STATISTICAL ANALYSIS PLAN

Protocol 4053-101

A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations, acronyms, and terms are used in this statistical analysis plan.

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-curve
C_{max}	maximum plasma concentration
DMD	Duchenne muscular dystrophy
eCRF	electronic case report form
ECG	electrocardiogram
ECHO	echocardiogram/echocardiography
IA	interim analysis
IHC	immunohistochemistry
MedDRA	Medical Dictionary for Regulatory Activities
CCI	[redacted]
PFT	pulmonary function test
PK	pharmacokinetics
PMO	phosphorodiamidate morpholino oligomer
CCI	[redacted]
PT	preferred term
CCI	[redacted]
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standard MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization
6MWT	6-minute walk test

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a detailed description of the statistical methods and procedures that will be used to analyze and report results for Study 4053-101, titled "A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping".

This SAP has been prepared based on Protocol Amendment 8, dated 08 November 2017.

3. STUDY OBJECTIVES

3.1. Primary Objectives

Part 1: The primary objective of Part 1 of this study is to evaluate the safety and tolerability of 4 escalating doses (dose titration at 4, 10, 20, and 30 mg/kg/week) of SRP-4053 (also known as golodirsen) administered once weekly for at least 2 weeks per dose level compared with placebo.

Part 2: The primary objectives of Part 2 (with weekly, open-label golodirsen at dose level determined in Part 1 and an untreated group) are:

- to assess ambulation, endurance, and muscle function as measured by change from Baseline at Week 144 on the 6-minute walk test (6MWT) in treated and untreated patients
- to assess the biological activity of golodirsen via dystrophin expression at Week 48 compared with pretreatment

3.2. Secondary Objectives

Part 1: The secondary objective of Part 1 of this study is to determine the pharmacokinetics (PK) of 4 escalating dose levels of golodirsen administered once weekly for at least 2 weeks per dose level compared to placebo.

Part 2: The secondary objectives of Part 2 of this study are:

- to assess the safety, tolerability, and PK of golodirsen administered weekly
- to assess respiratory function in treated and untreated patients

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4. STUDY DESCRIPTION

4.1. Study Overview

This is a first-in-human, multicenter, multiple-dose study to assess the safety, tolerability, efficacy, and PK of once-weekly IV infusions of golodirsen in patients with genotypically confirmed Duchenne muscular dystrophy (DMD) with an eligible deletion amenable to exon 53 skipping (eg, 42-52, 45-52, 47-52, 48-52, 49-52, 50-52; 52; 54-58). This study will be conducted in 2 parts.

Part 1 is a randomized, double-blind, placebo-controlled, dose-titration evaluation to assess the safety, tolerability, and PK of 4 dose levels of golodirsen in 12 patients with DMD over approximately 12 weeks.

Part 2 is a long-term, 168-week, open-label evaluation to assess the efficacy and safety of the selected dose level of golodirsen (determined in Part 1) with untreated patients participating in scheduled assessments for 144 weeks. All 12 treated patients from Part 1 will continue in Part 2. Part 2 will also enroll 12 new patients for open-label treatment with golodirsen. These patients must have a clinical diagnosis of DMD confirmed by the finding of a genomic deletion amenable to exon 53 skipping. In addition, up to 24 patients, who will not receive treatment, will be enrolled in Part 2 to serve as an untreated group. The patients in the untreated group will be DMD patients with a genetically confirmed deletion of exon(s) not amenable to treatment by exon 53 skipping, but who otherwise meet the same eligibility criteria as treated patients newly recruited to Part 2. Patients in the untreated group will discontinue the Treatment Phase at Week 144.

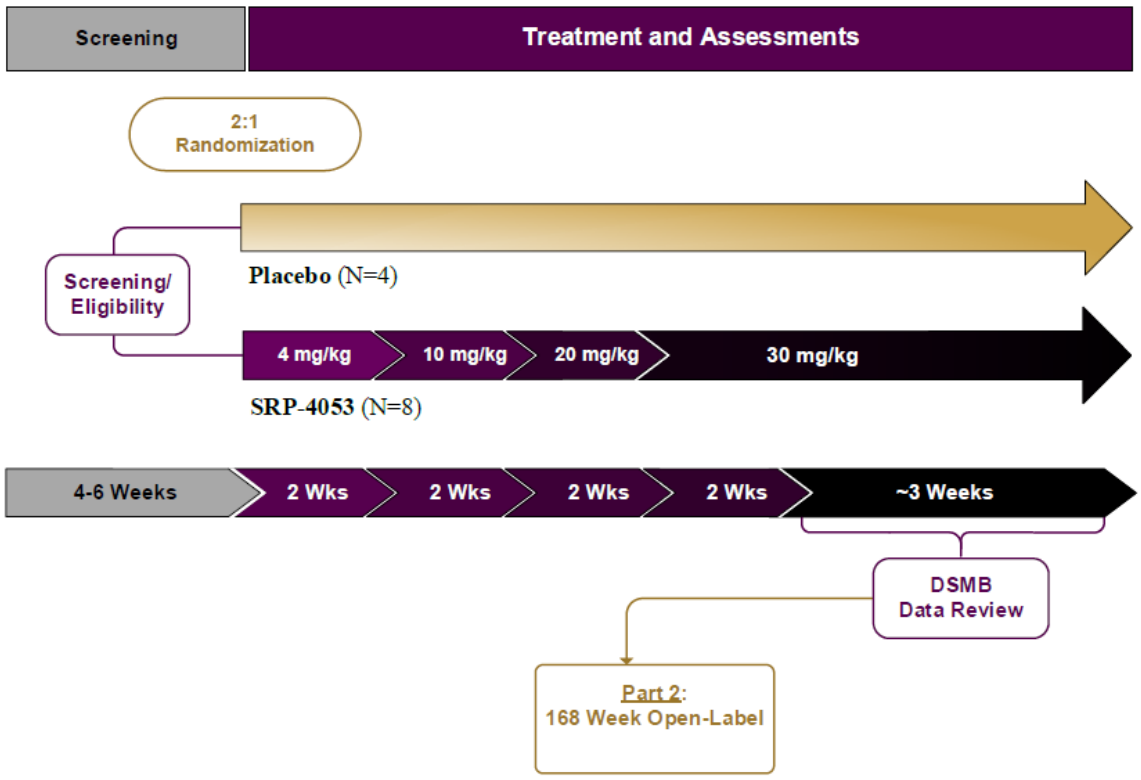
Part 1 will be approximately 12 weeks in duration. Part 2 will last approximately up to 168 weeks.

4.2. Part 1 (Randomized Double-Blind Dose Titration)

DMD patients will participate in a 4- to 6-week Screening period to ensure eligibility, prior to randomization to golodirsen or placebo. Twelve patients will be randomized (2:1) to receive golodirsen (n = 8) or placebo (n = 4). Patients will receive a weekly IV infusion of placebo or golodirsen at escalating dose levels, each for at least 2 weeks: 4 mg/kg/week in Weeks 1 to 2; 10 mg/kg/week in Weeks 3 to 4; 20 mg/kg/week in Weeks 5 to 6; and 30 mg/kg/week beginning at Week 7. Demographic data, baseline assessments and disease characteristics, and muscle biopsy will be collected before randomization. Patients will undergo scheduled assessments as well as routine safety evaluations over the course of Part 1.

Figure 1 is a schematic of the study design for Part 1.

Figure 1: Study Schematic for Part 1, Randomized, Double-blind Dose Titration



4.3. Part 2 (Open Label and Untreated Patient Group)

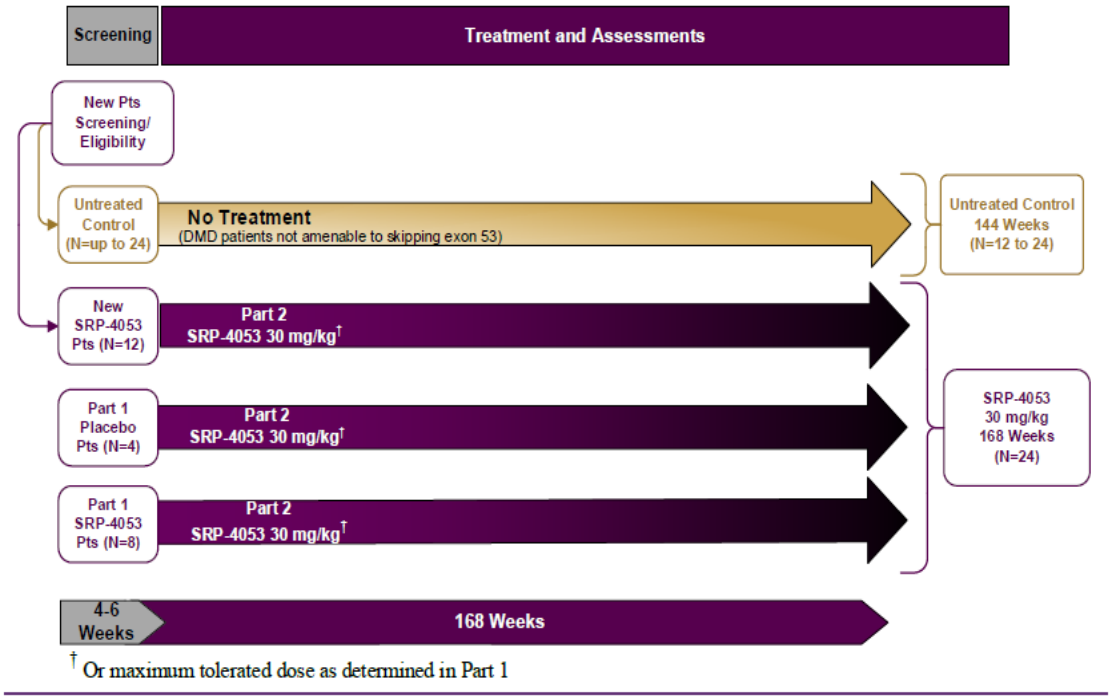
All 12 DMD patients (both golodirsen and placebo) from Part 1 will rollover to Part 2 and begin open-label treatment with golodirsen at 30 mg/kg/week (or the highest tolerated dose determined in Part 1) on Week 1 of Part 2. In addition, 12 new treatment-naïve DMD patients with mutations amenable to exon 53 skipping will be enrolled for open-label treatment, along with up to 24 untreated DMD patients with deletion mutations not amenable to exon 53 skipping, who will participate through Week 144. All new Part 2 patients will be evaluated within a 4- to 6-week Screening period to confirm eligibility.

Demographic data, baseline assessments and disease characteristics, and muscle biopsy samples (for patients amenable to exon 53 skipping only) of newly enrolled patients in Part 2 will be collected during the screening period. Patients will undergo scheduled assessments as well as routine safety evaluations over the course of Part 2; however, untreated patients will undergo the required assessments at a reduced schedule until Week 144.

In Part 2, all treated patients will receive golodirsen at 30 mg/kg weekly (or the highest tolerated dose determined in Part 1) for up to 168 weeks. Untreated patients will discontinue the Treatment Phase (period) at Week 144. All treated patients in Part 2 will be required to undergo a second muscle biopsy at Week 48 of Part 2. Biopsies at

Week 48 must occur: a) within 2 weeks after the Week 48 visit, b) after the clinical evaluation for Week 48, and c) at least 48 hours after the most recent infusion. Figure 2 is a schematic of the study design for Part 2.

Figure 2: Study Schematic for Part 2, Open-Label and Untreated Patient Group



4.4. Sample Size and Power

Sample size for this study is based upon qualitative considerations; no formal sample size calculations will be performed. The anticipated sample size is approximately up to 48 total patients, including 12 patients (8 golodirsen and 4 placebo) in Part 1 and up to 48 (24 treated patients [12 from Part 1 and 12 new patients] and up to 24 untreated patients) in Part 2.

4.5. Randomization and Blinding

4.5.1. Randomization of Treatments

After qualifying for study entry in Part 1, DMD patients with an out-of-frame deletion confirmed as amenable to exon 53 skipping will be randomized using a 2:1 ratio to either golodirsen (8 patients) or placebo (4 patients). Randomization will be performed prior to dosing on Week 1 using an interactive voice response (IVR) system.

There will be no randomization in Part 2 of the study.

4.5.2. Blinding of Treatment in Part 1

Part 1 is a double-blind, placebo-controlled dose titration where all patients, parents, Investigators, and all site staff not involved with study drug preparation will be blinded to

treatment assignment. The double-blind, placebo-control design is intended to reduce potential bias during data collection and evaluation of clinical (safety) parameters.

In Part 2, all treated patients (rollover patients from Part 1 and patients new to Part 2 who are amenable to exon 53 skipping) will receive open-label golodirsen (at the dose determined in Part 1) as weekly IV infusions. No blinding is required.

4.6. Study Endpoints and Other Variables

The study endpoints for which the statistical methods will be described in this SAP comprise all safety, muscle biopsy-based endpoints, and efficacy endpoints.

4.6.1. Safety Endpoints

The safety and tolerability of a golodirsen dosed at 4, 10, 20, and 30 mg/kg/week for at least 2 weeks per dose will be assessed through a review and evaluation of the following:

- incidence of Treatment-emergent Adverse Events (TEAEs)
- incidence of Treatment-emergent Serious adverse events (SAEs)
- incidence of clinical laboratory abnormalities (hematology, chemistry, coagulation, urinalysis)
- incidence of abnormalities in vital signs and physical examinations
- incidence of abnormalities on electrocardiograms (ECGs) and echocardiograms/echocardiography (ECHOs)

4.6.2. Pharmacokinetic Endpoints

The following PK parameters will be determined for both Parts 1 and 2, as appropriate:

- maximum plasma concentration (C_{max})
- time to maximum plasma concentration (t_{max})
- area under the plasma concentration-curve (AUC)
- apparent volume of distribution at steady state (V_{ss})
- elimination half-life ($t_{½}$)
- total clearance (CL)
- mean residence time (MRT)
- urinary clearance (CLR), for Part 1 only

4.6.3. Muscle Biopsy Biological Endpoints (Part 2 Only)

The following biological endpoints will be derived from muscle biopsy samples:

- change from Baseline at Week 48 in dystrophin protein levels determined by Western blot.
- change from Baseline at Week 48 for the following:

- dystrophin intensity levels determined by immunohistochemistry (IHC)
- percentage of dystrophin-positive fibers determined by IHC
- exon 53 skipping determined by measurement and sequence verification of exon 53 skipped messenger ribonucleic acid (mRNA)

4.6.4. Efficacy Endpoints (Part 2 Only)

4.6.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is change from Baseline at Week 144 in the 6MWT.

4.6.4.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint is change from Baseline through Week 144 in forced vital capacity percent predicted (FVC%p).

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4.7. Planned Analyses

4.7.1. Periodic Safety Analyses

Periodic safety analyses will be performed for safety reviews, Investigator Brochure (IB) update, and regulatory submissions (Development Safety Update Report [DSURs], FDA meeting briefing book). These periodic safety analyses will continue to be performed approximately every 6 to 12 months during this study. The Data and Safety Monitoring Board (DSMB) will conduct ongoing reviews of the safety data during the study.

4.7.2. Interim Analyses

Muscle Biopsy Interim Analysis

A Muscle Biopsy Interim Analysis (IA) was performed after all golodirsen-treated patients from Part 1 and Part 2 had completed the Week 48 muscle biopsy in Part 2 of the study. The IA included data for demographic and baseline characteristic, duration of exposure to study drug, and laboratory assessments of muscle biopsy tissue CCI [redacted]. The details of the Muscle Biopsy IA were specified in a separate muscle biopsy statistical analysis plan (Muscle Biopsy SAP), which was approved on 10 August, 2017 before the Muscle Biopsy IA was performed.

Administrative Reviews

Administrative reviews of the efficacy results may be conducted (in a blinded fashion for Part 1 data before the IA and in an unblinded fashion for Part 1 data after the IA and Part 2 data) prior to or when all patients complete the Part 2 Week 48 visit, and again when the patients complete the Part 2 Week 96 visit, to assist in the planning of future studies for patients amenable to exon 53 skipping.

Regulatory Submissions

Additional IAs may be performed to aid regulatory submissions, based on a defined data cutoff date. All data that occurred on or before the cutoff date will be included in the analysis. These IAs will be conducted once all data in the database included in the cutoff are cleaned, quality assured, and locked. These analyses will follow the methods described in this document.

4.7.3. Final Analysis

A final analysis of safety and efficacy will be conducted once the last patient completes the entire study and the resulting database is cleaned, quality assured, locked, and unblinded. All statistical analyses will be performed by or under the supervision of the Sponsor.

All available data will be included in data listings and tabulations.

5. GENERAL STATISTICAL METHODS AND CONVENTIONS

5.1. General Methods

For continuous variables, descriptive statistics will include the number of patients with data to be summarized (n), mean, standard deviation (SD), median, minimum, and maximum.

For categorical/qualitative variables, descriptive statistics will include frequency counts and percentages. The total number of patients in a treatment group will be used as the denominator for percentage calculations, unless stated otherwise.

For time-to-event data with censoring, the Kaplan-Meier method will be used to summarize the data if appropriate.

Unless stated otherwise, summaries of all endpoints will be by treatment group (see below for definitions of treatment groups) for 2 "Analysis Parts" (Part 1, and Combined Parts 1 and 2):

Part 1: Patients in Part 1 include all patients who entered Part 1 of the study and who received either golodirsen or placebo. Data will include all assessments and events that occurred prior to the Part 2, Week 1 dose of 30 mg/kg of golodirsen. The analyses for Part 1 will be primarily for safety.

Part 1 analysis treatment groups are:

- patients who received golodirsen at 30 mg/kg during Weeks 7 to 12 (+ Part 1 unscheduled dosing)
- patients who received golodirsen at <=20 mg/kg during Weeks 1 to 6
- patients who received golodirsen at any dose level during Weeks 1 to 12 (+ Part1 unscheduled dosing)
- patients who receive placebo in Part 1

Combined Parts 1 and 2: Patients in Combined Parts 1 and 2 include all patients who entered in Part 1 or Part 2. Assessments and events that occurred in Part 1 for patients who were on placebo during Part 1 will be excluded. Assessments and events that occurred in Part 1 for patients who received golodirsen will be included. Combined Parts 1 and 2 Analysis treatment groups will be for both efficacy and safety data analyses.

Combined Parts 1 and 2 Analysis treatment groups are:

- all golodirsen treated patients: Patients who receive golodirsen in any part of the study
- Group 1: Patients who receive placebo in Part 1 followed by golodirsen in Part 2, or patients who enter Part 2 and receive golodirsen
- Group 2: Patients who receive golodirsen in Part 1 and continue golodirsen in Part 2

- Untreated patient group

Note that Group 1 and Group 2 are not protocol-specified treatment groups; rather, they are groups of patients with different durations of golodirsen treatment over course of the study.

The untreated patient group is intended to evaluate the natural history of the disease for patients who are not amenable to exon 53 skipping, and is not considered as a control group for golodirsen treated patients due to the following: 1) untreated patients have different genetic mutations (not amenable to exon 53 skipping) from treated patients (amenable to exon 53 skipping), and a much wider range of deletions,
2) untreated patients have much less assessment frequency of adverse events during study, and 3) the untreated patient group contains patients of a milder genotype (eg, exon 44 skippable).

5.2. Handling of Missing Data

5.2.1. Imputation of Missing Values

If the patient is confirmed to be nonambulant (as defined in Section 5.9), a value of 0 (zero) meters will be imputed for any missing values after the patient becomes nonambulant for the 6WMT distance[redacted]

If a patient had missing data for any other reason, values will not be imputed.

5.2.2. Imputation of Laboratory Values

Laboratory data that are continuous in nature, but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit plus or minus 2 significant digits, respectively (eg, if the results of a continuous laboratory test is < 20 or 2.0, a value of 19.99 or 1.99, respectively, will be assigned in computing summary statistics). KIM-1 values that are reported as below the level of quantitation (<0.112) will deviate from the above rule and be imputed as 0.099.

5.2.3. Handling of Incomplete Dates

An incomplete date will occur when the exact date an event occurred or ended cannot be obtained for a patient. Incomplete dates will be imputed as follows:

- For a partial or missing medication date, the medication will be classified as a concomitant medication unless the available part of the date indicates it is impossible for the drug to be concomitant. For example, if only the year for the stop date is available and the year is prior to the year of dosing, the medication will be classified as a prior medication.

- For a partial or missing adverse event (AE) onset date, the event will be classified as treatment-emergent if the month and/or year of the onset date are on or after the initiation of treatment (golodirsen or placebo, as appropriate) and within 28 days of the last dose of treatment for treated patients, or if the month and/or year of the onset date are on or after the date of the qualifying visit for untreated patients.
- For the purpose of calculating the time since DMD diagnosis or duration of prior corticosteroid use, if the date of DMD diagnosis or the start date of corticosteroid use has a missing day, but known month and year, then the 15th of the month will be used in the calculation. If the date has a missing day and month and only the year is known, December 31st of the recorded year will be used in the calculation.

In all cases, the original missing or incomplete dates will be presented in the data listings.

5.2.4. Imputation of Relationship or Severity for Adverse Events

In the summary of AEs, events with missing relationship or severity will be presented as “Related” or "Severe," respectively. However, missing values will be presented in the data listings as missing.

5.3. Analysis Sets

Three analysis sets will be utilized with the definitions below applying to patients amenable to exon 53 skipping and patients in the untreated group (nonamenable to exon 53 skipping), as appropriate.

Safety Set: For Part 1, the safety set will include all randomized patients who receive at least 1 dose of study drug. For Part 2, the safety set will include all randomized patients from Part 1 and all Part 2 patients amenable to exon 53 skipping who receive any amount of investigational drug product, and all untreated patients who enter Part 2.

Efficacy Set: All randomized patients from Part 1 and all Part 2 patients who have at least 1 postbaseline functional assessment.

Pharmacokinetic Set: All randomized patients from Part 1 who receive the planned full dose of investigational drug product and for whom there are adequate PK samples from which to estimate PK parameters. The PK Set will be further described in a separate PK SAP.

5.4. Multiple Testing and Comparisons

No adjustment will be made for the testing of multiple endpoints.

5.5. Adjustment for Covariates

Not applicable.

5.6. Subgroups

Due to small sample size, no subgroup will be identified for this study.

5.7. Presentation Over Time

For endpoints that are collected serially over time (eg, 6MWT distance, clinical laboratory tests), assessments/test values will be assigned to a specific timepoint (eg, study week) based upon the eCRF page on which the assessments/test values were reported. However, if a patient discontinues from the study early, then the end-of-study (EOS) visit will be assigned to the nearest scheduled visit based on the duration on study provided that the EOS visit is within ±2 weeks (14 days) of that scheduled visit.

Only for an efficacy endpoint, an unscheduled assessment may be used in the summary by timepoint if the unscheduled assessment was within 2 weeks of a missing scheduled assessment. Summaries of efficacy endpoints will include Part 2 visits and results will be summarized by the nominal visit from Part 2.

For safety endpoints, unscheduled assessments will not be included in the summary by timepoint.

5.8. Algorithm, Computation and Definition of Derived Variables

Day 1

Day 1 will be defined as the date of the first study drug (golodirsen or placebo) administration for golodirsen or placebo-treated patients, or the date immediately after the latest day of the Baseline Visit (ie, Baseline, Day 2) for untreated patients.

Golodirsen Day 1

Golodirsen Day 1 will be defined as the day of the first golodirsen drug administration. Untreated patients will not have a Golodirsen Day 1.

Study Day

Study day will be defined as Event Date - Day 1 + 1, if the Event Date is on or after Day 1; otherwise, as Event Date - Day 1, if the Event Date precedes Day 1.

Golodirsen Study Day

Golodirsen study day will be defined as Event Date - Golodirsen Day 1 + 1 if the Event Date is on or after Golodirsen Day 1; otherwise, as Event Date - Golodirsen Day 1, if the Event Date precedes Golodirsen Day 1. Untreated patients will not have a Golodirsen Study Day.

Duration of Study

Duration of study will be calculated as the duration in weeks from Day 1 to the date of study completion/discontinuation as recorded on the END OF STUDY eCRF (if completed) or the date of the last study assessment or procedure.

Duration of Treatment

Duration of golodirsen treatment will be calculated as the duration in weeks from the date of first dose of golodirsen to the date of the last golodirsen administration as recorded on the STUDY DRUG ADMINISTRATION eCRF plus 6 days, (ie, last dose date - first dose date + 1 + 6)/7. Similarly, duration of golodirsen treatment at dose <=20mg/kg will

be calculated as the duration in weeks from the date of first dose of golodirsen to the date of the last golodirsen administration at dose level <=20 mg/kg + 6 days. Duration of golodirsen treatment at dose of 30 mg/kg will be calculated as the duration in weeks from the date of first dose of golodirsen at 30 mg/kg to the date of the last golodirsen administration at dose level of 30 mg/kg + 6 days. Duration of placebo treatment will be calculated as the duration in weeks from the date of first dose of placebo to the date of the last placebo administration + 6 days.

The duration in weeks calculated above will then be categorized to 1 of the following intervals: < 24, 24 to < 48, 48 to < 72, 72 to < 96, or ≥ 96.

Baseline

Part 1: Baseline will be defined as the last value prior to the first dose of study drug (golodirsen or placebo) administration.

Combined Parts 1 and 2: Baseline will be defined as the last value prior to the first dose of golodirsen administration for treated patients, or the last value on or before the Day 1 date for untreated patients.

For 6WMT, the average of Baseline, Day 1 and Baseline, Day 2 will be used (if available).

Change from Baseline

Change from Baseline will be calculated as follows:

Change from Baseline = On-Treatment Value – Baseline Value

The change may be classified into a categorical variable, as appropriate.

Percent Change from Baseline

Percent change from Baseline will be calculated as follows:

*Percent change from Baseline = (Change from Baseline / Baseline Value) *100*

Percent change from Baseline will not be calculated if baseline value is 0.

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Time Since DMD Diagnosis

The time since DMD diagnosis, in months, will be calculated as (Day 1 - Date of DMD diagnosis + 1)/30.4375.

Duration of Prior Corticosteroid Treatment

The duration of corticosteroid treatment, in months, will be calculated as (Day 1 - Date on which the patient started corticosteroid treatment + 1)/30.4375.

Treatment-emergent Adverse Event

An AE will be considered treatment-emergent if it starts in the time period starting with the initiation of the first dose of golodirsen and ending 28 days after the last dose of golodirsen for golodirsen-treated patients, or on or after the Day 1 date for untreated patients.

Treatment-related Adverse Event

A treatment-related AE is any AE reported on the ADVERSE EVENTS eCRF that is marked as definitely related, or probably/possibly related to golodirsen.

Treatment-emergent Laboratory Abnormality

A treatment-emergent laboratory abnormality will be defined as any laboratory abnormality occurring or worsening after the initiation of golodirsen dosing and within 28 days of the last dose of golodirsen for golodirsen-treated patients, or occurring or worsening on or after the Day 1 date for untreated patients.

Prior Medication

A prior medication will be any medication taken and completed prior to the first dose of golodirsen for golodirsen-treated patients, or before the Day 1 date for untreated patients.

Concomitant Medication

A concomitant medication will be any medication that is taken in the time period starting with the initiation of the first dose of golodirsen dosing and ending 28 days after the last dose of golodirsen for golodirsen-treated patients, or on or after the Day 1 date for untreated patients.

Pulmonary Function Test Calculations

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FVC% predicted will be calculated using the prediction equations described by Hankinson (Hankinson 1999) based on patient's age, race, ethnicity, and height as following:

FVC% predicted = $b_0 + b_1 * age + b_2 * age^2 + b_3 * height^2$, where b_0, b_1, b_2, and b_3 are coefficients.

FVC% predicted will also be calculated using the Wilson method (Wilson 1984).

For all PFT derived parameters, standing height will be used. If it is unable to be captured, PFT derived parameters will be missing.

Calculated Height

Calculated height will be used based on the following formula:

Height (cm) = 4.605U + 1.308A + 28.003

where U is the length of the ulna measured by using an anthropometer or calipers, and A is the patient's age in years.

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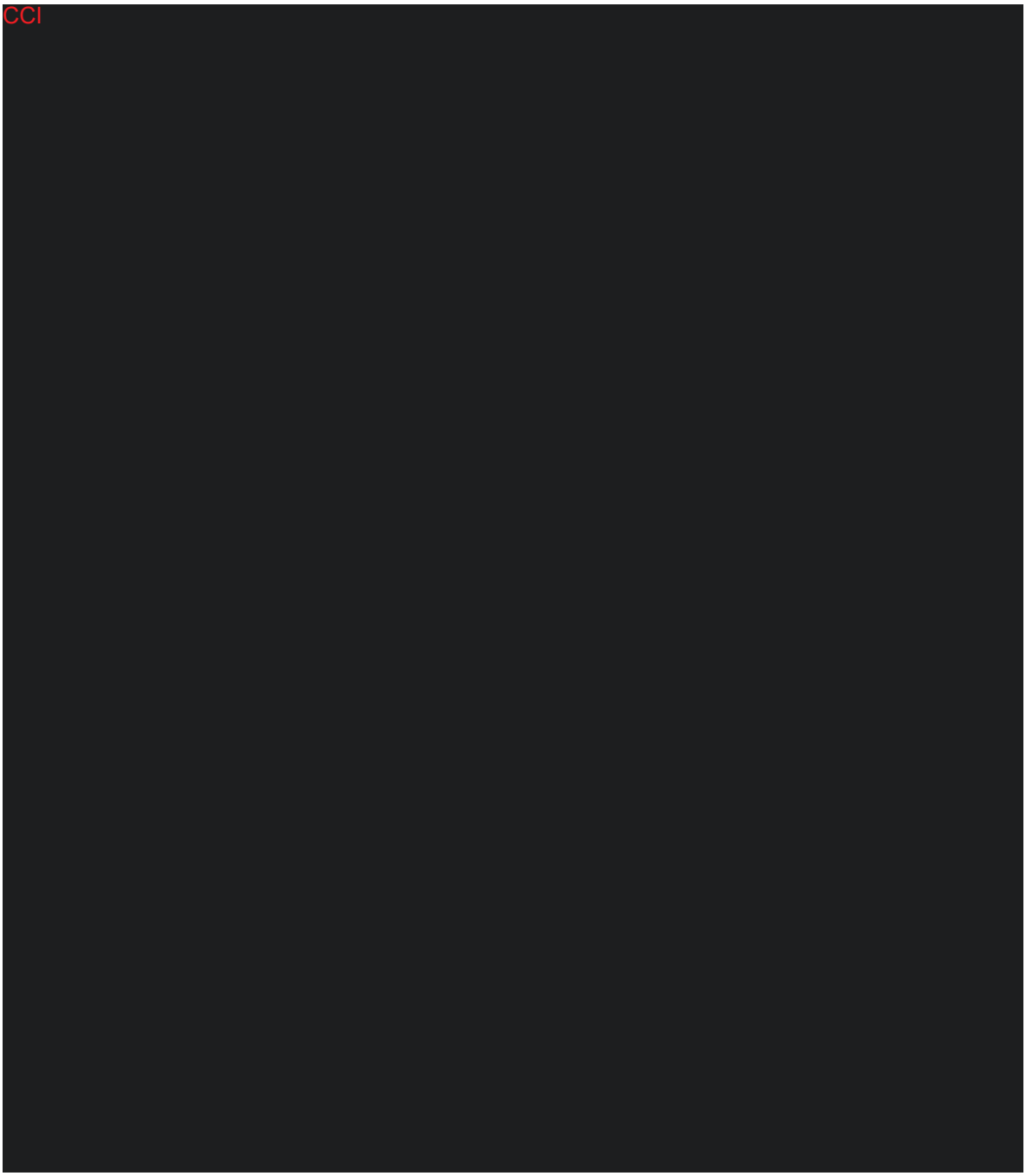

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5.9. Programming Conventions

This section details general conventions to be used to produce tables, figures, and listings. Departures from these general conventions will be specified in appropriate sections.

- For continuous or quantitative variables, mean and median values will be formatted to 1 more decimal place(s) than the measured value on the eCRF. Standard deviation and standard error values will be formatted to 2 more decimal places than the measured value on the eCRF. Minimum and maximum values will be presented with the same number of decimal places as the measured value on the eCRF. Percentages will be presented with 1 decimal place.
- For categorical variables, the number and percentage of a category will be presented in the form XX (YY%), where the percentage is YY.
- Percentages of patients with laboratory toxicities will be based on nonmissing values unless stated otherwise.
- Study Day and Part 2 Day will appear in the data listings, as appropriate.
- Date variables will be formatted as DDMMMYYYY for presentation. In the case of an unknown day, month, and/or year information, “UN”, “UNK”, or “UNKN”

will be presented. For example, a date with a missing month and day will be presented as UNUNKYYYY.

- SAS® Version 9.4 or higher will be the statistical software package used for all analyses, unless otherwise specified.
- R version 3.2.2 or higher and DAAG package 1.22 or higher will be used for 1-sample permutation test.
- The Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) Implementation Guide (ADaMIG) V1.0 for preparing data sets will be used for this study.
- The CDISC Study Data Tabulation Model Implementation Guide (SDTMIG) V3.2 will be used for preparing data sets will be used for this study.
- Tables, figures, and listings will be presented in landscape orientation.
- Listings will be sorted by treatment sequence, patient, and date, unless otherwise specified.

6. STATISTICAL ANALYSES

6.1. Patient Disposition

Patient disposition will be summarized for Combined Parts 1 and 2 for the 4 analysis treatment groups described in Section 5.1 for all patients enrolled, and will include the frequency count and percentage for the following categories: patients who enrolled into the study, patients randomized in Part 1, patients who entered study in Part 2, patients who completed the study, patients who are ongoing in the study (if applicable), and patients who discontinued early. The reasons for discontinuation will also be summarized. Descriptive statistics will be presented for duration of study (weeks).

Patient disposition and patient eligibility (including inclusion/exclusion criteria) will be presented in data listings.

6.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by Analysis Part and treatment groups described in Section 5.1 for the Safety Analysis Set. These variables will include age (years), race, ethnicity, Baseline height (cm), Baseline weight (kg), Baseline body mass index (BMI; kg/m^2), time since DMD diagnosis (months) to Baseline, corticosteroid type (Deflazacort or Prednisone), corticosteroid frequency (continuous versus intermittent), mutation type(s), duration of prior corticosteroid treatment (months) to Day 1, and Baseline 6MWT distance (m). Additional baseline variables may be included.

Patient-level demographic data and baseline characteristics will be presented in a data listing.

6.3. Prior and Concomitant Medications

Concomitant medications will be coded by preferred term using the most recent World Health Organization (WHO) Drug Dictionary (WHODRUG, 01DEC2013). The number and percentage of subjects in the safety population taking concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug preferred term by Analysis Part and treatment groups described in Section 5.1 . At each level of summarization, a patient is counted once if he/she reported 1 or more medications at that level.

All medications, whether prior or concomitant, will be presented in data listings. Separate listings of glucocorticoids and prior experimental DMD drugs will be provided.

6.4. Medical History

Medical history data for the safety set will be presented in data listings.

6.4.1. Physiotherapeutic Interventions

A listing of all physiotherapeutic interventions will be provided.

6.5. Protocol Deviations

A listing of major protocol deviations will be provided. The major protocol deviations will be identified based on a review of the study data prior to the database lock and will include the nature of the deviation (eg, inclusion/exclusion, prohibited therapies).

6.6. Exposure to Study Drug

The exposure to golodirsen and placebo will be summarized by Analysis Part and treatment groups described in Section 4.1 for the Safety Analysis Set. The variables will include the following (as applicable): cumulative exposure administered (mg), number of infusions of treatment, number of infusions of golodirsen at 30 mg/kg, and duration on golodirsen or placebo (weeks). Additionally, for the summary of Combined Parts 1 and 2 exposure, duration on golodirsen category will be summarized for the following intervals: < 24 Weeks, 24 to < 48 Weeks, 48 to < 72 Weeks, 72 to < 96 Weeks, and ≥ 96 Weeks.

Patient-level dosing information will be provided in a data listing.

6.7. Safety Analyses

Safety analyses byAnalysis Part and treatment groups described in Section 5.1 (both Part 1 and combined Part 1 and Part 2 treatment groups) will include summaries of the following:

- the type, frequency, severity, timing, and relationship to the investigational drug product of AEs, SAEs, and discontinuations due to AEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 17.1 or higher) and will be reported by primary system organ class (SOC) and preferred term (PT).
- safety laboratory testing including hematology, coagulation, serum chemistry, and urinalysis
- vital signs
- physical examinations
- 12-lead ECGs (through Week 144)
- ECHOs (through Week 144)

6.7.1. Adverse Events

In general, only TEAEs will be summarized. Nontreatment-emergent events will be recorded in the data listings. For all AE tables, the number and percentage of patients reporting AEs will be grouped using the MedDRA SOC and PT and summarized by Analysis Part, the treatment group as described in Section 5.1, and by dose level for the Part 1 summary.

- an overall summary table of AEs will be produced and will include the frequency and percentage of patients with TEAE
- treatment-related TEAE

- severe TEAE
- SAE
- treatment-related SAE
- AE leading to discontinuation of study drug
- the number of events at each severity level (mild, moderate, or severe)

Multiple occurrences of the same AE (at the preferred term level) in the same patient will be counted only once in the frequency tables. If a patient experiences multiple episodes of the same event with a different relationship/severity, the event with the strongest relationship or maximum severity to the investigational drug product will be used to summarize AEs by relationship and severity.

The following summary tables will be produced:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by PT
- treatment-related TEAEs by SOC and PT
- treatment-related TEAEs by SOC, PT, and severity
- treatment-related TEAEs by PT
- treatment-emergent SAEs
- treatment-related, treatment-emergent SAEs

In addition, all SAEs, regardless of their treatment-emergent status will be summarized by SOC and preferred term PT.

The following listings will be produced:

- nontreatment-emergent AEs
- all TEAEs
- AEs leading to discontinuation
- SAEs

6.7.2. Deaths

A summary of deaths and reasons for deaths will be presented by Analysis Part and treatment group. A patient-level listing will be provided.

6.7.3. Adverse Events of Special Interest

Summaries of TEAEs of special interest will be summarized by SOC and PT for each Analysis Part and treatment group as defined in Section 5.1 and by dose level for the Part 1 summary. All standard MedDRA queries ([SMQs] based on MedDRA

Version 17.1) listed below will include broad and narrow terms. The AEs of special interest (AESI) are:

- infusion-related reaction (AEs occurring within 24 hours of the start of any infusion [including events occurring on the same date as an infusion where infusion start time or AE onset time was not reported])
- hypersensitivity (hypersensitivity SMQ)
- infusion site reaction (extravasation events SMQ and the following PTs: application site erythema, application site rash, catheter site hematoma, catheter site hemorrhage, catheter site-related reaction, infusion site rash, infusion site swelling)
- renal toxicity (acute renal failure SMQ)
- leukopenia and neutropenia (hematopoietic leukopenia SMQ)
- severe cutaneous adverse reactions (severe cutaneous adverse reactions SMQ)
- drug-induced hepatotoxicities (cholestasis and jaundice of hepatic origin SMQ, hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions SMQ, hepatitis, noninfectious SMQ, liver neoplasms, benign [including cysts and polyps] SMQ, liver malignant tumors SMQ, liver tumors of unspecified malignancy SMQ, liver-related investigations, signs and symptoms SMQ, liver-related coagulation and bleeding disturbances SMQ)
- cardiac events (cardiomyopathy SMQ, cardiac failure SMQ, and arrhythmia-related investigations, sign and symptoms SMQ)
- coagulopathy (hemorrhage terms [excluding lab terms] SMQ, hematopoietic thrombocytopenia SMQ, PTs in the embolism and thrombosis High Level Group Terms [HLGT])

An overall summary of AESI events will include total number of events, number of serious events, number of related events, number of not related events, number of mild events, number of moderate events, number of severe events, and number of events occurring on the same day as an infusion.

6.7.4. Clinical Laboratory Evaluation

A shift table will present the number and percentage of patients in each cell resulting from cross-tabulating the status (low, normal, and high) of the highest/lowest postbaseline value versus that of the baseline for each laboratory test, if applicable, by Analysis Part and treatment group as defined in Section 5.1 . If a specific test can have both a significant low and high, then a shift table will be generated for each direction. The percentage will be based on the total number of patients in the Safety Set. A status of missing may be added, if necessary. This analysis will be repeated for last postbaseline result. For golodirsen treated patients, only results that occurred within 28 days of the last dose of golodirsen will be included.

Only the highest value will be summarized for alanine aminotransferase (ALT), alkaline phosphatase, amylase, aspartate aminotransferase (AST), cholesterol, C-reactive protein,

creatine kinase, creatinine, cystatin C, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin, triglycerides, uric acid, absolute basophils, absolute eosinophils, basophil percent, eosinophil percent, activated partial thromboplastin time, international normalized ratio, prothrombin time, and urine KIM-1, and urine protein. Only the lowest value will be summarized for albumin, creatinine clearance, and platelets. Both the highest and lowest values will be summarized for bicarbonate, blood urea nitrogen (BUN), calcium, chloride, glucose, potassium, protein, sodium, absolute lymphocytes, absolute monocytes, absolute neutrophils, hematocrit, hemoglobin, lymphocyte percent, monocyte percent, neutrophils percent, white blood cell (WBC) count, and urine pH and specific gravity.

The frequency and percentage of patients meeting the potentially clinically significant abnormality criteria (defined in Appendix Table 1, Appendix Table 2, Appendix Table 3) at any time point postbaseline will be summarized by Analysis Part and treatment group. Additionally, the total number of potentially clinically significant abnormalities will be summarized.

Baseline value, most extreme and last observation and the corresponding change from Baseline will be summarized by Analysis Part and treatment group.

All patient-level clinical laboratory values will be displayed in data listings. In addition, values meeting the potentially clinically significant abnormalities criteria will be presented in data listings. Treatment-emergent abnormalities will be indicated in the listing.

6.7.5. Vital Signs and Other Physical Findings

The frequency and percentage of patients meeting any of the potentially clinically significant abnormality criteria (defined in Appendix Table 4) at any time point postbaseline will be summarized by Analysis Part and treatment group as defined in Section 5.1 . Additionally, the total number of potentially clinically significant abnormalities will be summarized.

Baseline value, most extreme and last observation and the corresponding change from Baseline will be summarized by Analysis Part and treatment group. Most extreme value is considered as the largest absolute change from Baseline for systolic blood pressure, diastolic blood pressure, and respiratory rate, and highest value for pulse and temperature. Most extreme value will not be summarized for height, weight, BMI, ulnar length, or calculated height. For golodirsen treated patients, only results that occurred within 28 days of the last dose of golodirsen will be included.

Vital signs will be listed for all patients. In addition, values meeting the predefined markedly abnormal criteria will be presented in a data listing. Treatment-emergent abnormalities will be indicated. Height and weight will also be listed.

6.7.6. Electrocardiograms and Echocardiogram

The frequency and percentage of patients with values meeting the potentially clinically significant abnormality criteria (defined in Appendix Table 5) at any time point will be summarized by Analysis Part and treatment group as defined in Section 5.1 for both

ECGs and ECHOs. The number of potentially clinically significant abnormalities will also be presented.

Baseline value, most extreme (ECGs only) and last observation and the corresponding change from Baseline will be summarized by treatment group. Most extreme ECG value is the largest change for QTcF, QRS and PR intervals, highest value for QT and largest absolute change for heart rate. For golodirsen treated patients, only results that occurred within 28 days of the last dose of golodirsen will be included.

All patient-level values for ECG and ECHO variables will be displayed in a data listing. In addition, values meeting the predefined markedly abnormal criteria will be presented in a data listing. Treatment-emergent abnormality will be indicated.

6.7.6.1. Other Safety Assessments

Abnormal physical examination results will be listed.

6.8. Efficacy Analyses

For any efficacy assessment that is taken on 2 consecutive days within a visit (ie, 6MWT at Baseline and Screening), the average value will be used. If the assessment is taken only on 1 day, then the value on that day will be used. A value that is marked as invalid on the eCRF will be considered a missing value.

All efficacy endpoints will be summarized descriptively by time point and treatment group for Combined Parts 1 and 2 as defined in Section 5.1 . Change from Baseline for each endpoint will also be summarized by time point and treatment group, if applicable.

6.8.1. Analysis of Primary Efficacy Endpoint

The primary functional efficacy endpoint of change from Baseline at Week 144 (Part 2) in the 6MWT will be summarized by treatment group. Additionally, all other Part 2 visits will be displayed. Missing values of 6MWT distance will be imputed as specified in Section 5.2.1 .

The mean values with bars for standard errors will be displayed graphically over time by treatment group.

6.8.2. Analysis of Secondary Efficacy Endpoint

The secondary functional efficacy endpoint of change from baseline through Week 144 (Part 2) in forced vital capacity percent predicted (FVC%p) will be summarized by treatment group.

The mean values with bars for standard errors will be displayed graphically over time by treatment group.

6.9. Pharmacokinetic Analyses

The PK of golodirsen will be determined from multiple plasma and urine samples collected serially following the first weekly doses of the dose-titration phase on Weeks 1, 3, 5, and 7 of Part 1 and from plasma samples collected at Weeks 1, 24, 48, 96, and 144

in Part 2. Individual plasma levels of golodirsen will be listed with the corresponding time related to investigational drug product administration and summary statistics will be generated by per-protocol time of collection. Pharmacokinetic parameters for golodirsen will be calculated using noncompartmental analysis for Part 1 and using population PK analysis in Part 2. It may be necessary to combine the data from Parts 1 and 2 to adequately perform the population PK analysis. Data collected on Week 12 in Part 1 will be included in the population PK analysis, but not used for the noncompartmental analysis. Actual sampling times will be used in all final PK analyses. Per-protocol times will be used to calculate mean plasma concentrations for graphical displays. The PK parameters that will be determined include: C_{max}, t_{max}, AUC, V_{ss}, $t_{½}$, CL, MRT and CLR (Part 1 only).

Pharmacokinetic data from Part 2 will be analyzed based on a population PK model using plasma concentration data and appropriate demographic and baseline characteristics.

The details of PK analyses will be described in a separate PK SAP.

6.10. Pharmacodynamic (Muscle Biopsy) Analyses

The statistical analyses of muscle biopsy endpoints were described in a separate muscle biopsy SAP, which was finalized and approved on 10 August, 2017.

The primary biological endpoint of change from Baseline at Week 48 (Part 2) in dystrophin protein levels as determined by Western blot was analyzed based on a 1-sample permutation test.

The secondary biological endpoints (dystrophin intensity levels by IHC, percentage of dystrophin positive fibers by IHC) were analyzed similarly to the primary biological endpoint.

6.11. Immunogenicity Analysis

Descriptive statistics for antidystrophin and anti-PMO antibodies will be generated. The relationship between anti-PMO antibodies and clinical safety parameters may be assessed if appropriate.

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[redacted]

7. CHANGES IN PLANNED ANALYSES

7.1. Changes from Clinical Protocol-Planned Analyses

Compared to the clinical protocol (Amendment 7, dated 08 November, 2017), there is no change in this SAP.

7.2. Changes from Previous Statistical Analysis Plans

Not applicable.

8. REFERENCES

CCI

Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. American Journal of Respiratory Critical Care Med 1999;159(1):179-87.

Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in Caucasian adults and children. Thorax 1984;39(7):535-8.

9. APPENDIX: Criteria of Abnormalities

Appendix Table 1 Chemistry Laboratory Abnormalities of Interest

Test	Unit	Predefined Change		Markedly Abnormal Criteria
		Decrease	Increase	
Fasting blood glucose[a]	mmol/L	3.1	3.2	NA
BUN	mmol/L	NA	NA	Value >1.5× Baseline and >ULN
Creatinine	µmol/L	NA	35	Value > ULN
Sodium	mmol/L	8	8	NA
Potassium	mmol/L	1.1	1.0	Value > 5.5 mmol/L or <3 mmol/L
Chloride	mmol/L	9	8	NA
Uric acid	µmol/L	NA	NA	>1× ULN
Calcium[b]	mmol/L	0.30	0.30	NA
Total cholesterol	mmol/L	NA	1.73	NA
AST (SGOT)	U/L	NA	NA	Value ≥ 3× Baseline Value
ALT (SGPT)	U/L	NA	NA	Value ≥ 2× Baseline Value
Gamma glutamyl transferaxe	U/L	NA	NA	Value > 3X Baseline OR > ULN
Alkaline phosphatase	U/L	NA	NA	Value > 1.5 × ULN
Total protein[c]	g/L	11	10	NA
Albumin	g/dL	1	1	< LLN or > ULN
Total bilirubin[d]	µmol/L	NA	10	Value > 1.5× ULN
Lactate dehyrogenase	U/L	NA	NA	Value ≥ 2× Baseline Value
Creatine phosphokinase	U/L	NA	NA	Value ≥ 2× Baseline Value
Triglycerides	mmol/L	NA	2.88	NA
Cystatin C	mg/L	NA	NA	> ULN

[a]Convert to SI unit by multiplying mg/dL value by 0.0555
[b]multiply mg/dL value by 0.25;
[c]multiply g/dL value by 10
[d]multiply mg/dL value by 17.1.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LLN = lower limit of normal; NA = Not Applicable; ULN = upper limit of normal

Appendix Table 2 Hematology Laboratory Abnormalities of Interest

Test	Unit	Markedly Abnormal Criteria
Hematocrit	1	<LLN
Hemoglobin	g/L (or mmol/L)	<LLN
Red blood cell count	trillion/L	<LLN
White blood cell count	10^p/L	>1.5 × ULN or <LLN
Platelet count	10^9/L	<150 or < 200 with a decrease of at least 100
Basophils (abs)	10^9/L	> ULN or <LLN
Eosinophils (abs)	10^9/L	> 1.5 × ULN or <LLN
Lymphocytes (abs)	10^9/L	<LLN
Monocytes (abs)	10^9/L	<LLN
Neutrophils (abs)	10^9/L	>1.5 × ULN or <1000

LLN = lower limit of normal; ULN = upper limit of normal

Appendix Table 3 Urinalysis Laboratory Abnormalities of Interest

Test	Markedly Abnormal Criteria
Protein in urine	> 1+

Appendix Table 4 Vital Sign Abnormalities of Interest

Variable	Units	Markedly Abnormal Criteria Lower limit	Markedly Abnormal Criteria Upper limit
Systolic blood pressure	mmHg	<80	>130
Diastolic blood pressure	mmHg	<40	>90
Pulse Rate	beats/minute	<50	>130

Appendix Table 5 Electrocardiogram and Echocardiogram Abnormalities of Interest

Variable	Units	LLN	ULN	Age Group (years)	Markedly Abnormal Criteria
Heart Rate	Beats / minute	50	120		NA
QTcF Interval	msec	NA	NA	All	Screening Visit > 450
				< 12	> 480
				≥ 12	> 500
				All	< 320 Increase > 60
QRS Interval	msec	NA	NA	< 12	Intraventricular conduction delay (IVCD) or any QRS conduction disturbance with a QRS > 110 msec
				≥ 12	IVCD or any QRS conduction disturbance with a QRS > 120msec
PR Interval	msec	NA	NA	< 12	> 190
				≥ 12	> 220
LVEF	%	NA	NA	All	< 55%
Fractional Shortening	%	NA	NA	All	< 29%

LLN = lower limit of normal; ULN = upper limit of normal