STATISTICAL ANALYSIS PLAN

Protocol 4045-101

A Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study Followed by an Open-Label Safety and Efficacy Evaluation of SRP-4045 in Advanced Stage Patients with Duchenne Muscular Dystrophy Amenable to Exon 45 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
CL	total clearance
CL_R	urinary clearance
C_{max}	maximum plasma concentration
DMD	Duchenne muscular dystrophy
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
ECG	electrocardiogram
ECHO	echocardiogram/echocardiography
EOS	End-of-Study
IVR	Interactive Voice Response
IV	intravenous
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
CCI	
MRT	mean residence time
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PK	pharmacokinetics
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PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standard MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
t_{max}	time of maximum plasma concentration
$t_{1/2}$	elimination half-life
V_{ss}	apparent volume of distribution at steady state
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 4045-101, titled "A Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study Followed by an Open-Label Safety and Efficacy Evaluation of SRP-4045 in Advanced Stage Patients with Duchenne Muscular Dystrophy Amenable to Exon 45 Skipping".

This SAP has been prepared based on Protocol Amendment 3, dated 29 March 2018.

3. STUDY OBJECTIVES

3.1. Primary Objectives

The primary objective of this study is to evaluate the safety and tolerability of 4 escalating intravenous (IV) doses (4, 10, 20, and 30 mg/kg) of SRP-4045 (casimersen) administered once weekly for at least 2 weeks per dose level compared with placebo.

3.2. Secondary Objectives

The secondary objective of this study is to determine the pharmacokinetic (PK) profile of 4 escalating IV dose levels of casimersen.

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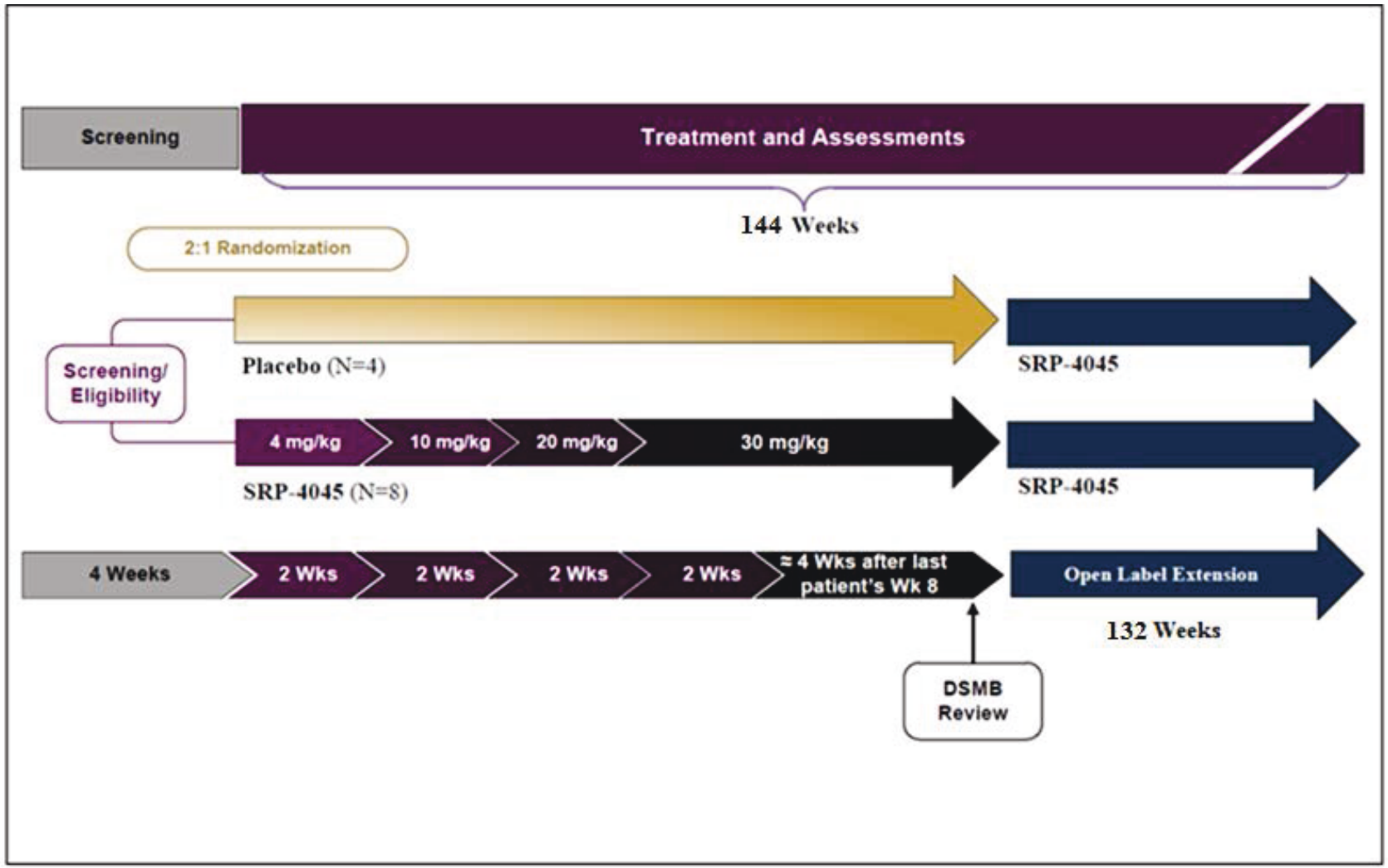
4. STUDY DESCRIPTION

4.1. Study Overview

This is a first-in-human, multicenter, randomized, double-blind, placebo-controlled, dose-titration study designed to assess the safety, tolerability, and PK of once-weekly IV infusions of casimersen in advance-stage patients with genotypically confirmed Duchenne muscular dystrophy (DMD) with an eligible deletion amenable to exon 45 skipping (eg, 12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, or 46-55).

Twelve patients will be randomized (2:1) in double-blind fashion to receive SRP-4045 (n=8) or placebo (n=4). Patients will receive a once-weekly IV infusion of SRP-4045 or placebo at escalating dose levels, each for at least 2 weeks: 4 mg/kg at Weeks 1-2; 10 mg/kg at Weeks 3-4; 20 mg/kg at Weeks 5-6; and 30 mg/kg beginning at Week 7. During the dose titration period of the study, dosing will be interrupted or halted if specific predefined stopping criteria are met, or if interruption is otherwise warranted at the discretion of the Sponsor or Investigator. Once the last patient has received 2 infusions at 30 mg/kg (Week 8), an independent Data Safety Monitoring Board (DSMB) will review cumulative safety data. Review by the DSMB is necessary for advising the Sponsor about whether the safety data allow for longer-term dosing with SRP-4045. Patients will continue to receive their randomized treatment (SRP-4045 or placebo) in a blinded fashion until the DSMB review is complete. Based on the results of this review, the Sponsor will determine whether to roll over the patients into the open-label extension period. During the open-label extension, patients will receive SRP-4045 at 30 mg/kg (or the highest tolerated dose as determined during the dose titration) administered weekly. All activities for these subjects will be outlined in a LTE study protocol.

Figure 1: Study Schematic



4.2. 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 12 total patients (8 casimersen and 4 placebo) in double-blind period and the same 12 patients will receive SRP-4045 in the open-label period). The selected sample size is considered sufficient to provide initial safety evaluation of SRP-4045 and to provide adequate data to allow for estimation of PK parameters.

4.3. Randomization and Blinding

4.3.1. Randomization of Treatments

After qualifying for study entry by confirming all eligibility criteria, DMD patients with an out-of-frame deletion mutation confirmed as amenable to exon 45 skipping will be randomized using a 2:1 ratio to either casimersen (8 patients) or placebo (4 patients). Randomization will be performed prior to dosing at Baseline/Week 1 using an Interactive Voice Response (IVR) system.

4.3.2. Blinding of Treatment

This study includes a double-blind, placebo-controlled dose-titration period of at least 12 weeks during which all patients, parents, Investigators, and site staff not involved with drug product preparation will be blinded to treatment assignment. A double-blind, placebo-controlled study design will be used to reduce potential bias during data collection and evaluation of outcome parameters. Eight patients will receive weekly IV doses of SRP-4045, and 4 patients will receive weekly IV doses of placebo in a blinded fashion until approximately 4 weeks after the last enrolled patient received 12 weeks of treatment. Only individuals (ie, the qualified pharmacist and back-up pharmacists) who are authorized to verify dose and dose assignment will be unblinded to treatment assignment. These individuals will not interact with study participants and will be instructed not to divulge randomization assignment to others under any circumstances, unless directed to do so by the Investigator in the interest of patient safety

During the open-label extension period, treatment assignment at the double-blind period will remain blinded until final database lock for the final data analysis.

4.4. Study Endpoints and Other Variables

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

4.4.1. Safety Endpoints

The safety and tolerability of casimersen doses at 4, 10, 20, and 30 mg/kg for at least 2 weeks per dose for double-blind and open-label period will be assessed through a review and evaluation of the following:

- incidence of treatment-emergent adverse events (TEAEs)
- 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)

4.4.2. Pharmacokinetic Endpoints

The following PK parameters will be determined for both the double-blind and open-label periods:

- 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 (CL_R)

For the open-label extension period, CCI will be explored. Serum PK parameters listed above will be determined for Week 60.

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4.5. Planned Analyses

4.5.1. Periodic Safety Review

Periodic safety analyses were performed for safety reviews, the Investigator's Brochure update, and regulatory submissions (Development Safety Update Report). These periodic safety analyses were monitored by a Data Safety Monitoring Board (DSMB) and were reviewed approximately every 6 to 12 months during this study.

4.5.2. Final Analysis

A final analysis of safety, PK, and efficacy will be conducted once the last patient completes the entire study and the resulting database is cleaned, quality assured, locked, and unblinded. The study team will be unblinded to perform the final analysis. 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.

Unless stated otherwise, summaries of all endpoints will be by treatment group (see below for definitions of treatment groups) for 3 "Analysis Periods" (Double-Blind Period, Casimersen Period and Combined Double-Blind and Open-Label Periods):

Double-Blind Period: Data will include all assessments and events that occurred prior to the first dose of 30 mg/kg of casimersen in the open-label period. The analyses for the double-blind period will be primarily for safety.

Double-blind Period analysis treatment groups are:

- patients who received placebo during the double-blind Period
- patients who received casimersen at 4 mg/kg (Weeks 1-2), 10 mg/kg (Weeks 3-4), 20mg/kg (Weeks 5-6), and 30mg/kg (Weeks 7-8)
- <=20 mg/kg during Week 1 to 6 (only used for select endpoints)
- patients who received casimersen at 30 mg/kg during Weeks 7 to the end of the double-blind period
- patients who received casimersen at any dose level during Weeks 1 to the end of the double-blind period

Casimersen Period: For AEs and other safety-related data analysis, data will include all assessments and events that occurred while patients received casimersen. Assessments and events that occurred in the double-blind period for patients who were on placebo during the double-blind period will be excluded. Assessments and events that occurred during the double-blind period for patients who received casimersen will be included.

Casimersen Period Analysis treatment group is:

- all casimersen treated patients: Patients who receive casimersen in any portion of the study

Combined Double-blind and Open-label Periods: For efficacy data analysis, data will include all assessments and events during both treatment periods of the study.

Combined Double-blind and Open-label Periods Analysis treatment groups are:

- Placebo-Casimersen: Patients who receive placebo in the double-blind period followed by casimersen in the open-label period

- Casimersen-Casimersen: Patients who receive casimersen in both the double-blind and open-label periods
- Overall: All patients who are treated on the study with either placebo or casimersen

5.2. Handling of Missing Data

5.2.1. 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.

5.2.2. Imputation of Missing Values

Missing laboratory values will be imputed as described in section 5.2.1. Missing dates will be imputed as described in section 5.2.3. If a patient had missing data for any other reason, values will not be imputed.

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 (casimersen or placebo, as appropriate)
- For 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

Four analysis sets will be utilized with the definitions as appropriate.

Safety Set: For the double-blind period, the safety set will include all randomized patients who receive at least 1 dose of study drug (casimersen or placebo). For the combined double-blind and open-label period, the safety set will include all randomized patients who receive at least 1 dose of study drug (casimersen or placebo).

Efficacy Set: All randomized patients who received at least 1 dose of study drug (casimersen or placebo) and have at least 1 post-baseline functional assessment.

Pharmacokinetic Set: All randomized patients who receive the planned dose of study drug (casimersen or placebo) 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.

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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, clinical laboratory tests), assessments/test values will be assigned to a specific time point (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 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 time point if the unscheduled assessment was within 2 weeks of a missing scheduled assessment. Summaries of efficacy endpoints will include open-label period visits and results will be summarized by the nominal visit.

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

5.8. Algorithm, Computation and Definition of Derived Variables

Day 1

Day 1 will be defined as the date of the first study drug administration (casimersen or placebo).

Casimersen Day 1

Casimersen Day 1 will be defined as the day of the first casimersen drug administration.

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.

Casimersen Study Day

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

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). The following formula will be used:

Duration (weeks) = (Last visit date – Day 1 Date + 1)/7

Duration of Treatment

Duration of casimersen treatment will be calculated as the duration in weeks from the date of first dose of casimersen to the date of the last casimersen 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 casimersen treatment at dose <=20 mg/kg will be calculated as the duration in weeks from the date of first dose of casimersen to the date of the last casimersen administration at dose level <=20 mg/kg + 6 days. Duration of casimersen treatment at dose of 30 mg/kg will be calculated as the duration in weeks from the date of first dose of casimersen at 30 mg/kg to the date of the last casimersen 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, 96 to < 120, or ≥ 120.

Patient Years

Patient Years will be calculated as the years from the first dose of casimersen to the date of the last casimersen administration as recorded on the STUDY DRUG ADMINISTRATION eCRF plus 6 days (ie, last dose date - first dose date + 1 + 6)/365.25. Similarly, patient years of casimersen treatment at dose <=20 mg/kg will be calculated as the years from the date of first dose of casimersen to the date of the last casimersen administration at dose level <=20 mg/kg + 6 days. Patient years of casimersen

treatment at dose of 30 mg/kg will be calculated as the years from the date of first dose of casimersen at 30 mg/kg to the date of the last casimersen administration at dose level of 30 mg/kg + 6 days. Patient years of placebo treatment will be calculated as the years from the date of first dose of placebo to the date of the last placebo administration + 6 days

Baseline

Double-Blind Period (safety): Baseline will be defined as the last value prior to the first dose of study drug (casimersen or placebo) administration.

Casimersen Period (safety): Baseline will be defined as the last value prior to the first dose of casimersen administration.

Combined Double-Blind and Open-Label Period (efficacy): Baseline will be defined as the last value prior to the first dose of study drug (casimersen or placebo) administration.

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Treatment-emergent Adverse Event

An AE will be considered treatment-emergent if it started, worsened or became serious on or after the start of first infusion.

Treatment-related Adverse Event

A treatment-related AE is any AE reported as definitely related, or probably/possibly related to study drug.

Treatment-emergent Laboratory Abnormality

A treatment-emergent laboratory abnormality will be defined as any laboratory abnormality occurring or worsening after the initiation of study drug dosing and within 28 days of the last dose of study drug.

Prior Medication

A prior medication will be any medication taken and completed prior to the first dose of study.

Concomitant Medication

A concomitant medication will be any medication that is taken in the period starting with the initiation of the first dose of study drug dosing and ending 28 days after the last dose of study drug.

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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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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 Casimersen 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.
- 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 Double-Blind and Open-label Period for the 2 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 (double-blind treatment period), patients randomized, patients who entered the OLE period of the study, 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 will be presented in data listings.

6.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by Analysis Period and treatment groups described in Section 5.1 for the Safety Analysis Set. Demographics and baseline characteristics will be presented for the double-blind treatment period as well as the casimersen period. These variables will include age (years), race, ethnicity, Baseline ulnar length (cm), Baseline calculated 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) at Baseline, and Baseline 6MWT distance (m), and ambulatory status at Baseline. 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 period and treatment groups described in Section 5.1. For the summary of the double-blind period, only dose levels of ≤ 20 mg/kg and 30 mg/kg will be presented for casimersen as well as total casimersen. At each level of summarization, a patient is counted once if he 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.

6.5. Physiotherapeutic Interventions

A listing of all physiotherapeutic interventions will be provided.

6.6. 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).

6.7. Exposure to Study Drug

The exposure to casimersen and placebo will be summarized by Analysis period and treatment groups described in Section 5.1 for the Safety Analysis Set. For the double-blind period analysis, summaries for individual dose levels will not be presented. Only the overall casimersen exposure will be described. The variables will include the following (as applicable): cumulative amount of drug received administered (mg), total number of infusions received, number of infusions of casimersen at 30 mg/kg, duration on casimersen or placebo (weeks), and patient years. Additionally, for the summary of Combined Double-blind and Open-label Periods exposure, duration on casimersen category will be summarized for the following intervals: < 24 Weeks, 24 to < 48 Weeks, 48 to < 72 Weeks, 72 to < 96 Weeks, 96 to < 120 Weeks, and ≥ 120 Weeks.

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

6.8. Safety Analyses

Safety analyses by Analysis period and treatment groups described in Section 5.1 (double-blind period and casimersen period) will include summaries of the following:

- the type, frequency, severity, timing, and relationship to the study drug of AEs, SAEs, and discontinuations due to AEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 17.1 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
- ECHOs

6.8.1. 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 period and, the treatment group as described in Section 5.1, and by dose level for the Double-Blind Period summary.

An overall summary table of TEAEs will be produced and will include the frequency and percentage of patients with TEAEs, treatment-related TEAEs, severe TEAEs, nonserious AEs, SAEs, treatment-related SAEs, AEs 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 study 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 descending frequency of PT
- treatment-related TEAEs by SOC and PT
- treatment-related TEAEs by SOC, PT, and severity
- treatment-related TEAEs by descending frequency of PT
- treatment-emergent nonserious AEs
- treatment-emergent SAEs
- treatment-related, treatment-emergent SAEs

The following listings will be produced:

- all AEs
- AEs leading to discontinuation
- all SAEs

6.8.2. Deaths

A summary of deaths and reasons for deaths will be presented by Analysis period and treatment group. A patient-level listing will be provided. Adverse Events of Special Interest

TEAEs of special interest will be summarized by SOC and PT for each Analysis Period and treatment group as defined in Section 5.1 and by dose level for the Double-Blind 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 (IRR) (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)
- renal toxicity (acute renal failure SMQ)

Summaries of adjudicated-IRRs will also be generated. Adjudicated IRRs will be identified by Pharmacovigilance review of all IRRs as defined above.

An overall summary of AESI events will include total number of events, number of serious events, number of treatment-related events, number of unrelated 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 (within 24 hours or on the same day with no time). A listing of each AESI strategy and a listing of AEs related to study drug for each AESI strategy will be generated.

6.8.3. Additional AE for Review

Additional TEAEs for review will be summarized by SOC and PT for each Analysis Period and treatment group as defined in Section 5.1 and by dose level for the double-blind period summary. All standard MedDRA queries ([SMQs] based on MedDRA Version 17.1) listed below will include broad and narrow terms. The AEs for additional review are:

- •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)
- •leukopenia and neutropenia (haematopoietic 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, non-infectious 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 (haemorrhage terms [excluding lab terms] SMQ, haematopoietic thrombocytopenia SMQ, PTs in the embolism and thrombosis High Level Group Terms [HLGT])

An overall summary of additional AE for review will include total number of events, number of serious events, number of treatment-related events, number of unrelated 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 (within 24 hours or on the same day with no time).

A listing of each AE for additional review strategy and a listing of AEs related to study drug for each AE for additional review strategy will be generated.

6.8.4. 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 post-baseline value versus that of the Baseline for each laboratory test, if applicable, by analysis period 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 post-baseline result.

Only the highest value will be summarized for alanine aminotransferase (ALT), alkaline phosphatase, amylase, aspartate aminotransferase (AST), C-reactive protein, creatine kinase, creatinine, cystatin C, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin, 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, and platelets. Both the highest and lowest values will be summarized for blood urea nitrogen (BUN), calcium, chloride, glucose, potassium, 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 post-baseline will be summarized by Analysis Period and treatment group. Additionally, the total number of potentially clinically significant abnormalities will be summarized.

Baseline value, highest/lowest value and last observation and the corresponding change from Baseline will be summarized by Analysis Period 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.

6.8.5. 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 post-baseline will be summarized by Analysis Period and treatment group as defined in Section 5.1. Additionally, the total number of potentially clinically significant abnormalities will be summarized.

Baseline value, highest/largest absolute change and last observation and the corresponding change from Baseline will be summarized by analysis period and treatment group. The largest absolute change from Baseline will be summarized for systolic blood pressure, diastolic blood pressure, and respiratory rate, and the highest value for pulse and temperature. If the largest absolute change from Baseline occurs in

both directions equally, then the higher value will be summarized. The highest/largest absolute change value will not be summarized for height, weight, BMI, ulnar length, or calculated height. Only results that occurred within 28 days of the last dose of study drug, or before initiation of a new study drug will be included.

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

6.8.6. 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 Period 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, highest/largest absolute change/largest change (ECGs only) and last observation and the corresponding change from Baseline will be summarized by treatment group. The largest change will be summarized for QTcF, QRS and PR intervals, the highest value for QT and largest absolute change for heart rate. If the largest absolute change from Baseline is occurs in both directions equally then the higher value will be summarized. Only results that occurred within 28 days of the last dose of study drug, or before initiation of a new study drug will be included.

All patient-level values for ECG and ECHO variables will be displayed in a data listing. In addition, values meeting the potentially clinically significant criteria will be presented in a data listing. Treatment-emergent abnormalities will be indicated.

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6.10. Pharmacokinetic Analyses

The PK of casimersen will be determined from plasma and urine samples collected serially following the first weekly doses on Weeks 1, 3, 5, and 7 and 60 and from plasma samples collected at Weeks 12, 24, 36, 48, 72, 84, 96, 108, 120, 132. Individual plasma levels of casimersen will be listed with the corresponding time related to study drug product administration (actual time), and summary statistics will be generated by per-protocol time of collection (nominal time). Pharmacokinetic parameters for casimersen will be calculated using 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.

Pharmacokinetic data will also be analyzed based on CCI using plasma concentration data and appropriate demographic and baseline characteristics.

The details of PK analyses will be described in a separate PK and/or CCI SAP.

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When and where warranted, PK parameters (eg, AUC) and selected safety and efficacy results may be further summarized (stratified) by antibody status (antibody negative vs. positive) and treatment group.

7. CHANGES IN PLANNED ANALYSES

7.1. Changes from Clinical Protocol-Planned Analyses

The following changes from the protocol planned analyses are noted:

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- Only treatment-emergent SAEs will be summarized. Nontreatment-emergent SAEs will be listed.
- Summary of total volume of study drug (mL) was removed from summary of exposure.

7.2. Changes from Previous Statistical Analysis Plans

Not applicable.

8. REFERENCES

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9. APPENDICES: 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
AST (SGOT)	U/L	NA	NA	Value ≥ 3× Baseline Value
ALT (SGPT)	U/L	NA	NA	Value ≥ 2× Baseline Value
Gamma glutamyl transferase	U/L	NA	NA	Value > 3×X Baseline OR > ULN
Alkaline phosphatase	U/L	NA	NA	Value > 1.5 × ULN
Albumin[c]	g/dL	1	1	< LLN or > ULN
Total bilirubin[d]	µmol/L	NA	10	Value > 1.5× ULN
Lactate dehydrogenase	U/L	NA	NA	Value ≥ 2× Baseline Value
Creatine phosphokinase	U/L	NA	NA	Value ≥ 2× Baseline Value
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 <0.000001

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
Respiratory Rate	breaths/min	<12	>20
Temperature	ºC	<36.0	>38.0
Weight	kg	Decrease of 7% or more	NA

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 >450 >480 >500
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