NCT #NCT01976091

Statistical Analysis Plan

Sarepta Therapeutics, Inc.

Phase I/IIa Gene Transfer Clinical Trial for LGMD2D (alpha-sarcoglycan deficiency) using scAAVrh74.tMCK.hSGCA

Protocol ID: 9004-101

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Covance Inc. CDCS

Clinical Development Commercialization Services

Table of Contents

Reviewers

The following reviews of the SAP were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted]		Version 1.0	Covance
		Version 1.0	Covance
		Version 1.0	Sarepta Therapeutics Inc.
		Version 1.0	Sarepta Therapeutics Inc.
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Version History

Version #	Description of Changes	Version Date
V1.0	Initial version	25Apr2022

Glossary of Abbreviations

Abbreviation	Definition
α-SG	Alpha-sarcoglycan
AE	Adverse event
DLT	Dose limiting toxicity
eCRF	Electronic case report form
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
FAS	Full analysis set
FDA	Food and drug administration
[redacted]	[redacted]
LGMD2D	Limb-girdle muscular dystrophy type 2D
MedDRA	Medical dictionary for regulatory activities
MTD	Maximum tolerated dose
[redacted]	[redacted]
PBMC	Peripheral blood mononuclear cells
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred term
SAE	Serious adverse event
6MWT	Six-minute walk test
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
[redacted]	[redacted]
SMQs	Standardized MedDRA Queries
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal
vg	Vector genomes

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	10Feb2017	11.0

2. Protocol Details

2.1 Study Objectives

2.1.1 Primary Objective

- Determine the safety of intravascular administration of self-complementary scAAVrh74.tMCK.hSGCA delivered via a major lower limb artery targeting all of the lower limb muscles of Limb-girdle muscular dystrophy type 2D (LGMD2D) (alpha-sarcoglycan [α-SG] deficient) subjects

2.1.2 Secondary Objectives

Assessment of the efficacy of the same vector measured by:

- The distance walked in 6 minutes

2.1.3

- [redacted]
- [redacted]
- [redacted]

2.2 Overall Study Design

This study is a dose escalation, Phase I/IIa study of self-complementary scAAVrh74.tMCK.hSGCA vector and transgene to LGMD2D (α-SG deficient) subjects delivered via a major lower limb artery of each leg sequentially by isolated limb infusion.

Three cohorts (Cohorts 1A, 1B, and 2) will undergo gene transfer in a standard three-six dose escalation scheme to establish maximum tolerated dose (MTD) using toxicity. One adult wheelchair-dependent patient will be enrolled in Cohort 1A, three subjects will be enrolled in Cohort 1B, and three subjects will be enrolled in Cohort 2. The first cohort (1A) will receive a vector dose of 1×10^{12} vg/kg (optimized weight to height) in a single limb with delivery to the whole limb. This same dose will be

delivered to both limbs in Cohort 1B. Cohort 2 will receive a total dose of 3 x 10^{12} vg/kg per limb delivered to both lower extremities. The vector will be infused into an indwelling vascular sheath placed in the femoral artery. This will be a one-time vector infusion to an isolated limb with an approximately 10-minute dwell time.

Short-term safety over a two-year period will be evaluated. Subjects will be tested at baseline, infusion visit (days 0-1), and return for follow up visits on days 2, 7, 14, 30, 60, 90, and 180 and at months 9 (physical therapy only), 12, 18, and 24. [redacted]

2.3 Sample Size and Power

Seven LGMD2D subjects with α-SG deficiency by muscle biopsy or DNA testing will be enrolled at Nationwide Children's Hospital for the gene transfer study:

- Cohort 1A: One (n=1) adult LGMD2D wheelchair-dependent subject will receive single-limb perfusion at the low dose: 1x10^{12} vg/kg per lower extremity.
- Cohort 1B: Three (n=3) LGMD2D subjects will receive bilateral whole limb perfusion at the low dose: 1x10^{12} vg/kg per lower extremity.
- Cohort 2: Three (n=3) LGMD2D subjects will receive bilateral whole limb perfusion at the high dose: 3x10^{12} vg/kg per lower extremity.

If safety data is satisfactory at low dose in single limb (Cohort 1A), the same dose will be used for bilateral lower limb infusion (Cohort 1B). With satisfactory safety data, high dose will be used for bilateral lower limb infusion (Cohort 2).

3. Efficacy and Safety Endpoints

3.1 Primary Efficacy Endpoints

Not applicable.

3.2 Secondary Efficacy Endpoints

- Six-minute walk test (6MWT)

3.3 [redacted]

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

3.4 Safety Endpoints

- Adverse events
- Laboratory assessments including hematology, chemistry, and urinalysis
- Vital signs
- Physical examination
- Immunology response to rAAVrh74 and hSGCA
  - Anti-AAVrh74 Antibody Titer
  - T-Cell Response to ELISpot Peptide Pools (Number of Spot Forming Cells per Million peripheral blood mononuclear cells [PBMC])
    - AAVrh74 Peptide Pool 1 of 3
    - AAVrh74 Peptide Pool 2 of 3
    - AAVrh74 Peptide Pool 3 of 3
    - hSGCA Peptide Pool 1 of 1
    - GFP Peptide Pool (Negative Control)
    - DMSO (Blank)

4. Analysis Populations

4.1 Full Analysis Set (FAS)

The Full Analysis Set includes all subjects who are enrolled and receive gene transfer.

5. Data Handling

5.1 Time Points and Visit Windows

Day 1 is defined as the day when subjects received gene transfer. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

The baseline value will be defined as last scheduled or unscheduled value collected prior to Day 1, unless otherwise specified. For post-baseline, only data from scheduled visits will be included in the summary tables.

5.2 Handling of Missing Data

Missing data will not be imputed.

6. Statistical Methods

6.1 General Principles

All data processing, summarization and analyses will be performed using Covance's SAS® Environment /Version 9.4 (or later) of the SAS® statistical software package.

The following principles will be applied to all TFLs unless otherwise stated:

Principle	Value
Cohort labels and order presented	Cohort 1A Cohort 1B Cohort 2
Tables	Data in summary tables presented by cohort and overall, and visit (where applicable).
Listings	All data collected presented by cohort, subject, and visit (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum.
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]
Denominator for percentages	Number of subjects at each cohort unless stated otherwise in table shell(s)
Include "Missing" as category	Yes, included for demographics and other baseline characteristics when the number of missing is greater than zero for at least one cohort and one age group. Missing post-baseline values will not be summarized, unless otherwise specified.
Display for percentages	One decimal place, except for 100%
Display for 0 percentages	0
Display to one more decimal place than collected value	Mean, Median, Percentiles
Display to two more decimal places than collected value	Standard Deviation
Date Format	DDMMMYYYY

6.2 Subject Disposition

Subject disposition will be listed and summarized by cohort, and overall, and will include:

- Number of subjects enrolled
- Number of subjects in FAS
- Number and percentage of subjects who complete the study

- Number and percentage of subjects who discontinue the study, including a breakdown of the reasons for premature study discontinuation

6.3 Protocol Deviations

Not applicable.

6.4 Demographics and Other Baseline Characteristics

Demographic data recorded in eCRF will be listed and summarized by cohort and overall for the FAS. Standard descriptive statistics will be presented for the continuous variables of:

- Age at enrollment (years), calculated as (date of informed consent – date of birth + 1)/365.25 rounded down to the nearest integer
- Age of disease onset (years)

The number and percentage of subjects will be presented for the categorical variables of:

- gender (Female, Male)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Unknown or Not Reported)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown or Not Reported)

6.4.1 Medical History

Medical history data recorded in eCRF will be listed. The number and percentage of subjects with any medical history will be summarized by medical history term by cohort and overall, for the FAS. Table will be sorted in descending overall frequency by medical history term.

6.4.2 Prior and Concomitant Medications/Therapies

Prior and concomitant medications/therapies will be listed. Prior medications or therapies are defined as medications or therapies with a start date and a stop date prior to Day 1. Concomitant medications or therapies are defined as medications or therapies with a start date on or after Day 1, or those with a start date before Day 1 and a stop date on or after Day 1 or ongoing. If a medication or therapy cannot be classified as one of the above categories due to incomplete start/end dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed together and summarized, separately, by cohort and overall, for the FAS. The number and percentage of subjects using each medication/therapy will be summarized. Tables will be sorted in descending overall frequency by medication/therapy.

6.5 Efficacy Analyses

All efficacy analyses will be performed using FAS. All efficacy data recorded in eCRF will be listed.

6.5.1 Primary Efficacy Analysis

Not applicable.

6.5.2 Secondary Efficacy Analysis

The secondary efficacy measure is total distance covered in the 6MWT (meters) as recorded in the eCRF. Standard descriptive statistics will be used to summarize observed values, changes from baseline, and percent changes from baseline (i.e., changes from baseline divided by baseline values) at each visit (on days 60, 90, 180, and at months 9, 12, 18, and 24) by cohort and overall.

6.5.3 [redacted]

[redacted]

6.6 Safety Analyses

All safety analyses will be performed using FAS.

6.6.1 Extent of Exposure

All exposure data recorded in eCRF will be listed.

6.6.2 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 22.0].

AEs will be graded by the Investigator as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4: Life-threatening consequences; urgent intervention indicated

- Grade 5: Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The relationship between an AE and study drug is assessed as definite, probable, possible, unlikely, or not related. A treatment-related AE is an AE considered by the investigator as definitely, possibly, or probably related to study drug or with unknown/missing relationship to study drug.

All AE data recorded in eCRF will be listed. In addition, a listing of serious AEs (SAEs) will be produced.

Treatment-emergent AEs (TEAEs) will be summarized by cohort and overall. TEAEs are AEs that occur or worsen in severity on or after gene transfer. AEs with missing start date will be considered as TEAEs.

TEAEs will be summarized by cohort and overall. An overview table will summarize the number and percentage of subjects with at least one of the following TEAEs, where subjects with more than one TEAE in a particular category are counted only once in that category:

- Any TEAE
- TEAE by maximum severity grade
- Treatment-related TEAE
- Any treatment-emergent SAE (TESAE)
- Treatment-related TESAE
- TESAE leading to death

The number of total TEAEs will be also included in the overview table.

The number and percentage of subjects reporting each AE will be summarized by System Organ Class (SOC) and Preferred Term (PT), or PT. Tables will be sorted in descending overall frequency by SOC, and then in descending overall frequency by PT within SOC, and then alphabetically. The table summarized by PT will be sorted in descending overall frequency by PT and then alphabetically. The following summaries will be produced:

- TEAEs, by SOC and PT
- TEAEs, by PT
- TEAEs, by SOC, PT, and maximum severity grade
- Treatment-related TEAEs, by SOC and PT
- TESAEs, by SOC and PT
- Treatment-related TESAEs, by SOC and PT
- TESAEs leading to death, by SOC and PT

In the above summaries, subjects with more than one AE within a particular SOC will be counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT will be counted only once for that PT. For summaries by maximum

severity grade, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe grade within that SOC or PT.

6.6.2.1 TEAEs Meeting the Criteria of Each Risk

The following tables will be created:

- Summary of TEAE meeting the criteria of important risk by SOC, PT by important risk
- Summary of treatment-related TEAEs meeting the criteria of important risk by SOC, PT by important risk
- Summary of TEAEs meeting the criteria of important risk by SOC, PT, and maximum severity by important risk
- Summary of TESAEs meeting the criteria of important risk by SOC, PT by important risk

All standardized MedDRA Queries (SMQs) based on MedDRA [Version 22.0] listed below will include broad and narrow terms.

6.6.2.1.1 Important Potential Risks

- **Hepatotoxicity**: SMQ Hepatic failure, Fibrosis and cirrhosis and other liver damage-related conditions; SMQ Hepatitis, non-infectious; SMQ Cholestasis and jaundice of hepatic origin; SMQ Liver-related investigations, signs and symptoms; SMQ Liver-related coagulation and bleeding disturbances
- **Hypersensitivity including autoimmune inflammation:** SMQ Hypersensitivity; PT Autoimmune myositis; PT Autoimmune myocarditis; PT Autoimmune hepatitis; PT Haemolytic uraemic syndrome; PT Atypical haemolytic uraemic syndrome; PT Thrombotic microangiopathy; PT Acute kidney injury; PT Microangiopathic haemolytic anaemia; PT Red cell fragmentation syndrome and HLT Immune response protein analyses NEC
- **Thrombocytopenia:** SMQ Hematopoietic thrombocytopenia

6.6.2.1.2 Other Risks

The summarization tables in section 6.6.2.1 will also be provided for other risks including:

- **Vector shedding and transmission:** PT Viraemia; PT Transmission of an infectious agent via product and HLT Pathways and sources of exposure
- **Rhabdomyolysis:** SMQ Rhabdomyolysis/myopathy
- **Viral integration:** SMQ Malignancies

In the above summaries, subjects with more than one AE within a particular risk category will be counted only once for that risk category. Subjects with more than one AE within a particular SOC will be counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT will be counted only once for that PT. For summaries by maximum severity grade, subjects with multiple AEs

within a particular risk, SOC or PT will be counted under the category of their most severe grade within that risk, SOC or PT.

6.6.3 Laboratory Evaluations

All laboratory data recorded in eCRF will be listed.

The observed laboratory data, change from baseline, and percent changes from baseline for the following hematology and general chemistry laboratory tests will be summarized using standard descriptive statistics by cohort and overall, and by visit. For urinalysis laboratory tests listed below, the number and percentage of subjects with each assessment category will be presented.

Laboratory Category	Laboratory Test
Hematology	White blood cell (WBC), Hemoglobin, Hematocrit, Platelet count, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Red cell distribution width (RDW), Red blood cell (RBC), Neutrophil, Segmented neutrophil, Lymphocyte, Monocyte, Eosinophils, Basophils, Bands, Mean platelet volume (MPV)
Chemistry	Sodium, Potassium, Chloride, Carbon dioxide, Blood urea nitrogen (BUN), Creatinine, Glucose, Total protein, Total bilrubin, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Gamma glutamyl transferase (GGT), Amylase, Creatine kinase (CK), Cystatin C, Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (aPTT), Fibrinogen
Urinalysis	Color, Appearance, Specific gravity, pH, Protein, Glucose, Ketones, Bilirubin, Occult Blood, Nitrite, Urobilinogen, Leukocyte Esterase, Microscopic Urine, RBC, WBC, Mucus, Epithelial Cells Specimen Microscopic Examination

Line plots of liver function tests including ALT, AST, total bilurubin, GGT, total protein, ALP, platelets, INR, and PT over time will be created by subject.

The eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) plots will be provided, ALT (x baseline) and GGT (x upper limit of normal [ULN]) will be plotted against total Bilirubin (x ULN) based on maximum elevation any time post baseline.

6.6.4 Vital Signs

All vital signs data recorded in eCRF will be listed. The following vital signs observed data, changes from baseline, and percent changes from baseline will be summarized using standard descriptive statistics by cohort and overall, and by visit:

- Systolic and diastolic blood pressure (mmhg)
- Pulse rate (bpm)
- Respiration rate (breaths/min)
- Body temperature [oral] (°C)

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

For post-baseline, only data from scheduled visits will be included in the summary table. Post-procedure vital signs that are recorded hourly for four hours following the injection and then every 4 hours prior to discharge will be listed only.

6.6.5 Physical Examination

All physical examination data recorded in eCRF will be listed.

For each physical examination body system, the number and percentage of subjects with normal/abnormal/not examined results will be summarized by cohort and overall for the FAS.

6.6.6 Immunology

All immunology data recorded in eCRF will be listed.

6.7 [redacted]

6.7.1 [redacted]

6.7.2 [redacted]

6.7.3 [redacted]

6.8 [redacted]

- [redacted]
- [redacted]