Statistical Analysis Plan	
Official Title:	A Single-Blind, Phase 2 Study to Evaluate the Safety and Efficacy of Tideglusib 400mg or 1000mg for the Treatment of Adolescent and Adult Congenital and Juvenile-Onset Myotonic Dystrophy
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A Single-Blind, Phase 2 Study to Evaluate the Safety and Efficacy of Tideglusib 400mg or 1000mg for the Treatment of Adolescent and Adult Congenital and Juvenile-Onset Myotonic Dystrophy

AMO Pharma Ltd Study No: AMO-02-MD-2-001

[redacted]

Statistical Analysis Plan

Version: Amendment 1 Final

Date: 01 December 2017

For [redacted] – Lead Statistician

[redacted]

For AMO Pharma Ltd

If signing manually, please include: Signature + Date + Full Name + Position

[redacted]

Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criterion
ALT	Alanine amino transferase
ANCOVA	Analysis of Covariance
$AUC_{0\text{-}12hr}$	Area Under the Serum Concentration Time Curve from Time Zero to Hour 12
AST	Aspartate amino transferase
BMI	Body Mass Index
BP	Blood Pressure
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression - Improvement scale
CGI-S	Clinical Global Impression - Severity scale
CI	Confidence Interval
C_{max}	Maximum Serum Concentration
C_{min}	Minimum Serum Concentration
C_{SS}	Steady State Concentration
DSMC	Data Safety Monitoring Committee
DRM	Data Review Meeting
DXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiography
FAS	Full Analysis Set
FVC	Forced Vital Capacity
[redacted]	[redacted]
INR	International Normalised Ratio
LLOQ	Lower Limit of Quantification
LS	Least Squares
MAR	Missing at Random
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measures
NHPT	Nine Hole Peg Test
NTEAE	Non-Treatment Emergent Adverse Event

OSU	Ohio State University
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PT	Preferred Term
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
$T_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment Emergent Adverse Event
T_{max}	Time of the Maximum Observed Serum Concentration
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO	World Health Organization

1 INTRODUCTION

This document details the statistical analysis of the data that will be performed for the AMO Pharma Ltd study: A Single-Blind, Phase 2 Study to Evaluate the Safety and Efficacy of Tideglusib 400mg or 1000mg for the Treatment of Adolescent and Adult Congenital and Juvenile-Onset Myotonic Dystrophy.

The proposed analysis is based on the contents of protocol version 4.0 (dated 09-JAN-2017). In the event of future amendments to the protocol, this statistical analysis plan (SAP) may be modified to account for changes relevant to the statistical analysis.

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

The analysis and statistics reporting will be conducted at [redacted] using SAS version 9.2 or higher.

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

For categorical variables, the number and percentage of subjects in each category will be presented, based on the number of non-missing observations apart from disposition of subjects, protocol deviations, background and demographic characteristics, prior and concomitant medications and adverse events where the percentage will be based on the number of subjects in the analysis set.

Where mentioned in this SAP, “active treatment” will relate to tideglusib treatment.

Unless otherwise stated, baseline is defined as the last non-missing value (including scheduled and unscheduled assessments) prior to the subject receiving active treatment.

In the final analysis of the combined Cohort 1 and Cohort 2 subject data, data will be summarised in tabular form by the intended dose group according to the cohort (Tideglusib 400mg and Tideglusib 1000mg) apart from disposition of subjects, protocol deviations, and background and demographic data which will be summarised by dose group and overall subjects. In the analysis to be conducted at completion of Cohort 1, the data will be summarised in tabular form for the Tideglusib 1000mg dose group only.

Listings will be sorted by dose group, subject number and time of assessment.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

Primary Objective:

To investigate the safety and tolerability, between baseline and end-of-treatment, of tideglusib in adolescent and adult subjects with congenital or juvenile-onset myotonic dystrophy.

Secondary Objectives:

To investigate the blood pharmacokinetics of tideglusib in adolescent and adult subjects with congenital or juvenile-onset myotonic dystrophy.

To investigate differences in outcomes reflective of efficacy, between baseline and end-of-treatment, with tideglusib in adolescent and adult subjects with congenital or juvenile-onset myotonic dystrophy.

2.2 Study Design

This is a single-blind, [redacted] study in adolescent and adult subjects with congenital or juvenile-onset type 1 myotonic dystrophy.

Approximately 16 subjects in total are planned to be enrolled and receive active treatment.

Participation for individual subjects will consist of an initial Screening of up to [redacted] (minimum of [redacted]) followed by a [redacted] treatment phase. After this, subjects in Cohort 1 will be treated with single-blinded 1000mg tideglusib once daily orally for 12 weeks and Cohort 2 will be treated with single-blinded 400mg tideglusib once daily orally for 12 weeks. A follow up visit will take place approximately [redacted] after the end of treatment visit.

Once [redacted] out of the [redacted] subjects from Cohort 1, who have received active treatment with [redacted] of tideglusib, have completed active treatment or discontinued from the study [redacted] the Data Safety Monitoring Committee (DSMC) will meet to review the available data and a recommendation will be made to the Sponsor whether Cohort 2 should be initiated. [redacted]
Active dosing of Cohort 2 will only start when the [redacted] tideglusib. No screening will take place for Cohort 2 until after the recommendation has been made from the DSMC, to the Sponsor, on if Cohort 2 should be initiated.

If the decision is made to enrol all Cohort 2 subjects on the [redacted] dose then the summaries and analyses described in this SAP will be updated to analyse all subjects from cohorts 1 and 2 as a single dose group in the final analysis at the end of the study.

All outputs specified in this SAP will be produced for the final analysis of the combined Cohort 1 and Cohort 2 subject data. The exceptions to this are the by subject line plots detailed within Sections 5.1.1, 5.1.2, 5.1.3 and 5.1.4.1, as well as the ad hoc Cohort 1 outputs specified in section 3.1. These specific outputs will only be produced for the Cohort 1 analysis (see Sections 3 and 3.1) and will be included in the final study report as a separate set of Cohort 1 specific analyses on this data cut. They will not be reproduced on subsequent data unless, at the end of the study, it is considered beneficial to produce these again as part of ad hoc analyses.

See protocol section 8.3 for full detail of the study design.

2.3 Visit Structure

The visit structure and scheduled assessments are detailed in Table 1: Schedule of Events in the study protocol. Throughout this SAP, visits have been referred to either according to visit number or to the corresponding week number. The table below

indicates the relationship between visit number and week number. Visits will be referred to by week number in the tables, figures and listings, as described in Section 1 of the table, figure and listing shells.

Table 1: Visit labels

Visit	[redacted]									
Week	[redacted]									

2.4 Sample Size

Sufficient subjects will be entered into the study to ensure at least 16 are dosed with tideglusib. Enrolment will occur at one, or maybe two, study sites. Eight subjects will be dosed in each of the two dose groups.

No formal sample size calculation was performed.

2.5 Changes from the Protocol Planned Analysis

There is no planned analysis of the protocol defined secondary endpoints relating to the biomarker [redacted].

There are no further changes to the protocol planned analyses.

3 COHORT 1 ANALYSIS

Cohort 1 subject data will be analysed and evaluated once [redacted] Cohort 1 subjects have completed [redacted] (or discontinued prior to [redacted]). The data will be cleaned and soft locked at this point for analysis. The following Cohort 1 data outputs will be provided (see also Appendix 1 for a full list of outputs):

- All listings detailed within this SAP apart from those relating to study drug dispensing, study drug return, study drug [redacted], [redacted] levels, local laboratory results and physical examination.
- By subject line plots detailed within sections: 5.1.1 Muscle Function, 5.1.2 Clinician/Caregiver Symptom Scales, 5.1.3 Cognitive and Neurodevelopment and 5.1.4.1 DXA scan.
- Summaries of the number and percentage of subjects experiencing “treatment period” treatment-emergent adverse events (TEAEs), “post treatment period” TEAEs, all TEAEs and separately non-treatment-emergent adverse events (NTEAEs) will be presented by system organ class (SOC) and preferred term (PT).

3.1 Ad Hoc Cohort 1 Analysis

It was planned that on review of the above specified Cohort 1 data outputs, additional outputs could be produced on Cohort 1 data if considered useful to interpretation of the data. Following review of the Cohort 1 outputs specified in

Section 3, a set of ad hoc outputs were requested to support the [redacted]. The full list of ad hoc Cohort 1 outputs requested is given in Appendix 2. As these are ad hoc outputs, no accompanying table, listing and figure shells are provided. The layout and footnotes for each output were adapted from shells for equivalent outputs in this SAP. Sections 3.1.1 to 3.1.6 provide the full specification that was followed for the ad hoc Cohort 1 analyses. All of the ad hoc Cohort 1 outputs were produced in line with this specification following discussion and agreement with AMO Pharma Ltd.

3.1.1 [redacted] and [redacted] Comparisons for Selected Efficacy Endpoints

The mixed effect model repeated measures (MMRM) described in sections 5.1.1.2, 5.1.1.3, 5.1.1.5, 5.1.2.2, 5.1.2.3 will be adapted for selected endpoints to allow comparison of observed values at [redacted] to [redacted], as well as [redacted] to [redacted]. The model will be updated so that the dependent variable is the observed values at all scheduled visits for the endpoint from [redacted] to [redacted]. Visit will be kept as the only fixed effect. Contrasts will be obtained for the comparison of [redacted] to [redacted], as well as [redacted] to [redacted]

For each of these comparisons, the results to be presented will include the difference in adjusted Least Squares (LS) Means, together with the associated standard error (SE), 95% confidence intervals (CIs) and 2-sided p-values. In addition, the observed mean absolute change and observed mean percentage change for each comparison will be presented. If the assumptions of normality do not appear to hold for any endpoint, the observed median absolute change and observed median percentage change will also be presented as an alternative measure of the 'average' values. Finally, the Cohen's d value for each comparison will be presented.

In addition to performing the adapted MMRM analyses for the endpoints in the referenced sections, similar analyses will also be performed for the Clinical Global Impression - Improvement scale (CGI-I) and the Ohio State University (OSU) CGI-I. There are no MMRM analyses planned in this SAP for these endpoints and therefore the model will be adapted from the analysis of relaxation time in section 5.1.1.2 (CGI-I) and the analysis of total clinician-completed domain specific causes for concern VAS in section 5.1.2.2 (OSU CGI-I). As CGI-I and OSU CGI-I are not collected at [redacted], only the comparison between [redacted] and [redacted] will be performed.

Furthermore, the Peabody picture vocabulary test age-based standard score will also be analysed using an MMRM model as described above. No MMRM analysis is planned in this SAP for this endpoint and so the model will be adapted from the analysis of relaxation time in section 5.1.1.2. Observed scores at [redacted] and [redacted] will be included in the model.

Finally, a comparison from [redacted] to [redacted] in the Dual-energy X-ray Absorptiometry (DXA) – arms will be performed. As this endpoint is only collected at [redacted] and [redacted] the ANCOVA described in section 5.1.4.1 will be applied, with the removal of the dose group fixed effect.

3.1.2 Responder Analyses of CGI-I and OSU CGI-I Improvement at [redacted] and [redacted]

For each of the endpoints CGI-I and OSU CGI-I, a table will be produced to present the number and percentage of subjects showing improvement at [redacted] (as compared to CGI-S (OSU CGI-S) (clinical presentation) at [redacted]), as well as the number and percentage of subjects showing improvement at [redacted] (as compared to CGI-S (OSU CGI-S) (clinical presentation) at [redacted]). 'Improvement' will be defined as a CGI-I (OSU

CGI-I) score <=3 at the respective time point (corresponding to scores of: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved).

Each table will also present the p-value, obtained from McNemar's exact test, for the comparison between [redacted] and [redacted] of the proportion of subjects with improvement. This represents a comparison of improvement during active treatment compared to improvement during the [redacted] phase.

3.1.3 Bar Charts of Mean and SD by Visit for Selected Efficacy Endpoints

Bar charts will be produced for selected endpoints to present group mean +/-SD at [redacted] and [redacted] (except in the case of DXA Scan, CGI-I and OSU CGI-I results which will only be presented at [redacted] and [redacted]). At each visit, the mean value across all patients will be presented as a bar and the SD of the values at that visit will be presented as line extending above and below the top of each bar joining horizontal lines, denoting the mean +/- the SD. Subtitles, footnotes and axis labels will be adapted from the equivalent by subject line plots planned in this SAP for the respective endpoints, with an additional footnote to describe the presentation of mean values and SDs. The endpoints to be presented will be:

- Handgrip Myometry over Time (relaxation time, repeated for the dominant hand and non-dominant hand)
- Pulmonary Function Test (FVC) over Time
- Time Taken (Seconds) to Complete the Nine Hole Peg Test over Time (repeated for the dominant arm and non-dominant arm)
- Clinical Global Impression over Time (Improvement scores for [redacted] and [redacted])
- OSU Global Improvement Scale for Autism over Time (Improvement scores for [redacted] and [redacted])
- Peabody Picture Vocabulary Test over Time (age based standard score)
- DXA Scan (Body Composition - Lean Muscle Mass) over Time (arms category for [redacted] and [redacted])

3.1.4 Bar Charts of Percentage of Responders for CGI-I and OSU CGI-I at [redacted] and [redacted]

Bar charts will be presented for the percentage of subjects recording improvement at [redacted] and [redacted] for the CGI-I and OSU CGI-I endpoints. 'Improvement' will be defined as a score <=3 at the respective time point (corresponding to scores of: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved). A subheading will present the dose group with the corresponding population total and any other subtitles per the equivalent by subject line plot planned in this SAP. The percentage of subjects will be calculated as the number of subjects recording a score <=3 at the respective time point as a percentage of the full analysis set.

3.1.5 Line Plots of Percentage Changes Over Time for Selected Efficacy Endpoints

Line plots will be presented to display the percentage change over time for total clinician-completed domain specific causes for concern VAS, and caregiver top 3 concerns total VAS.

Two plots will be presented for each endpoint, one to present the percentage change from [redacted] to [redacted], another to present the percentage change from [redacted] to [redacted] and [redacted]. On each plot, the percentage change will be presented by subject as well as the group mean percentage change +/- SD across all subjects.

3.1.6 Scatterplots of Visit [redacted] Data for Selected Efficacy Endpoints

Scatterplots will be presented indicating observed values at [redacted] for each subject on selected endpoints. Subject number will be presented on the x-axis with the respective [redacted] observed value on the y-axis. Subtitles, labels and footnotes will be adapted from the respective by subject line plots planned in this SAP. Where the endpoint is presented for different categories (e.g. preferred/fastest speed or dominant/non-dominant hand), each category will be displayed on a separate page. The endpoints to be presented will be:

- Time to complete 10m walk test (repeated for preferred and fastest speed)
- Handgrip Myometry (Grip strength and Relaxation time, repeated for the dominant hand and non-dominant hand)
- Pulmonary Function Test (FVC)
- Nine Hole Peg Test (dominant arm)
- Clinician-completed domain specific causes for concern VAS (repeated for total and domain specific VAS scores)
- Caregiver Top 3 Concerns Total VAS
- Peabody Picture Vocabulary Test (age based standard score)

4 STUDY SUBJECTS

4.1 Disposition of Subjects

The number and percentage of all subjects enrolled, included in the full analysis set, safety analysis set, pharmacokinetic analysis set, who completed the study, prematurely discontinued treatment (where the subject discontinued prior to [redacted]), prematurely discontinued the study and study duration (date of completion/discontinuation – Visit [redacted] date + 1) will be summarised. The number and percentage of subjects will be summarised by their reasons for withdrawal from treatment (i.e. prior to [redacted] and separately from the study (i.e. prior to [redacted]). Eligibility for each of the analysis sets along with reasons for exclusion will be listed. Study completion/withdrawal data will be listed.

4.1.1 Analysis Sets

The **Enrolled Set** includes all subjects who passed screening irrespective of whether they received active treatment. The enrolled set will be used for subject disposition summaries.

The **Safety Analysis Set** (SAF) will include all subjects who had at least one administration of active treatment. The SAF will be used for all summaries of protocol

deviations, background and demographic characteristics, administration of investigational product and safety evaluation data.

The **Full Analysis Set** (FAS) will include all subjects in the SAF for whom any efficacy data were collected after first administration of active treatment. The FAS is the primary population for analyses of efficacy data.

The **Pharmacokinetic Analysis Set** (PKAS) will consist of all subjects for whom PK plasma concentration data (which includes concentrations below the lower limit of quantification (LLOQ)) are available at either [redacted] or [redacted] (pre-dose or post-dose).

Listings of study data will be based on all subjects who were enrolled in the study.

4.2 Protocol Deviations

Prior to database lock and prior to analysis of the Cohort 1 data, AMO Pharma Ltd will review the individual deviations and classify them as major or minor.

The number and percentage of subjects with at least one major protocol deviation will be summarised. Major protocol deviations will be summarised for each major deviation category. Major protocol deviation categories include:

- Subjects failing any eligibility criteria.
- Taking inadmissible concomitant medication.
- Subjects meeting withdrawal criteria but not withdrawn.
- Significant non-compliance with active treatment administration, [redacted] compliance.

Other major protocol deviations may be identified during the review.

Active treatment administration percentage compliance is given by:

$$\left(\frac{\text{Total amount of active treatment taken}}{\text{Total amount of active treatment expected to be taken}}\right) x100$$

The total amount (mg) of active treatment taken is given by:

[redacted] (sum of [redacted] sachets dispensed – sum of [redacted] sachets returned) +

[redacted] (sum of [redacted] sachets dispensed – sum of [redacted] sachets returned)

Where active treatment dispensing commences from [redacted]

The total amount (mg) of active treatment expected to be taken for Cohort 1 subjects is:

1. Treatment period x [redacted], for subjects with no [redacted], where the treatment period is given by:

   ([redacted] or withdrawal date if prior to [redacted] –[redacted] date.

2. [redacted] x (treatment period prior to [redacted]) + [redacted] x (treatment period after [redacted]), where the treatment period prior to [redacted] is given by:

   Date subject stopped taking [redacted] of active treatment– [redacted] date.

and the treatment period after [redacted] is given by:

([redacted] or withdrawal date if prior to [redacted] – date (taken from diary card) subject started taking [redacted] of active treatment + 1.

The total amount (mg) of active treatment expected to be taken for Cohort 2 subjects is:

Treatment period [redacted], where the treatment period is given in (1) above. [redacted], the derivation of the total amount of active treatment expected to be taken for Cohort 2 subjects will be as per the calculation for Cohort 1 subjects.

Details of all protocol deviations (date, deviation category, specific details and classification of major or minor) and subject eligibility will be listed.

4.3 Background and Demographic Characteristics

4.3.1 Demography

Demographic characteristics (age, sex, ethnic origin and race), dominant arm, body measurements (height, weight and BMI), collected at baseline will be summarised.

Age is calculated in years from the date of [redacted] of active treatment.

Body mass index (BMI) is calculated as (weight (kg)/height (m)^2).

All subject demographic data, also including informed consent, will be listed.

4.3.2 Medical/Surgical History

Medical/surgical history events will be coded using the latest MedDRA dictionary version. The number and percentage of subjects will be presented for ongoing conditions and previous conditions separately by SOC, and PT, where SOC and PT will be presented in decreasing frequency of the total number of subjects with medical history events. All events will be listed, which will include a flag for ongoing and previous conditions.

4.3.3 Myotonic Dystrophy Diagnosis

Myotonic dystrophy diagnosis (congenital or juvenile-onset) and the congenital and juvenile-onset signs and symptoms will be summarised. Baseline signs and symptoms will be summarised by SOC and PT and by SOC, PT and severity.

Myotonic dystrophy diagnosis information and baseline signs data will be listed.

4.4 Administration of Investigational Product

Percentage compliance with administration of active treatment will be summarised (see section 4.2 for the derivation).

The following active treatment exposure summaries will also be provided: total amount (mg) of active treatment taken (see section 4.2 for derivation) and the number of days of exposure to the active treatment derived from the subject diary card data as follows:

(Date of [redacted] of [redacted] of active treatment – date of [redacted] of [redacted] of active treatment + 1) + (Date of [redacted] of [redacted] of active treatment – date of [redacted] of [redacted] of active treatment + 1), where the [redacted] duration is only applicable to subjects who are [redacted]

In addition, the following active treatment exposure summaries will be provided for Cohort 1 subjects:

- the number of days of exposure to [redacted] tideglusib for all Cohort 1 subjects and separately for Cohort 1 subjects who are [redacted] from [redacted] tideglusib defined as:

  Date of [redacted] of [redacted] of active treatment – date of [redacted] of [redacted] of active treatment + 1.

- the number of days of exposure to [redacted] tideglusib for subjects who are [redacted] from [redacted] tideglusib defined as:

  Date of [redacted] of [redacted] of active treatment – date of [redacted] of [redacted] of active treatment + 1.

- the number of subjects that were [redacted]

[redacted] [redacted] dose, the additional variables outlined above for Cohort 1 will be derived for both Cohorts.

The above derived variables and study drug dispensing, study drug return, study drug down titration and subject diary card information will be listed.

5 EFFICACY EVALUATION

5.1 Efficacy Endpoints

The efficacy endpoints have been grouped into 4 efficacy endpoint "families" detailed in sections 5.1.1 to 5.1.4 below.

In addition to the analyses detailed in these sections, score card values [redacted]) will be derived for each subject based on the [redacted] given in Table 1 below, where any endpoint not meeting the criteria will be assigned a score of [redacted].

Score card values will be derived for each subject at each of [redacted] and [redacted] Where an endpoint is not scheduled to be collected at the respective visit, a score will not be derived and N/A will be displayed in the listing. Where an endpoint is scheduled to be collected but is missing, the score will be displayed as ND.

At [redacted] only, a total score card value will be calculated for each subject as the sum of the [redacted] If any endpoint score is missing at these scheduled visits, the total score will not be calculated for the respective visit and subject. The scorecard values for each of the [redacted] detailed in Table 1 and the total score card value will be listed by Visit for each subject.

Mean total scores at [redacted] will be calculated by dose group and compared using a t-test. Additionally, the [redacted] total scores will be compared between the two dose groups using a Wilcoxon rank-sum test. Summary statistics will be presented for the dose group total scores at [redacted] together with the p-values from the comparisons between

dose groups. Since this is a non-randomised trial, there will be a known potential for any comparison of dose groups to be biased. This will be addressed via examination of the by cohort summary statistics for baseline characteristics and baseline efficacy measurements. If it is determined that there are large differences between cohort characteristics at baseline, further exploratory analysis may be performed for the comparison of total scores with adjustment for baseline characteristics.

Table 2: [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

5.1.1 Muscle Function

5.1.1.1 10 Metre Walk/Run Test

In the event that a subject does not complete a walk/run test, then that test result will not be included in derivation of the observed mean of the repeat assessments, which will use only "valid" results where the subject completed the assessment. A "valid" result will be any non-missing result where the recorded distance covered is not <10 metres. Where the distance is <10 metres, the test result will be assumed missing.

A MMRM will be fitted to the change from baseline to weeks [redacted] and [redacted] in the time taken (seconds) to complete the 10 metre walk/run test at the preferred speed (calculated for each visit as the mean of the repeat assessments). The model will include the baseline value as a covariate, dose group, 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. A compound symmetry covariance matrix will be used for the repeated visits within subject.

Adjusted LS Means for the dose group means at each visit estimated by the above model will be presented, together with the associated SE, 95% CIs and 2-sided p-values.

The observed mean (of the repeat assessments at a visit) for the time taken (seconds) to complete the 10 metre walk/run test and the change from baseline will be summarised over time separately for the preferred speed and the fastest speed. The observed mean at the start of the [redacted] run-in [redacted] and at baseline ([redacted]) and the change from [redacted] to [redacted] in the observed mean will also be summarised separately for the preferred speed and the fastest speed.

The observed mean (of the repeat assessments at a visit) in the time taken (seconds) to complete the 10 metre walk/run test will be presented using by subject line plots over time ([redacted], [redacted] [redacted] and [redacted] by dose group separately for the preferred speed and the fastest speed. In addition, line plots will present the adjusted LS mean changes from baseline and SEs over time, as estimated by the MMRM model, by dose group for the time taken (seconds) to complete the 10 metre walk/run test at the preferred speed. Raw mean changes from [redacted] to [redacted] will be presented on the same plot.

In order to assess the relationship between change from baseline to week [redacted] in the time taken to complete the 10 metre walk/run test at the preferred speed and the change from baseline to week [redacted] in total lean muscle mass, the change in the mean of the repeat assessments from baseline to week [redacted] in the time taken to complete the 10 metre walk/run test at the preferred speed will be plotted against the change from baseline to week [redacted] in total lean muscle mass.

The 10 metre walk/run test data will be listed.

5.1.1.2 Grip Strength and Muscle Relaxation Time

Grip strength and relaxation time are recorded in 2 separate trials for both the dominant and non-dominant hands, where in each trial there are 3 repeat assessments. For analysis purposes, the mean of the 2 trial results will be used, where for each trial the mean of the repeat assessments is taken.

A MMRM model will be fitted to the change from baseline to weeks [redacted] and [redacted] in the above derived mean per visit in the grip strength (kg) and separately for the muscle relaxation time (seconds) for the dominant hand. The model will include the baseline value as a covariate, dose group 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. The following variance/covariance matrix structures for the repeated visits within a subject will be assessed: Compound symmetry, 1st order autoregressive, Toeplitz and unstructured. The variance/covariance matrix structure that results in the smallest Akaike information criterion (AIC), indicating the best model fit will be selected.

The results from the above model will be presented as described in section 5.1.1.1.

The above derived mean grip strength and relaxation time and change from baseline will be summarised over time separately for the dominant and non-dominant hands. In addition, the observed mean at [redacted] and [redacted] and the change from [redacted] to [redacted] in the

observed mean will also be summarised separately for grip strength and relaxation time and for the dominant and non-dominant hands. The observed mean will also be presented using by subject line plots over time ([redacted] and [redacted]) by dose group separately for grip strength and relaxation time and for the dominant and non-dominant hands. In addition, line plots will present the adjusted LS mean changes from baseline and SEs over time, as estimated by the MMRM model, by dose group for grip strength and separately for the muscle relaxation time for the dominant hand. Raw mean changes from [redacted] to [redacted] will be presented on the same plot.

Grip strength and relaxation time data will be listed.

5.1.1.3 Respiratory Forced Vital Capacity

A MMRM model will be fitted to the change from baseline to weeks [redacted] and [redacted] in the mean of the repeat assessments at a visit in respiratory forced vital capacity (FVC). The model will be fitted and results presented as described in section 5.1.1.1.

The observed mean (of the three repeat assessments) of the FVC and the change from baseline over time will be summarised. In addition, the observed mean at [redacted] and [redacted] and the change from [redacted] to [redacted] in the above observed mean will also be summarised. The observed mean will also be presented using by subject line plots over time ([redacted] and [redacted]) by dose group. In addition, line plots will present the adjusted LS mean changes from baseline and SEs over time, as estimated by the MMRM model, by dose group for FVC. Raw mean changes from [redacted] to [redacted] will be presented on the same plot.

FVC data will be listed.

5.1.1.4 Actigraphy

For each subject and visit, actigraphy data will be selected for analysis based on the following rules:

1. Take the first 7 consecutive days following the visit date (where Day 1 of the 7 days is the day after the visit date).
2. Exclude the first and last of these 7 days to leave 5 consecutive days.
3. Considering the remaining 5 days, exclude any day with less than 5 hours of wear time in total (this does not have to be consecutive hours).
4. Following the above steps, if less than 3 days remain, exclude all actigraphy data for this visit for the subject (visit is treated as missing and subject to the imputation methods outlined in this SAP for MMRM analyses)

Following application of the above rules, an assessment will be performed to determine how many subjects have non-missing data meeting the criteria at each of the visits (with particular reference to Baseline and [redacted]

For each subject and visit, the measurements to be summarised and analysed will be 'Weekly total per hour of wear time'. This will be derived as the total value across all valid days for the visit (selected in steps 1-4 above) divided by the total hours wear time across these valid days. This calculation will be performed separately for

the weekly total number of steps per hour of wear time, weekly total number of 3 minute bouts of activity per hour of wear time, weekly total number of >10 minute bouts of activity per hour of wear time. A 3 minute bout of activity will consist of 3 minutes of activity, with zero minutes 'drop time' and 300 activity counts per minute.

The weekly total number of steps per hour wear time, total number of 3 minute bouts of activity per hour wear time, total number of >10 minute bouts of activity per hour wear time will be derived at each visit from [redacted] onwards.

Baseline will be taken from the 7 days of activity recorded commencing from the day after the [redacted] date. The Actigraph activity recorded during the 7 days following each visit, will be assigned to the next visit i.e. the actigraphy data recorded during the 7 days commencing the day after the [redacted] (week [redacted]) date will be assigned to [redacted] (week [redacted]) and so on.

A MMRM model will be fitted to the change from baseline to the above assigned weeks [redacted] in the weekly total number of 3 minute bouts of activity per hour wear time. The model will be fitted and results presented as described in section 5.1.1.2.

The observed weekly total: number of steps per hour wear time, number of 3 minute bouts of activity per hour wear time and number of >10 minute bouts of activity per hour wear time and the corresponding change from baseline will be summarised. The weekly totals per hour wear time will also be presented using by subject line plots over time (assigned [redacted] (baseline), assigned [redacted], assigned [redacted] and assigned [redacted] by dose group. In addition, line plots will present the adjusted LS mean changes from baseline and SEs over time, as estimated by the MMRM model, by dose group for the weekly total number of 3 minute bouts of activity per hour wear time.

Actigraphy data will be listed.

5.1.1.5 Nine Hole Peg Test

A MMRM model will be fitted to the change from baseline to weeks [redacted] in the time taken (seconds) to complete the nine hole peg test (NHPT) for the dominant arm. The model will be fitted and results presented as described in section 5.1.1.2.

The observed time taken to complete the NHPT and corresponding change from baseline over time will be summarised separately for the dominant and non-dominant arms. In addition, the time taken to complete the NHPT at [redacted] and [redacted] and the change from [redacted] to [redacted] will also be summarised separately for the dominant and non-dominant arms. The observed time taken will be presented using by subject line plots over time ([redacted], [redacted], [redacted] and [redacted]) by dose group separately for the dominant and non-dominant arms. In addition, line plots will present the adjusted LS mean changes from baseline and SEs over time, as estimated by the MMRM model, by dose group for the time taken to complete the NHPT for the dominant arm. Raw mean changes from [redacted] to [redacted] will be presented on the same plot.

NHPT data will be listed.

5.1.2 Clinician/Caregiver Symptom Scales

5.1.2.1 Clinical Global Impressions

An ANCOVA will be fitted to the change from baseline to end of treatment in the clinical global impression – severity of illness scale (CGI-S). The ANCOVA will include the baseline value as a covariate and dose group as a fixed effect. Adjusted LS Means for the dose group means at the end of treatment estimated by the above model will be presented, together with the associated SE, 95% CIs and 2-sided p-values.

CGI-S and change from baseline will be summarised over time using summary statistics. CGI-S at [redacted] and [redacted] and the change from [redacted] to [redacted] in CGI-S will also be summarised using summary statistics. In addition, line plots will present the adjusted LS mean changes from baseline to end of treatment and SEs, as estimated by the ANCOVA, by dose group for the CGI-S. Raw mean changes from [redacted] to [redacted] will be presented on the same plot.

A MMRM model will be fitted to the observed values at weeks [redacted] and [redacted] in the clinical global impression – improvement scale (CGI-I). The model will include dose group 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. The following variance/covariance matrix structures for the repeated visits within a subject will be assessed: Compound symmetry, 1st order autoregressive, Toeplitz and unstructured. The variance/covariance matrix structure that results in the smallest Akaike information criterion (AIC), indicating the best model fit will be selected. Adjusted LS Means for the dose group means at each visit estimated by the above model will be presented, together with the associated SE and 95% CIs. The 2-sided p-values will also be presented at each visit for the comparison of the adjusted LS Means to a CGI-I score of 4 (representing "No Change").

CGI-I observed values will be summarised over time using summary statistics. By subject line plots of the CGI-I results will be presented over time ([redacted], [redacted] and [redacted]) by dose group. In addition, line plots will present the adjusted LS means and associated SEs for the observed values over time, as estimated by the MMRM model, by dose group for the CGI-I.

The CGI-I and CGI-S data will be listed.

5.1.2.2 Clinician-completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy

A MMRM model will be fitted to the change from baseline to weeks [redacted] and [redacted] in the total clinician-completed domain specific causes for concern VAS score. The model will be fitted and results presented as described in section 5.1.1.1.

The observed total clinician-completed domain specific causes for concern VAS score and domain specific VAS scores and corresponding change from baseline will be summarised over time. In addition, the above scores at [redacted] and [redacted] and the change from [redacted] to [redacted] will be summarised. The observed total clinician-completed domain specific causes for concern VAS score and domain specific VAS scores will also be presented over time ([redacted] and [redacted]) using by subject line plots by dose group. In addition, line plots will present the adjusted LS mean changes from baseline and SEs over time, as estimated by the MMRM model, by dose group for

the total clinician-completed domain specific causes for concern VAS score. Raw mean changes from [redacted] to [redacted] will be presented on the same plot.

The relationship between the change from baseline to week [redacted] in the total clinician-completed domain specific causes for concern VAS score and the change from baseline to week [redacted] in total lean muscle mass will be evaluated by plotting the change from baseline to week [redacted] in the total clinician-completed domain specific causes for concern VAS score against the change from baseline to week [redacted] in total lean muscle mass.

The clinician-completed domain specific causes for concern VAS data will be listed.

5.1.2.3 Top 3 Concerns Visual Analogue Scale (VAS)

The top 3 caregiver and subject concerns recorded for each subject will be mapped to the clinician-completed domain specific causes for concern.

A MMRM model will be fitted to the change from baseline to weeks [redacted] and [redacted] in the top 3 concerns VAS total score (derived as the total of the VAS scores for the three concerns) separately for the caregiver and subject. The model will be fitted and results presented as described in section 5.1.1.1.

The observed top 3 concerns VAS total score and corresponding change from baseline will be summarised over time separately for caregiver and subject. In addition, the above VAS scores at [redacted] and [redacted] and the change from [redacted] to [redacted] will be summarised. The observed top 3 concerns VAS total score will also be presented over time ([redacted] and [redacted]) using by subject line plots by dose group, separately for the caregiver and subject. In addition, line plots will present the adjusted LS mean changes from baseline and SEs over time, as estimated by the MMRM model, by dose group for the top 3 concerns VAS total score separately for the caregiver and subject. Raw mean changes from [redacted] to [redacted] will be presented on the same plot.

The top 3 concerns data, including the mapped domains and VAS scores will be listed. The listing will include change from baseline for the individual concerns VAS scores as well as the total VAS scores for each subject or caregiver.

5.1.3 Cognitive and Neurodevelopment

5.1.3.1 Ohio State University (OSU) Autism Rating Scale

A MMRM model will be fitted to the change from baseline to weeks [redacted] and [redacted] in the OSU autism rating scale total impairment mean. The model will be fitted and results presented as described in section 5.1.1.1.

The observed OSU autism rating scale social interaction impairment mean, communication impairment mean, restricted patterns mean and total impairment mean and corresponding change from baseline will be summarised over time. In addition, the observed means at [redacted] and [redacted] and the change from [redacted] to [redacted] will also be summarised.

The OSU autism rating scale data will be listed.

5.1.3.2 OSU CGI-S and CGI-I

The OSU CGI-S and CGI-I will be analysed and summarised as described in section 5.1.2.1. The MMRM analysis of OSU CGI-I results will be fitted to the observed

values at weeks [redacted] and [redacted]. A compound symmetry covariance matrix will be used for the repeated visits within subject. The by subject line plot of OSU CGI-I results will include [redacted] and [redacted].

The OSU CGI-S and CGI-I data will be listed.

5.1.3.3 Peabody Picture Vocabulary Test

An ANCOVA will be fitted to the change from baseline to end of treatment in the Peabody picture vocabulary test age-based standard score. The model will be fitted and results presented as described in section 5.1.2.1 for CGI-S.

The observed raw score, age-based standard score, percentile rank and age equivalent in years and corresponding change from baseline over time will be summarised. In addition, the above scores at [redacted] and [redacted] and change from [redacted] to [redacted] will also be summarised. The above Peabody picture vocabulary test endpoints (apart from the age equivalent (years) endpoint) will also be presented over time (V2, [redacted] and [redacted] using by subject line plots by dose group. In addition, line plots will present the adjusted LS mean changes from baseline to end of treatment and SEs, as estimated by the ANCOVA, by dose group for the Peabody picture vocabulary test age-based standard score. Raw mean changes from [redacted] to [redacted] will be presented on the same plot.

The Peabody picture vocabulary test data will be listed.

5.1.4 Biomarker

5.1.4.1 Dual-energy X-ray Absorptiometry (DXA) Whole Body Scan of Lean Muscle Mass

An ANCOVA will be fitted to the change from baseline to end of treatment in the DXA scan total lean muscle mass (g). The model will be fitted and results presented as described in section 5.1.2.1 for CGI-S.

The observed muscle mass and corresponding change from baseline to end of treatment will be summarised separately for the arms, the legs and the total muscle mass. The observed muscle mass for the arms, the legs and total muscle mass will also be presented over time ([redacted] and [redacted]) using by subject line plots by dose group. In addition, line plots will present the adjusted LS mean changes from baseline to end of treatment and SEs, as estimated by the ANCOVA, by dose group for the DXA scan total lean muscle mass (g).

Lean muscle mass data will be listed.

5.1.4.2 [redacted]

[redacted]

5.2 Handling of Missing Data

There is no requirement for imputation of missing data in the MMRM models detailed in section 5.1, since the MMRM models handle missing data by assuming that missing data is missing at random (MAR), so that mean changes from baseline are estimated assuming that subjects with missing data will perform in the same way as

subjects with the same baseline covariate values and the same observed data so far.

In the ANCOVA models, if a subject has missing data at week [redacted] the subject will be excluded from the analysis and so will be assumed to be missing completely at random (MCAR).

Prior to database lock, the data will be reviewed to assess whether any subjects were unable to complete an assessment due to “extreme” factors affecting their ability to complete an assessment e.g. due to a serious deterioration in their physical state. In the event that such subjects are identified, appropriate methods for handling this specific type of missing data will be used.

For example, in the event that some fraction q of the subjects become non-ambulatory, the results for this analysis can then be scaled to reflect the proportion of non-ambulatory subjects. For example, suppose, for a given endpoint within N=8, q=2/8 =25% of the subjects were non ambulatory at [redacted] weeks. Suppose the mean change from baseline at [redacted] weeks in the 6/8 who were ambulatory is $\bar{x}$ with estimated SE s, then the scaled result allowing for the non ambulatory subjects is then $\bar{x}/(1-q) = \bar{x}/(1-0.25)$. The log scale SE of this scaled result can then be estimated as $\sqrt{\frac{s^2}{\bar{x}^2} + \frac{q}{N(1-q)}}$.

6 PHARMACOKINETICS

The details of any blood concentration/pharmacokinetic analyses will be described in a separate PK analysis plan.

7 SAFETY EVALUATION

7.1 Adverse Events

Adverse events will be coded using the latest MedDRA dictionary version.

A NTEAE is defined as an AE that started on or after the administration of placebo treatment but before the start of the administration of active treatment.

A TEAE is defined as an AE that started on or after the start of the administration of active treatment. If adverse event dates are incomplete and it is not clear whether the adverse event was treatment-emergent, it will be assumed to be treatment-emergent.

A “treatment period” TEAE is defined as an AE that started on or after the start of active treatment but before 2 days after active treatment was discontinued. A “post treatment period” TEAE is defined as an adverse event that started from 2 days after the active treatment was discontinued.

Adverse events of special interest (AESIs) are recorded if it is identified from a review of the haematology and biochemistry results that the subject has clinically significant liver function test elevation.

The following summaries of the total number of “treatment period” TEAEs, “post treatment period” TEAEs and all TEAEs (both “treatment period” and “post treatment period” TEAEs) will be provided at the event and subject levels as indicated:

- TEAEs (events and subjects).
- TEAEs by relationship to active treatment (events and subjects).
- TEAEs by severity (mild/moderate/severe) (events and subjects).
- Serious TEAEs (events and subjects).
- Serious active treatment related TEAEs (events and subjects).
- TEAEs leading to withdrawal (subjects only).
- TEAEs leading to discontinuation of active treatment (subjects only).
- Active treatment related TEAEs leading to discontinuation of active treatment (subjects only).
- TEAEs leading to death (subjects only).

The following summaries of NTEAEs will be provided at the event and subject levels as indicated:

- NTEAEs (events and subjects).
- NTEAEs by severity (mild/moderate/severe) (events and subjects).
- Serious NTEAEs (events and subjects).
- NTEAEs leading to withdrawal (subjects only).
- NTEAEs leading to death (subjects only).

In the above summaries, if a subject experienced more than one NTEAE/TEAE, the subject will be counted once using the most related event for the “by relationship to active treatment” summary and at the worst severity for the “by severity” summary.

The number and percentage of subjects experiencing “treatment period” TEAEs, “post treatment period” TEAEs and all TEAEs will be presented by:

1. System Organ Class (SOC) and Preferred Term (PT).
2. PT.
3. SOC, PT and severity.
4. SOC, PT and relationship (related/unrelated) to active treatment.

In addition, the number and percentage of subjects experiencing NTEAEs will be presented by:

1. SOC and PT.
2. SOC, PT and severity.

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

Further details of the above four tables are given below:

1. If a subject experienced more than one NTEAE/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 NTAE/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.

Adverse event data will be listed in full and this will also include a treatment emergent flag, a treatment period TEAE flag, a post treatment period TEAE flag, a flag for AESIs, the time of onset of event relative to first dosing of active treatment, and duration of AE.

7.2 Clinical Laboratory Evaluations

Observed values and change from baseline in haematology, prothrombin time, international normalisation ratio, biochemistry and urinalysis assessments will be summarised over time. If the test results are reported in categorical format, the results will be summarised by subject counts and percentage for each category.

Each haematology, prothrombin time, international normalisation ratio, biochemistry and urinalysis parameter will be classed as low, normal, high based on the reference ranges. Shift tables in relation to the normal range from baseline over time will be presented.

Haematology including serology, prothrombin time, international normalisation ratio, biochemistry and urinalysis data will be listed separately including change from baseline, reference ranges flagging all out of range values and also flagging any assessments with at least one clinically significant value.

Separate listings of out of range laboratory measurements recorded throughout the study will be provided. Separate listings will also present local laboratory results where these are collected.

7.3 Vital Signs

Vital sign observed values and change from baseline by parameter (unit) will be summarised over time.

In addition, ‘substantial’ changes from baseline will be categorised as follows: change from baseline in systolic/diastolic blood pressure (systolic BP [>±40 mmHg], diastolic BP [>±20 mmHg]) and heart rate (>±30 bpm). The number and percentage of subjects with changes from baseline as categorised above will be summarised separately for positive and negative changes over time and at any post-baseline time point.

All vital sign data will be listed including reference ranges flagging all out of range values, change from baseline including flags for substantial changes from baseline.

7.4 Electrocardiography

Electrocardiography (ECG) observed values and change from baseline will be summarised over time.

The incidence of outliers in absolute QT, QTcF and QTcB intervals (>450, >480, and >500 msec), and the change from baseline in QT, QTcF and QTcB intervals (>30 and >60 msec both positive and negative changes) will be summarised over time and at any post-baseline time point.

In addition, the overall interpretation of the ECG (Normal, Abnormal NCS, and Abnormal CS) will also be summarised over time.

All ECG results will be listed including reference ranges flagging all out of range, overall interpretation and change from baseline values.

7.5 Prior and Concomitant Medications

Medications will be coded using the latest World Health Organization Drug dictionary (WHO Drug) version.

Prior medications are defined as those that started and ended prior to the administration of active treatment. Medications that are ongoing at the first administration of the active treatment or started after time of first administration of active treatment will be deemed to be concomitant medications. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of subjects taking prior and concomitant medications will be summarised separately by medication class and standardised medication name, where medication class and standardised medication name will be presented in decreasing frequency of the total number of subjects with medications. In summary tables, subjects taking multiple medications in the same medication class or having the same standardised medication recorded multiple times in the study will be counted only once for that specific medication class and standardised medication name.

Medication data will be listed, where concomitant medications will be flagged.

7.6 Physical Examination

Details of timings of physical examinations will be listed.

7.7 Pregnancy test

Details of the pregnancy test will be listed.

APPENDIX 1

The following Cohort 1 data outputs will be provided after soft lock of the Cohort 1 subjects as described in Section 3:

Listings:

Demography and baseline characteristics

Listing 16.2.1.1 Subject Completions and Withdrawals

Listing 16.2.2.1 Eligibility - Inclusion and Exclusion Criteria
Listing 16.2.2.2 Protocol Deviations
Listing 16.2.3.1 Analysis Sets
Listing 16.2.4.1 Demography
Listing 16.2.4.2 Medical/Surgical History
Listing 16.2.4.3 Prior and Concomitant Medications
Listing 16.2.4.4 Baseline Signs and Symptoms
Listing 16.2.4.5 Diagnosis

Diary card data
Listing 16.2.5.4 Subject Diary Card

Efficacy

Listing 16.2.6.1 10-metre Walk/Run Test
Listing 16.2.6.2 Handgrip Myometry
Listing 16.2.6.3 Pulmonary Function Test
Listing 16.2.6.4 Actigraphy
Listing 16.2.6.5 Nine Hole Peg Test
Listing 16.2.6.6 Clinical Global Impression - Severity of Illness Scale (CGI-S) and Global Improvement Scale (CGI-I)
Listing 16.2.6.7 Clinician-completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy
Listing 16.2.6.8 Subject Top Three Concerns
Listing 16.2.6.9 Caregiver Top Three Concerns
Listing 16.2.6.10 OSU Autism Rating Scale - DSM-IV (OARS-4)
Listing 16.2.6.11 OSU Global Severity/Improvement Scale for Autism
Listing 16.2.6.12 Peabody Picture Vocabulary Test
Listing 16.2.6.13 DXA Scan
Listing 16.2.6.15 Score Card Endpoints

Safety

Listing 16.2.7.1 Adverse Events

Listing 16.2.8.1.1 All Haematology Values
Listing 16.2.8.1.2 Subjects with Out of Range Haematology Values
Listing 16.2.8.2.1 All Biochemistry Values
Listing 16.2.8.2.2 Subjects with Out of Range Biochemistry Values
Listing 16.2.8.3.1 All Urinalysis Values
Listing 16.2.8.3.2 Subjects with Out of Range Urinalysis Values

Listing 16.2.8.4.1 [redacted] Values
Listing 16.2.8.4.2 Subjects with Out of Range [redacted]
Listing 16.2.8.5 Pregnancy Test
Listing 16.2.9.1 Vital Signs
Listing 16.2.9.2 ECG Results

Tables:

Table 14.3.1.2.1 Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term
Table 14.3.1.2.2 Summary of Non-Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term

Figures:

Figure 14.2.1.1 Plot of Time Taken (Seconds) to Complete 10-metre Walk/Run Test over Time
Figure 14.2.2.1 Plot of Handgrip Myometry over Time
Figure 14.2.3.1 Plot of Pulmonary Function Test over Time
Figure 14.2.4.1 Plot of Actigraphy over Time
Figure 14.2.5.1 Plot of Time Taken (Seconds) to Complete the Nine Hole Peg Test over Time
Figure 14.2.6.1 Plot of Clinical Global Impression over Time
Figure 14.2.7.1 Plot of Clinician-completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy over Time
Figure 14.2.8.1 Plot of Subject Top Three Concerns VAS Total Score over Time
Figure 14.2.9.1 Plot of Caregiver Top Three Concerns VAS Total Score over Time
Figure 14.2.10.1 Plot of OSU Global Improvement Scale for Autism over Time
Figure 14.2.11.1 Plot of Peabody Picture Vocabulary Test over Time
Figure 14.2.12.1 Plot of DXA Scan (Body Composition - Lean Muscle Mass) over Time

APPENDIX 2

The following ad hoc Cohort 1 data outputs will be provided after soft lock of the Cohort 1 subjects as described in Section 3.1:

Tables:

Table 14.2.2.2_AH1 Analysis of Relaxation Time (Seconds) for the Dominant Hand over Time
Table 14.2.3.1_AH1 Analysis of FVC (litres) over Time
Table 14.2.5.1_AH1 Analysis of the Time Taken (Seconds) to Complete the Nine Hole Peg Test for the Dominant Arm over Time
Table 14.2.6.1_AH1a Analysis of Clinical Global Impression of Improvement Scale (CGI-I) over Time
Table 14.2.6.1_AH1b Summary of Clinical Global Impression of Improvement Scale (CGI-I) - Number of Subjects with Improvement at Baseline and End of Treatment
Table 14.2.7.1_AH1 Analysis of Clinician-completed Domain Specific Causes for Concern VAS Total Score (cm) over Time
Table 14.2.9.1_AH1 Analysis of Caregiver Top Three Concerns VAS Total Score (cm) over Time
Table 14.2.11.1_AH1a Analysis of OSU Global Improvement Scale for Autism (OSU CGI-S) over Time
Table 14.2.11.1_AH1b Summary of OSU Global Improvement Scale for Autism (OSU CGI-I) - Number of Subjects with Improvement at Baseline and End of Treatment
Table 14.2.12.1_AH1 Analysis of the Peabody Picture Vocabulary Test Age-Based Standard Score over Time
Table 14.2.13.1_AH1 Analysis of Change from Baseline in the DXA Scan Arms Lean Muscle Mass (g) to End of Treatment

Figures:

Figure 14.2.1.1_AH1 Scatter Plot of Time Taken (Seconds) to Complete 10-metre Walk/Run Test at Week [redacted]
Figure 14.2.2.1_AH1a Bar Chart of Handgrip Myometry over Time – Mean Value +/- Standard Deviation
Figure 14.2.2.1_AH1b Scatter Plot of Handgrip Myometry at Week [redacted]
Figure 14.2.3.1_AH1a Bar Chart of Pulmonary Function Test over Time – Mean Value +/- Standard Deviation
Figure 14.2.3.1_AH1b Scatter Plot of Pulmonary Function Test at Week [redacted]
Figure 14.2.5.1_AH1a Bar Chart of Time Taken (Seconds) to Complete the Nine Hole Peg Test over Time – Mean Value +/- Standard Deviation
Figure 14.2.5.1_AH1b Scatter Plot of Time Taken (Seconds) to Complete the Nine Hole Peg Test at Week [redacted]
Figure 14.2.6.1_AH1a Bar Chart of Clinical Global Impression over Time – Mean Score +/- Standard Deviation
Figure 14.2.6.1_AH1b Bar Chart of Percentage of Subjects with Improvement at Baseline (End of [redacted]) and End of Treatment - Clinical Global Impression

Figure 14.2.7.1_AH1a Plot of Change from Week [redacted] to Week [redacted] in Clinician-completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy
Figure 14.2.7.1_AH1b Plot of Change from Baseline to End of Treatment in Clinician-completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy
Figure 14.2.7.1_AH1c Scatter Plot of Clinician-completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy at Week [redacted]
Figure 14.2.9.1_AH1a Plot of Change from Week [redacted] to Week [redacted] in Caregiver Top Three Concerns VAS Total Score (cm)
Figure 14.2.9.1_AH1b Plot of Change from Baseline to End of Treatment in Caregiver Top Three Concerns VAS Total Score (cm)
Figure 14.2.9.1_AH1c Scatter Plot of Caregiver Top Three Concerns VAS Total Score (cm) at Week [redacted]
Figure 14.2.10.1_AH1a Bar Chart of OSU Global Improvement Scale for Autism over Time – Mean Score +/- Standard Deviation
Figure 14.2.10.1_AH1b Bar Chart of Percentage of Subjects with Improvement at Baseline (End of [redacted] and End of Treatment – OSU Global Improvement Scale for Autism
Figure 14.2.11.1_AH1a Bar Chart of Peabody Picture Vocabulary Test over Time – Mean Value +/- Standard Deviation
Figure 14.2.11.1_AH1b Scatter Plot of Peabody Picture Vocabulary Test at Week -2
Figure 14.2.12.1_AH1a Bar Chart of DXA Scan (Body Composition - Lean Muscle Mass) over Time – Mean Value +/- Standard Deviation