1.4.2 Summary of Treatment-Emergent Adverse Events Leading to Withdrawal by Country, MedDRA System Organ Class and Preferred Term

Table 14.3.1.6.2 Summary of Treatment-Emergent Adverse Events Leading to Death by Country, MedDRA System Organ Class and Preferred Term

Table 14.3.1.7.2 Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of IMP by Country, MedDRA System Organ Class and Preferred Term

Table 14.3.1.8.2 Summary of Treatment-Emergent Adverse Events by Country, MedDRA System Organ Class, Preferred Term and Severity

Table 14.3.1.9.2 Summary of Treatment-Emergent Adverse Events by Country, MedDRA System Organ Class, Preferred Term and Relationship to Study Treatment

Table 14.3.1.11.2 Treatment-Emergent Bronchopulmonary Adverse Events (BAEs) by Country

The following additional tables will also be provided once at least 50 subjects have been randomised and have completed at least one month of treatment:

Table 14.3.1.10.1 Summary of Treatment-Emergent Adverse Events by Steroid Type at Baseline, MedDRA System Organ Class and Preferred Term

Table 14.3.1.10.2 Summary of Treatment-Emergent Adverse Events by Country, Steroid Type at Baseline, MedDRA System Organ Class and Preferred Term

For the purposes of IDMC safety reviews, the summaries relating to antibiotic use will be excluded from the above two tables as this is not relevant to safety. These summaries will only be included for the final analysis (and interim analyses if required).

The summary tables listed above will be repeated using the blinded (dummy) randomisation so that the blind is maintained, and these outputs will be sent to

Italfarmaco at each safety review. Italfarmaco will not receive any figures or listings for the safety reviews.

At each safety review, individual outputs will be compiled into a single pdf file for tables, figures and listings respectively with hyperlinks applied to navigate to each output. The compiled files will be provided alongside the individual output files.

7.7 Outputs to be Reviewed at the Interim Analysis

The outputs to be included in the interim analysis will consist of:

Summary table for observed values and change from baseline in VL MFF as assessed by MRS over time

Analysis table presenting results from an ANCOVA on mean change from baseline to 12 months in VL MFF as assessed by MRS.

In addition the following output will be prepared in order to provide to the IDMC if requested following their review of the above tables:

Listing of subject results for VL MFF as assessed by MRS over time.

Specific details regarding the presentation of these outputs are given in a separate 'Interim Analysis 1 Table, Figure and Listing Shells' document.

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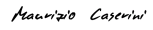
Maurizio Caserini m.caserini@italfarmaco.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signed by link sent to m.caserini@italfarmaco.com Signature ID: DE5C96C0-EB71-4C74-9DA6-DE7D4CD3B1B8 Using IP Address: 185.212.107.47 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Approvo il documento	Sent: 13 April 2022 | 18:33 Viewed: 14 April 2022 | 10:47 Signed: 14 April 2022 | 10:49
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Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	13 April 2022 | 18:26
Certified Delivered	Security Checked	14 April 2022 | 10:47
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Randomised, Double Blind, Placebo Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Givinostat in Ambulant Patients with Duchenne Muscular Dystrophy

Italfarmaco Study No: DSC/14/2357/48
Veristat Study No: ICO16001

EudraCT No: 2016-000401-36

IND No: 126598

Statistical Analysis Plan Addendum 1

Version: Final 1.0

Date: 14th July 2022

For Veristat
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Contents

LIST OF ABBREVIATIONS

NSAA	North Star Ambulatory Assessment
NTF	Note to file
PODCI	Paediatric Outcomes Data Collection Instrument
SAP	Statistical Analysis Plan
TFL	Table, Figure and Listing

1 INTRODUCTION

This is an addendum to both the final statistical analysis plan (SAP) Version 6.0, dated 13th April 2022, and the following key file notes (NTF) which were agreed prior to study unblinding:

- SOP-CLIN-16-FORM-NTF_muscle_strength_SIGNED, dated 4th May 2022
- SOP-CLIN-16-FORM-NTF_hardcoding_07_FE, dated 9th May 2022
- SOP-CLIN-16-FORM-NTF_hardcoding_17_FE, dated 4th May 2022
- SOP-CLIN-16-FORM-NTF_hardcoding_19_FE, dated 11th May 2022
- SOP-CLIN-16-FORM-NTF_hardcoding_21_FE, dated 12th May 2022
- SOP-CLIN-16-FORM-NTF_hardcoding_24_FE, dated 18th May2022
- SOP-CLIN-16-FORM-NTF_hardcoding_30_FE, dated 7th May 2022
- SOP-CLIN-16-FORM-NTF_hardcoding_38_FE, dated 5th May 2022
- SOP-CLIN-16-FORM-NTF_PODCI_SIGNED, dated 23rd May 2022

This addendum documents key changes, corrections or further clarification regarding specific derivations and analyses described in the SAP or file notes following database lock. Full details of the changes and the reasons for these are detailed below.

2 CHANGES TO THE FINAL SAP

2.1 Change 1

According to the SAP Sections 4.3.2 and 4.4.2, for the Paediatric Outcomes Data Collection Instrument (PODCI) endpoint, change from baseline over time for raw and standardised subscale scores are to be presented and analysed separately for 'parent' or 'self' evaluator. However, on review of the data following database lock and prior to unblinding, it was confirmed that there are a number of cases where a subject has completed a mixture of questionnaires by different evaluators from screening to end of study. Unfortunately, the SAP does not cover this type of scenario.

Italfarmaco and Veristat discussed possible solutions with consideration that a subject will only have a baseline questionnaire completed for one type of evaluator even though this may differ from the evaluator for the post-baseline visit. In order to avoid limitation to only subjects with consistent evaluator across baseline and post-baseline for calculating change from baseline values, a pooled approach has been identified. This was supported by the assumption that scores from questionnaires completed by 'self' where the subject is <10 years of age are considered not fully reliable. However, scores from questionnaires completed by 'self' where the subject is >=10 years old can be considered reliable and comparable to scores from questionnaires completed by 'parent'.

In the data we will have a mixture of questionnaires completed by: 'Parent', 'Self >=10 years', 'Self <10 years', 'Missing' (where missing evaluator applies to completely imputed results where the assessment/visit was not done). Therefore, the approach will be as follows.

Questionnaires will be divided into two groups based on the type of evaluator:

- Group 1: 'Parent' + ('Self' >=10 years old)
- Group 2: 'Missing' + ('Self' <10 years old)

Group 1 non-missing subscale scores will remain unchanged. Group 1 missing subscale scores will be imputed as described in the SAP Sections 4.4.4.1, 4.4.4.2 and 7.5.8 using the approach for Class 1 missing data based on Group 1 non-missing results (for the respective subscale, visit, treatment, concomitant steroid and target/off-target group).

Group 2 subscale scores (both non-missing or missing scores) will be replaced with imputed values using the same approach for Class 1 missing data but also based on Group 1 non-missing results (for the respective subscale, visit, treatment, concomitant steroid and target/off-target group), rather than Group 2 non-missing results.

All values (Group 1 and Group 2 non-missing and imputed values) will then be analysed together as equivalent measures, i.e., all are included in calculation of change from baseline and summaries/analyses. The analysis tables will be presented based on these values without distinction between different evaluators. The amended table, figure and listing (TFL) shells for these presentations are supplied in the separate document 'TFL Shells Addendum 1'. These replace the following equivalent planned outputs in the TFL Shells Final 4.0: Tables 14.2.8.1.1 to 14.2.8.5.6 and Listings 16.2.6.8.1 to 16.2.6.8.4.

Reason for the change

As detailed above, this change has been implemented as the SAP defined approach did not allow for the mixture of questionnaires completed by different evaluators per subject as collected in the data.

2.2 Change 2

Section 7.4.1 of the SAP (PODCI Completed by Parent) includes the following instruction when describing the required derivations for some of subscale scores on the parent completed questionnaires: "any item rated "5" (Too young for this activity) is considered missing and is not added to the scale".

It was noted that for some questions on the parent completed questionnaire, the response indicating that the subject was too young for the activity is given a different number, for example '6' rather than '5'. In addition, there are some questions where the response is phrased slightly differently, for example: "Child is too young". Affected questions are questions 10 to 14 used for the 'Happiness' subscale.

To accommodate these differences, the approach was therefore corrected to consider any item as missing for subscale calculation if the text response contains the phrase 'too young' (regardless of the number of the response or exact phrasing of the full response). This was agreed to be the intention of the SAP instructions.

Reason for the change

The differences between question responses regarding 'too young' were overlooked in the SAP instructions for calculating subscale scores on the parent completed PODCI questionnaire. This change was implemented in order to correct this and ensure that any such responses were handled consistently in the scoring.

2.3 Change 3

Section 7.4.2.3 of the SAP (Sports and Physical Function) describes the derivations required for calculating the sports and physical function subscale scores for the subject completed PODCI questionnaires. This includes the following instruction:

- Q50 is recoded to missing if (Q50 = 4 and Q59 = 1)

However, it was noted that the question 59 relates to the response regarding 'Doing things with friends' limited by 'Health', whereas it was agreed that this instruction should instead refer to question 56 which is related to 'participating in sports' limited by 'Activity not in season'.

Therefore, this derivation was corrected to the following:

- Q50 is recoded to missing if (Q50 = 4 and Q56 = 1).

Reason for the change

This was a correction due to an erroneous question reference in the SAP instructions.

2.4 Change 4

It was noted that some of the rules for imputation in the SAP Section 7.5.13 (Time to Persistent Loss of Standing (Baseline Through End of Study)) are no longer relevant given the approach to impute individual missing North Star Ambulatory Assessment (NSAA) item scores as described in the SAP Section 7.5.4 (Physical Function as Measured by NSAA).

The rules for imputation of the NSAA rise from floor item in Section 7.5.13 were written to handle the situation where there are remaining missing individual NSAA item scores prior to deriving the time to persistent loss of standing endpoint. However, after this text was written and prior to SAP finalisation and database lock, the approach in Section 7.5.4 was updated to ensure that all item scores will be populated following imputation of the NSAA endpoint. Therefore, there is no requirement to apply the additional rule to carry forward item scores as described in Section 7.5.13. Instead, the decision was taken to use the values already imputed per the rules in Section 7.5.4 so that this is consistent.

It should be noted that, in some cases, the imputation rules in Section 7.5.4 mean that the rise from floor item score could be imputed to zero but without distinction between '0a' or '0b'. In these cases, the following approach was agreed:

- If item score = '0' and the class of missing data = 'Class 2' then assume '0b – Unable' for the purposes of the time to persistent loss of standing derivation.
- If item score = '0' and the class of missing data = 'Class 1' then assume '0a - Needs external support of object e.g., chair' for the purposes of the time to persistent loss of standing derivation.

Reason for the change

This change was considered appropriate to ensure consistency within the SAP across the imputation approaches for related endpoints.

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