STATISTICAL ANALYSIS PLAN

VERSION: 02
DATE OF PLAN: 08 MAY 2018

BASED ON:

Protocol Amendment 03 dated March 16, 2018

STUDY DRUG: CK-2127107

PROTOCOL NUMBER: CY 5021

STUDY TITLE:

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTIPLE DOSE STUDY OF CK-2127107 IN TWO ASCENDING DOSE COHORTS OF PATIENTS WITH SPINAL MUSCULAR ATROPHY (SMA)

SPONSOR:

Cytokinetics, Inc.
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South San Francisco, CA 94080

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

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TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company Cytokinetics Inc.	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: No trade name	**Page:**	
Name of Active Ingredient: CK-2127107		

Title of Study:
A Phase 2 Double-Blind Randomized Placebo-Controlled Multiple Dose Study of CK-2127107 in Two Ascending Dose Cohorts of Patients with Spinal Muscular Atrophy (SMA)

Studied period (years): 2016-2018	**Phase of development: Phase 2**

Objectives:

Primary:

To determine the potential PD effects of CK-2127107 suspension after multiple oral doses in patients with SMA.

Secondary:

To evaluate the safety and tolerability of multiple doses of CK-2127107 administered orally to SMA patients.

To evaluate the PK of CK-2127107 administered orally to SMA patients.

Methodology:

This study is a double-blind, randomized, placebo-controlled, multiple dose study of CK-2127107 in two sequential ascending dose cohorts of patients with SMA. The first cohort will receive 150 mg twice daily and the second cohort will receive 450 mg twice daily. In each cohort, patients will be randomized 2:1 to CK-2127107 versus placebo. Patients will be given single dose on Day 1 and then twice daily (BID) for remainder of 8 weeks.

Number of Subjects:

Approximately 72 patients (36 in each cohort) will be enrolled. Patients who discontinue the study drug prematurely will be replaced to ensure sufficient number of patients included in the analysis.

Diagnosis and main criteria for inclusion: The target population is patients who are diagnosed of SMA type II, III or IV and at least 12 years old.

Inclusion criteria:

- Able to comprehend and willing to sign an Informed Consent Form (ICF) for patients 18 years of age and older. For patients less than 18 years of age, parent(s)/legal guardian(s) of patients must provide written informed consent prior to participation in the study and informed assent will be obtained from minors at least 12 years of age when required by regulation.
- Males or females with genetically confirmed diagnosis of SMA who are Type II, III or IV and at least 12 years of age
- Ambulatory patients, once having achieved a standing position independently, must be able to complete at least one lap in the 6-minute walk test (at least 50 meters) within 6 minutes without assistance
- Non-ambulatory patients (defined as individuals who are effectively requiring a wheelchair for all mobility needs, they may be able to stand or walk short distances, but unable to walk 50 meters without assistance in 6 minutes). Non-ambulatory patients must be able to tolerate an upright sitting position, with support, continuously for 3 hours
- Forced vital capacity (FVC) > 20% predicted at screening

- Hammersmith Functional Motor Scale-Expanded (HFMS-E) score ≥ 10 and ≤ 54 at screening
- Contracture of the elbow flexion and knee flexion ≤ 90 degrees
- Pre-study clinical laboratory findings within the normal range or, if outside the normal range, deemed not clinically significant by the Investigator
- Able to swallow an oral suspension and in the opinion of the Investigator, is expected to continue to be able to do so for the duration of the trial. Administration via a feeding tube is not allowed.
- Male patients who have reached puberty must agree to do either of the following from Screening until 10 weeks after the last dose of the investigational product unless they have had a vasectomy and confirmed sperm count is zero:
  - Abstain from sexual intercourse, OR
  - If having heterosexual intercourse, must use a condom and their female partners who are of childbearing potential must use a highly effective contraception method*
- Female patients who have had their first period will be considered of childbearing potential unless they are anatomically and physiologically incapable of becoming pregnant. If of childbearing potential, the female patients must:
  - Have a negative urine/serum pregnancy test at Screening AND
  - Abstain from heterosexual intercourse from Screening until 10 weeks after the last dose of investigational product, OR
    - If having heterosexual intercourse, must use a highly effective contraception method* and require the male partners to use a condom from Screening until 10 weeks after the last dose of investigational product

  *Highly effective contraception methods include:

  - Established use of oral, injected or implanted hormonal methods of contraception
  - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Male patients must agree to refrain from sperm donation from Screening until 10 weeks after the final study drug administration

Exclusion criteria:

- History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator
- Hospitalization within 2 months of Screening
- History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (appendectomy, hernia repair, and/or cholecystectomy will be allowed)
- A clinically significant illness, including but not limited to cardiac, pulmonary, GI, musculoskeletal, or psychiatric illness, that might interfere with the patient's ability to comply with study procedures or that might confound the interpretation of clinical safety or efficacy data, within 4 weeks of Screening
- History of alcoholism or drug addiction within 2 years prior to Screening
- History of smoking more than 10 cigarettes (or equivalent amount of tobacco) per day within 3 months prior to Screening
- Patient has used a strong CYP3A4 inhibitor within 7 days prior to first dose of study drug or a strong CYP3A4 inducer within 14 days prior to first dose of study drug

• Any other medical condition that would interfere with performance of testing including (but not limited to) significant joint pain or arthritis limiting mobility, and chronic neuromuscular pain sufficient to require ongoing analgesic medication • Participation by two people at the same time that are living in the same household • Taking any other investigational study drug as a clinical trial participant, within 30 days or five half-lives, whichever is greater, prior to Screening • An ALT or AST greater than 2-fold the upper limit of normal (ULN) or has total bilirubin greater than the ULN at screening. These assessments may be repeated once at the investigator's discretion (within the screening window). • Currently taking nusinersin, or has taken it in the past, or plans to take it during the course the study
Test product, dose and mode of administration: The test product will be supplied as granules in bottles for oral suspension. The first cohort will receive 150 mg single dose on day 1 and BID thereafter, the second cohort will receive 450 mg single dose on day 1and BID thereafter.
Duration of treatment: 150 mg or 450 mg single dose on Day 1 and then twice daily (BID) for remainder of 8 weeks.
Reference therapy, dose and mode of administration: Placebo single dose on Day1 and then twice daily (BID) for remainder of 8 weeks.
Criteria for evaluation: *Efficacy*: Change from baseline to the end of week 8 and slope of the change in forced vital capacity (FVC), maximum inspiratory pressure (MIP)/maximum expiratory pressure (MEP), muscle strength, Hammersmith functional motor scale –expanded (HFMS-E), revised upper limb module (RULM), timed up and go (TUG) test and 6-minute walk test for ambulatory patients, global assessment, and SMA-HI. *Safety*: Clinical laboratory evaluations, 12-lead electrocardiograms, vital signs, physical exams, neurological exams, Beck Depression Inventory.
Statistical methods: Besides descriptive statistics, the analysis will be performed based on a mixed effect model that accounts for within patient correlation. For change from baseline analysis, the covariates will include dose level, visit, interaction between dose level and visit, ambulatory status, and the baseline value of the variable being analyzed. The difference between patients on active dose (all dose levels combined) and placebo will be evaluated by 95% CIs and two-sided p-values.

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LIST OF ABBREVIATIONS

Abbreviation	Term
6MWT	6-minute walk test
AE	adverse event
ALT	alanine aminotransferase (alanine transaminase)
ANOVA	analysis of variance
AST	aspartate aminotransferase (aspartate transaminase)
AUC	area under the plasma concentration-time curve
BID	twice daily
BDI	Beck Depression Inventory
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{trough}	pre-dose plasma concentration
eCRF	electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
ECG	electrocardiogram
FDA	Food and Drug Administration
FVC	forced vital capacity
HFMS-E	Hammersmith Functional Motor Scale-Expanded
ICF	informed consent form
ICH	International Conference on Harmonisation
IUD	intrauterine device
IUS	intrauterine system
MedDRA	Medical Dictionary for Regulatory Activities
MEP	maximum expiratory pressure
MIP	maximum inspiratory pressure
NCI	National Cancer Institute
PD	pharmacodynamic
PDS	pharmacodynamic analysis set
PK	pharmacokinetic

Abbreviation	Term
PKS	pharmacokinetics analysis set
QTc	corrected QT interval
PNCR	Pediatric Neuromuscular Clinical Research Group
RULM	revised upper limb module
SAE	serious adverse event
SD	standard deviation
SMA	spinal muscular atrophy
TEAE	treatment emergent adverse event
TUG	timed up and go
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a technical elaboration of the planned analyses and detailed data displays to be included in the Clinical Study Report (CSR) for the CY 5021 protocol amendment 03 dated March 16, 2018.

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to unblinding of the study data. Any additional analyses performed after unblinding will be deemed exploratory. Further study information can be found in the protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to determine the potential pharmacodynamics (PD) effects of CK-2127107 suspension after multiple oral doses in patients with SMA.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of multiple doses of CK-2127107 administered orally to SMA patients
- To evaluate the pharmacokinetics (PK) of CK-2127107 administered orally to SMA patients

2.2. Study Endpoints

2.2.1. PD Endpoints

- Potential PD effects including change from baseline and slope of change of measures of muscle strength and function, including forced vital capacity (FVC), maximum inspiratory pressure (MIP)/maximum expiratory pressure (MEP), muscle strength, Hammersmith Functional Motor Scale-Expanded (HFMS-E), revised upper limb module (RULM), timed up and go (TUG) Test, 6-Minute Walk Test (6MWT), patient/investigator's global assessment, and SMA-HI (Health Index).

2.2.2. Safety Endpoints

- Safety and tolerability endpoints including adverse events, clinical lab tests including creatinine, vital signs, ECG, physical and neurological examinations, and Beck depression inventory.

2.2.3. PK Endpoints

- PK parameters of CK-2127107 including C_{max}, C_{trough}, averaged C_{trough}, and AUC_{0-12}.

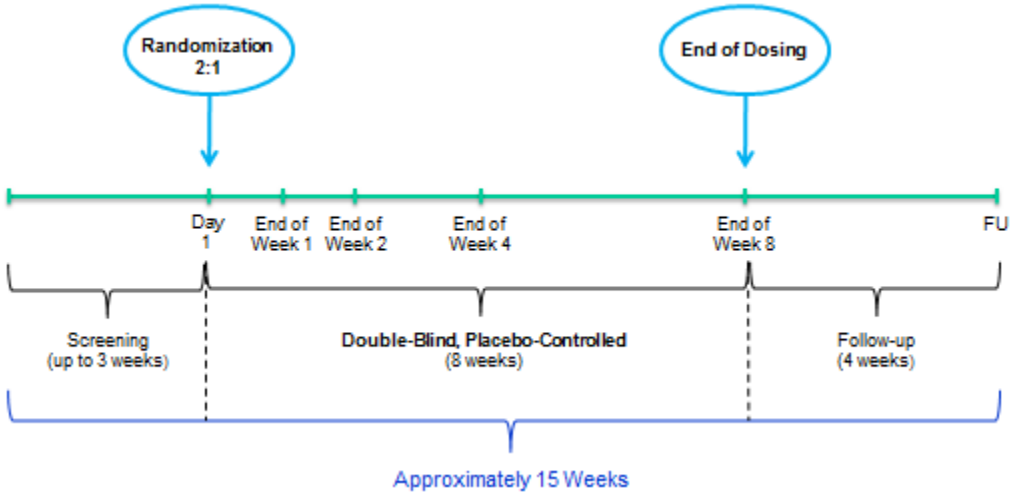
3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 2, double-blind, randomized, placebo-controlled, multiple dose study in two sequential ascending dose cohorts of patients with SMA. Within each cohort, approximately 36 patients will be randomized 2:1 to CK-2127107 versus placebo, stratified by ambulatory versus non-ambulatory status. Patients in Cohort 1 will receive CK-2127107 150 mg or placebo single dose on Day 1 and then twice daily (BID) for remainder of 8 weeks. Patients in Cohort 2 will receive CK-2127107 450 mg (or lower) or placebo single dose on Day 1 and then twice daily (BID) for remainder of 8 weeks.

The study was designed to enroll approximately 18 ambulatory and 18 non-ambulatory patients for each cohort. After 30 patients in Cohort 1 complete dosing, the safety and PK data available at that time from Cohort 1 will be reviewed, to confirm the dose level or reduce the dose level of CK-2127107 to be administered in Cohort 2.

There will be a total of seven study visits for patients in each cohort:



3.2. Definition of Study Drug

CK-2127107, a small molecule activator of the fast skeletal muscle troponin complex, is being developed to improve skeletal muscle function in disease states associated with muscular weakness and/or muscle fatigue.

Study drug will be supplied to the sites as CK-2127107 Granules for Oral Suspension and Placebo for CK-2127107 Granules for Oral Suspension. Study drug will be constituted by the site pharmacy for patient use.

3.3. Sample Size Consideration

3.3.1. Sample Size Justification

With a two-tailed alpha error of 0.05, 72 patients (24 on placebo and 48 on CK-2127107) are expected to complete the 8 weeks of double-blind treatment, which is estimated to provide 84%

power to detect a treatment difference of three points in HFMS-E score change from baseline to the end of the 8-week double-blind treatment between placebo and all CK-2127107 dose groups pooled with a common standard deviation of four points [1].

3.3.2. Sample Size Re-estimation

Replacement patients will be enrolled as necessary to ensure that at least 36 patients complete each Cohort and are evaluable for PD effect of CK-2127107. Re-estimation of sample size was not planned for this Phase 2 study.

3.4. Randomization

In each cohort, 36 patients will be centrally randomized 2:1 to CK-2127107 versus placebo, stratified by ambulatory versus non-ambulatory status.

3.5. Clinical Assessments

Clinical assessments of all visits are listed in the protocol (see Schedule of Events in Protocol Amendment 03).

4. PLANNED ANALYSES

4.1. Interim Analyses

4.1.1. Dose Level Review

After approximately 30 patients in Cohort 1 complete dosing schedule, the PK data of Cohort 1 available at that time will be analyzed by an external unblinded clinical pharmacologist to generate a PK package of tables and figures of summary statistics of the concentration and derived pharmacokinetic parameters. This package only containing aggregate blinded PK summary data will be sent to the Sponsor. No individual concentration data or PK parameters will be provided to the Sponsor. A snapshot of the clinical data for these 30 patients in Cohort 1 will be downloaded from the EDC. Cytokinetics will generate a package of tables, listings and figures of aggregate blinded safety data. The two packages will be reviewed by the Dose Level Review Committee consisting of representatives of the Sponsor, the Sponsor's collaborator (Astellas), and lead Principal Investigator at a dose level review meeting. Based on this review, the dose level for Cohort 2 will be recommended.

4.1.2. DMC Meeting

After the last patient in Cohort 1 completes 2 weeks of dosing, a snapshot of the clinical data of all patients in Cohort 1 available at this point will be downloaded from the EDC. The unblinded statistician will generate a DMC data package of tables, listings and figures for safety data using the actual randomized treatment assignment codes. The pharmacokinetic data presented for the dose level review will also be included along with the safety data. The package will be sent to the DMC directly for review, together with the dose level review recommendation for their endorsement. The DMC activities are described in the DMC charter. If the DMC endorses the dose level recommendation for Cohort 2, the enrollment for Cohort 2 will start immediately.

4.1.3. Possible Interim Analysis

If the aggregate blinded data do not allow a decision to proceed to Cohort 2 to be made, the database for Cohort 1 will be locked. An unblinded interim analysis will be conducted and the recommendation on how to proceed forwarded to the DMC before Cohort 2 is commenced.

In addition, upon completion of dosing in Cohort 1 or Cohort 2, the database may be locked or frozen and an interim analysis of the data may be conducted for planning future development.

The interim analysis will analyze all safety and efficacy endpoints using the same method as the final analysis outlined in this SAP.

4.2. Final Analyses

The final analysis will be conducted after all patients have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned and locked. All endpoints will be analyzed based on the final data after the database is locked.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

5.1. General Summary Table and Individual Patient Data Listing Considerations

Summary tables will present descriptive statistics such as mean, standard deviation, median, minimum, maximum for continuous variables, and number of patients, number of events, and the percentage, overall and by treatment, dose level, and ambulatory status in the planned analysis sets. For model based analysis, least square mean, difference of least square means between CK-2127107 and placebo, their standard errors and 95% confidence intervals, and two-sided p-values for the relative statistical inferences will be presented. Assumptions for statistical models will be evaluated. If assumptions are substantially violated, alternative analysis methods will be considered. Missing data will not be imputed unless specified. No adjustments for multiple comparisons will be made.

Listings will provide patient ID, demographics, dose level assigned and other relevant items, and sorted by patient ID and date of assessment.

5.2. General Post Text Summary Table and Individual Patient Data Listing Format Considerations

Post text summary tables and individual patient data list will be formatted through programming.

5.3. Data Management

Data will be entered into clinical database with programmed edit checks to ensure integrity. Adverse events and concomitant medications will be coded and each unique term will be reviewed.

5.4. Data Presentation Conventions

Continuous variables (e.g. age) are summarized using descriptive statistics (the number of patients with available data, the mean, standard deviation (SD), median and minimum and maximum). Categorical variables (e.g. race) are summarized using counts and percentages. Percentages are calculated using the total patients per dose level.

The following conventions are applied to all data presentations and summaries.

- For continuous variables, all mean and median values are formatted to one more decimal place than the measured value. Standard deviation values are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value.
- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.

- P-values, if applicable, will be presented to 4 decimal places. If the p-value is less than 0.0001 then it will be presented as <0.0001. If the rounded result is a value of 1.000, it will be displayed as >0.9999.
- Unless otherwise stated, any statistical tests performed will use 2-sided tests at the 5% significance level.

The table and listing shells and table of contents as part of this SAP provide the expected layout and titles of the tables, listings and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and not specified in the individual sections throughout the document.

5.5. Analysis Populations

5.5.1. Safety Analysis Set

The safety population will consist of all patients who receive at least one dose of study drug.

5.5.2. Pharmacokinetics Analysis Set (PKS)

The PK population will consist of all patients who have at least one evaluable PK parameter, provided they have no major protocol violations that could affect the PK of CK-2127107.

5.5.3. Pharmacodynamic Analysis Set (PDS)

The PDS consists of all patients who have at least one non-missing post-baseline assessment of the PD endpoints, provided they have no major protocol violations that could affect the PD effect of CK-2127107.

5.5.4. Use of Analysis Sets in Different Analyses and Summary Level

The analysis datasets to be used are described in the table below:

Table 1: Analysis Set and Summary Level

Analyses	Analysis Set
Patient Disposition (Section 7.1)	All Randomized Patients, Safety
Study Population (Section 7) except for 7.1 Patient Disposition	Safety, PDS
Efficacy (PD effect) Analyses (Section 8)	PDS
Safety and Tolerability (Section 9)	Safety
PK Analyses (Section 10)	PKS

5.6. Baseline Definition

Baseline assessments are defined as the last non-missing result prior to administration of the first dose of study drug, and will be identified by comparing both date and time of an assessment with that of the first dose. If 'time' of an assessment was not collected, baseline assessments can be identified based on 'date' only: the last non-missing result collected on or prior to the first dosing date will be selected.

5.7. Derived and Transformed Data

5.7.1. Baseline Age

Baseline age in years will be collected at screening.

5.7.2. Study Day

If the date of interest occurs on or after the first dose date then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose date then study day will be calculated as (date of interest – date of first dose). There is no study day 0.

5.7.3. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as: (change from baseline / baseline result) x 100(%).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

5.7.4. Visit Windows

The nominal visits will be used for all analyses. The unscheduled and early termination visits will be assigned to the closest nominal visit if data at the nominal visit is not available. See Appendix A for analysis visit windows.

5.7.5. Multiple Assessments

For assessments other than clinical laboratory tests, vital signs and ECG, if there are multiple assessments of the same nominal visit, the one closest to the target date of the nominal visit will be used. For repeated test results such as clinical laboratory, vital signs and ECG, the last result will be used.

5.7.6. Dose of Study Drug

The study drug is in the form of granules for oral suspension, to be constituted at the clinical site prior to dispensation, and each dose of study drug was given through 9 mL of oral suspension. The dose of CK-2127107 will be derived as follows:

- The dose of CK-2127107 for the placebo groups in Cohorts 1 and 2 will be set to 0.
- The dose of CK-2127107 for the CK-2127107 group of Cohort 1 will be calculated as (the amount of drug taken in mL / 9 mL) x 150 mg.

- The dose of CK-2127107 for the CK-2127107 group of Cohort 2 will be calculated as (the amount of drug taken in mL / 9 mL) x 450 mg.

5.7.7. Percent Predicted Forced Vital Capacity (FVC)

The forced vital capacity (FVC) is used to evaluate the pulmonary status. It measures how much air a person can exhale during a forced breath. The percent predicted FVC presents the test result as a percent of the predicted values for patient based on gender, age, height and race. It is calculated as (trial FVC / predicted FVC) x 100%.

The predicted FVC is calculated using the prediction equations developed by Knudson (Knudson et al., 1983), which factor the characteristics of gender, age, height and race into the prediction. The equations are shown below:

Gender	Age	Predicted FVC (liter)
Male	< 25	-6.8865 + 0.0739 x Age (yr) + 0.0590 x Height (cm)
	≥ 25	-8.7818 - 0.0298 x Age (yr) + 0.0844 x Height (cm)
Female	<20	-4.4470 + 0.0699 x Age (yr) + 0.0416 x Height (cm)
	20 to <70	-3.1947 - 0.0169 x Age (yr) + 0.0444 x Height (cm)
	≥ 70	-0.1889 - 0.0296 x Age (yr) + 0.0313 x Height (cm)

For African Americans, the predicted FVC is calculated using the above equations multiplying by an additional number, 0.88, to account for the racial difference in lung function. If the standing height is not measurable, the height can be derived from the ulna length (measured using calipers) as follows:

Gender	Derived Height (cm)
Male	4.605 x length of ulna (cm) + 1.308 x Age (yr) + 28.003
Female	4.459 x length of ulna (cm) + 1.315 x Age (yr) + 31.485

Note: If a patient is above 18 years old, 18 is used as the patient's age in the calculation.

For each clinical visit, a patient's FVC was evaluated in 3 trials. The best result among the 3 trials will be used for analysis.

5.7.8. Muscle Strength Mega Score

Patients' muscle strength was measured bilaterally using HHD for the three muscle groups: elbow flexion, knee extension and shoulder abduction. Muscle strength was evaluated twice for each measured body location. The maximum muscle strength of the two measurements is identified and transformed as a percent change from baseline using the equation: [(post-baseline value – baseline value) / baseline value] x 100. The transformed muscle strength will be set to missing if the baseline value is zero.

The mega-score is a composite score that averages strength across muscle groups. It is calculated as the mean of the non-missing transformed muscle strength scores among the six measured body locations, i.e., from the three muscle groups measured bilaterally.

5.7.9. Hammersmith Functional Motor Scale-Expanded (HFMS-E) PNCR Total Score

Expanded Hammersmith Functional Motor Scale (HFMS-E) was presented by the Pediatric Neuromuscular Clinical Research Group (PNCR) with an add-on module to distinguish motor skills among individuals with SMA Types II and III. HFMS-E evaluates current level of independent mobility and motor skills using a total of 33 test items with a score ranges from 0 (worse) to 2 (better) for each item. The PNCR total score is calculated as the sum of the scores among the 33 test items, and has a range from 0 to 66.

5.8. Handling of Missing Data

5.8.1. Missing Efficacy Endpoints

If percentage of missing values of efficacy endpoints is ≤ 20%, the efficacy analysis will be performed by mixed effect model as specified. The model will provide unbiased results without imputation given the missing patterns are missing at random (MAR). Even though the assumptions are not testable, no sensitivity analyses using different missing pattern assumptions will be needed due to the small percentage of missing data and the relatively exploratory nature of this phase 2 study.

5.8.2. Missing Start and Stop Dates for Prior and Concomitant Medication

No imputation of missing/partial dates will be performed. The available year or year and month in a partial date will be used and will be compared to first dosing year, month and day to determine whether to include the medication in the medication history or as a concomitant medication. If the available data do not give sufficient information to classify the medication, the medication will be classified as concomitant medication.

5.8.3. Missing Onset and Stop Dates for Adverse Events

For AEs with incomplete date information recorded in the eCRF, the imputation will follow the following algorithm:

1. For missing AE onset Day and Time:
    - If the AE onset Day is missing and the Month of AE onset is known, then the first day of the month of AE onset will be the imputed date of AE onset.
    - If no AE onset information is available, then the first dosing date will be the imputed AE onset date.
2. For missing AE end Day and Time:
    - If the AE end Day is missing and the AE end Month is earlier or later than that of the Follow-Up Visit, then the last day of the AE end month will be the imputed as the AE end date.

- If the AE end Day is missing and the AE end month is the same as that of the Follow-Up Visit, then the date of the Follow-Up Visit will be the imputed as the AE end date.
- If no AE end information is available, then

  – For patients who discontinued early from study drug, the imputed AE end date will be on the later of the last dosing date + 28 days or the last visit or contact date.

  – For patients who completed the study, the imputed AE end date and time will be the date of the Follow-Up Visit.

6. STUDY POPULATION

6.1. Patient Disposition

The number and percentage of patients who are randomized, who received at least one dose of study drug, who complete the planned dose level, and who prematurely discontinue from the planned dose level, will be presented overall and by treatment, dose level, and ambulatory status. Reasons for premature discontinuation as recorded on the termination page of the eCRF will be summarized as well.

All patients of the safety population including patients who discontinue prematurely from the study will be listed with their date of screening, date of last visit, dates of first and last dose, demographic information including age, sex and race, and dose at the time of discontinuation, date of early termination, and reasons for discontinuation.

6.2. Screen Failures

Data collected from screen failures, such as age, gender, ambulatory status and screening date, can be found in the patient summary report of the interactive web response system (IWRS) for this study.

6.3. Protocol Deviations

Protocol deviation is any divergence from the protocol that impacts a patient's safety, rights, or welfare or materially reduces the quality or completeness of the data.

Number and percentage of randomized patients meeting any protocol deviation criteria will be listed. The list will include patient id, visit (if applicable), severity of deviation (major/minor), and description of deviation.

The main significant protocol deviations will be collected in the protocol deviation CRF page as follows:

1 – Entered into the study even though they did not satisfy entry criteria

2 – Developed withdrawal criteria during the study and was not withdrawn

3 – Received wrong treatment or incorrect dose

4 – Received excluded concomitant treatment

Other protocol deviations such as unreported or underreported serious adverse events and improper breaking of the blind will be identified during the study monitoring and clinical/drug safety monitoring.

6.4. Demographic and Baseline Characteristics

Demographic parameters and baseline characteristics which include age, sex, race, ethnicity, height, weight, BMI, tobacco and alcohol use, etc. will be summarized overall and by treatment, dose level, and ambulatory status. Patient listings will be provided.

Descriptive statistics in terms of number of patients, mean, median, standard deviation and range will be presented for continuous variables. Frequency distributions in terms of number and percentage of patients will be presented for categorical variables.

6.5. Listing of Patient Inclusion and Exclusion Criteria

A listing of patients who enrolled but did not satisfy all inclusion/exclusion criteria will be provided.

6.6. Medical History and Medical Conditions Present at Entry

Medical history data will be summarized overall and by treatment, dose level, and ambulatory status for the safety population. The number and percentage of patients within each medical history item will be summarized by system organ class and preferred term. Patient listings with start date, stop date, system organ class, and preferred term will be provided.

Medical history data regarding Spinal Muscular Atrophy will be summarized for the safety population. The number and percentage of patients with or without family history and the type of spinal muscular atrophy history will be provided. Patient listing with symptom onset date, confirmed diagnosis date and information regarding gene mutations will be provided.

6.7. Prior Medication History and Medications Present at Entry

Prior medication history and medication present at entry will be summarized separately from concomitant medications.

6.8. Baseline Physical Examination

Baseline physical examination will be summarized and listed.

6.9. Baseline Vital Signs

Baseline vital signs will be summarized and provided in the table along with post-baseline vital signs.

6.10. Baseline Laboratory Data

Baseline laboratory data will be summarized and provided in the table along with post-baseline laboratory data.

6.11. Baseline Efficacy Evaluations

Baseline efficacy measures will be included in efficacy evaluation.

7. EFFICACY

7.1. General Considerations

In this Phase 2 study, analyses to explore the association between pharmacodynamics endpoints and actual dose, plasma concentration or plasma concentration bin will be performed. They are considered as the first step to establish the efficacy of CK-2127107. All p-values provided will be considered nominal and are for descriptive purposes.

The efficacy analyses of the following endpoints will be performed on the Pharmacodynamic Analysis Set (PDS).

7.1.1. Maximum Forced Vital Capacity (FVC)

- Change in FVC from baseline to the end of Week 8
- Slope of change in FVC from baseline to the end of Week 8

7.1.2. Maximum Inspiratory Pressure (MIP) / Maximum Expiratory Pressure (MEP)

- Change in MIP/MEP from baseline to the end of Week 8
- Slope of change in MIP/MEP from baseline to the end of Week 8

7.1.3. Muscle Strength Measured by Hand-Held Dynamometry

- Change in muscle strength mega-score from baseline to the end of Week 8
- Slope of change in muscle strength mega-score from baseline to the end of Week 8

7.1.4. Hammersmith Functional Motor Scale-Expanded (HFMS-E)

- Change in HFMS-E PNCR total score from baseline to the end of Week 8
- Slope of change in HFMS-E PNCR total score from baseline to the end of Week 8

7.1.5. Revised Upper Limb Module (RULM)

- Change in upper limb module-revised score from baseline to the end of Week 8
- Slope of change in upper limb module-revised score from baseline to the end of Week 8

7.1.6. Timed Up and Go (TUG) Test for Ambulatory Patients

- Change in timed up and go from baseline to the end of Week 8
- Slope of change in timed up and go from baseline to the end of Week 8

7.1.7. 6-Minute Walk Test (6MWT) For Ambulatory Patients

- Change in 6-Minute Walk distance from baseline to the end of Week 8
- Slope of change in 6-Minute Walk distance from baseline to the end of Week 8

7.1.8. Global Assessments

Responder is defined as an improvement response at the end of Week 8

- Proportion of responders of Global Assessments at the end of Week 8
- Odds ratios of responders of Global Assessments at end of Week 8 between active treatment or each active dose and placebo

7.1.9. SMA-HI

- Change in SMA-HI total score and sub-scores from baseline to the end of Week 8

7.2. Statistical Analyses

The change from baseline in continuous endpoints at the end of Weeks 1, 2, 4 and 8 will be analyzed by a mixed effect model that accounts for within patient correlation with unstructured covariance matrix. The covariates will include dose level, visit, interaction between dose level and visit, ambulatory status, and the baseline value of the variable being analyzed. Least square means and difference in least square means of the pooled active dose level or each dose level relative to placebo will be presented together with their standard errors, 95% CIs and p-values. The change from baseline of continuous endpoints will also be analyzed by ambulatory status with the same covariates in the model described above, except that the covariate "ambulatory status" will be removed from the model mentioned above. Categorical endpoints of global assessments and other PD parameters at available visits and follow-up will be analyzed by a logistic regression model that accounts for within patient correlation with unstructured covariance matrix. The covariates will include dose level, visit, interaction between dose level and visit and ambulatory status. Odds ratio, standard error and 95% CI, p-value of the odds ratio will be presented.

Slope of change from baseline for continuous endpoints will be analyzed by a mixed effect model with no intercept that will include dose level, days from the first dose of study treatment, interaction between dose level and days from the first dose of study treatment, ambulatory status, and baseline value of the variable being analyzed. The model will use days from the first dose of study treatment as a random covariate. Least square means and difference in least square means among dose levels of the slope will be presented together with their standard errors, 95% CIs and p-values.

Inferential statistical tests will be two-sided and will be performed at alpha levels of 0.05 and 0.10 to declare the significance of main effects and interaction effects, respectively.

The ambulatory status will be removed from the model for the PD parameters Timed Up and Go (TUG) test and 6-Minute Walk Test (6-MWT) which are assessed for ambulatory patients only.

7.3. Testing Statistical Assumptions Including Comparability at Baseline

Not applicable.

7.4. Statement of the Null and Alternate Hypotheses

The null and alternate hypotheses are stated:

- H_o: active dose (all dose levels combined) does not have a differential effect on the assessments of efficacy compared to placebo.
- H_A: active dose (all dose levels combined) does have a differential effect on the assessments of efficacy compared to placebo.

7.5. Subgroup Analyses

Although the sample size is small for this study, analyses by the following subgroups will be performed for key efficacy, PK, PD analyses, if data permit. Analyses presented by tertiles may be replaced with that presented by < median and ≥ median, as needed, if there are no sufficient data to produce model estimates.

- Age (12 to < 18 years old vs. ≥ 18 years old)
- SMA type (Type II vs. Types III and IV)
- Ambulatory status (ambulatory patients vs. non-ambulatory patients)
- Baseline HFMS-E PNCR total score (by tertiles)
- Baseline RULM score (by tertiles)
- Baseline Percent Predicted FVC (by tertiles)
- Baseline MEP (by tertiles)
- Baseline MIP (by tertiles)
- Baseline results of 6-Minute Walk Test (6MWT) (by tertiles) for ambulatory patients
- Baseline results of Timed Up & Go (TUG) Test (by tertiles) for ambulatory patients
- Baseline results of SMA Health Index (SMA-HI) (by tertiles)

In addition, the following subgroup analyses will also be conducted by ambulatory status:

- Baseline HFMS-E PNCR total score (by tertiles)
- Baseline RULM score (by tertiles)
- Baseline Percent Predicted FVC (by tertiles)
- Baseline MEP (by tertiles)
- Baseline MIP (by tertiles)
- Baseline results of SMA Health Index (SMA-HI) (by tertiles)

7.6. Multiple Comparisons and Multiplicity

Not applicable for this phase 2 study.

7.7. Analysis of the Efficacy Endpoints

7.7.1. Efficacy Analysis

All pharmacodynamic endpoints contribute to the efficacy of CK-2127107 for this Phase 2 study. The difference in least square means of the change from baseline at the end of Week 8 and the slope of change between patients on active dose (all dose levels combined) and placebo for the continuous endpoints, and the odds ratio at the end of Week 8 of patients on active dose (all dose levels combined) versus placebo for categorical endpoints will contribute to the efficacy analysis. The 95% confidence intervals and p-values will be presented.

7.7.2. Sensitivity Analyses of the Primary Efficacy Results

Not applicable

7.8. Analysis of the Efficacy Endpoints based on Exposure

7.8.1. Analysis Based on Concentration

The change in continuous pharmacodynamics endpoints from baseline to the end of Weeks 1, 2, 4 and 8 will be analyzed by a mixed effect model that accounts for within patient correlation with unstructured covariance matrix. The covariates will include a PK parameter (C_{trough}, C_{max}, averaged C_{trough}, or Week 8 AUC $_{0\text{-}12}$), plus visit, interaction between visit and the PK parameter, ambulatory status and the baseline value of the variable being analyzed. Least square means, the difference of LS Means, and their 95% confidence intervals will be presented, as well as the p-values. The categorical endpoints will be analyzed by a logistic regression model that accounts for within patient correlation with unstructured covariance matrix. The covariates will include a PK parameter (C_{trough}, C_{max}, averaged C_{trough}, or Week 8 AUC $_{0\text{-}12}$), plus visit, ambulatory status and the baseline value of the variable being analyzed. Odds ratios and their 95% confidence intervals will be presented. P-values will also be presented.

7.8.2. Analysis Based on Concentration Bin

Similar analyses will be performed with $C_{trough,}$ averaged $C_{trough,}$ $C_{max,}$ or AUC $_{0\text{-}12}$ as a continuous variable replaced by concentration or AUC bin as a categorical variable. The cutoffs for the bins will be determined upon the distribution of PK concentration data to ensure appropriate number of bins with roughly equal number of observations.

7.9. Summary of Reasons for Efficacy Non-Evaluability/Exclusion from Efficacy Analyses

Reasons for excluding individual patients from the PDS will be listed.

8. SAFETY AND TOLERABILITY

8.1. Adverse Event Preferred Term and Body/Organ System Summary Tables

Only Treatment-Emergent Adverse Events (TEAEs) will be summarized. They are AEs which are not present prior to the first dose of study drug and start thereafter, or present prior to the first dose of study drug and increase in severity thereafter.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify Adverse Events (AE) by system organ class and preferred term. The severity of adverse events will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0. Coding will be performed using version 18.0 of the MedDRA coding dictionary.

8.1.1. Summaries of Adverse Event Incidence Rates for All Patients

The number and percentage of patients with TEAEs will be summarized by system organ class, preferred term, treatment, dose level and overall, and will be further tabulated by CTCAE grade. For a specific TEAE, the patient will be counted only once if the TEAE was reported more than once per patient. For the summarization by CTCAE grade or relationship to study drug, if more than one event occurred with the same preferred term per patient, the patient will be counted only once for that preferred term using the highest severity and closest relationship to the study drug. Listings of all TEAEs by patient will also be presented.

8.1.2. Summaries of Adverse Incidence Rates for Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

Serious AEs (SAE) and AEs leading to treatment discontinuation or death will also be summarized by system organ class, preferred term, treatment, dose level, and overall. Listings will be presented, if appropriate, for patients who died and/or experienced serious AEs and for patients who discontinued due to TEAEs.

8.2. Total Duration of Therapy, Average Daily Dose, Maximum Daily Dose, Final Daily Dose of Study Medication, and Compliance

The duration and exposure of study drug will be summarized by dose level and overall for the safety population. Patient listing with date, day and time of dose, actual/average daily dose administered, reason for incorrect dose and dose interruption will be presented.

8.3. Concomitant and Other Medications

Medications other than the study drug reported on the eCRF will be summarized as concomitant medications for the safety population. Medications with an end date that is 7 days or more prior to the first dose of the study drug, or medications with a start date that is 30 days after the last dose of the study drug, will be excluded from the summary. The World Health Organization Drug dictionary will be used to classify medications by therapeutic class (ATC Class 3) and preferred name. If ATC Class 3 is not available, ATC Class 2 will be used in the summary. Coding will be performed using WHO Drug Dictionary Enhanced with Herbal June, 2015.

The number and percentage of patients who receive concomitant medication will be summarized by dose level, and therapeutic class and preferred term (using ATC Class Level III). Multiple drug usage by a patient will be counted only once in each category.

CYP3A4 inhibitor within 7 days prior to first dose of study drug or CYP3A4 inducer within 14 days prior to first dose of study drug will be summarized or listed.

In addition, a listing with start/stop date, days relative to the start of therapy, dose / unit / route / frequency, indication and purpose of all medications taken from screening through the end of study will be provided.

8.4. Routine Laboratory Data

Clinical laboratory evaluations, including hematology, serum chemistry, and urinalysis as detailed in the protocol, will be collected at Screening, Day 1, End of Week 2 visit, End of Week 8 visit, and at the Follow-Up Visit. Descriptive statistics of assessment value and change from baseline of laboratory parameters will be presented at each assessment point overall and by treatment, dose level, and ambulatory status. Baseline is defined as the last non-missing assessment value prior to study drug dosing. Repeat values will be used to replace the original value in the calculation of descriptive statistics.

The number and percentage of patients with Potentially Clinically Significant (PCS) laboratory values will be presented overall and by treatment, dose level, and ambulatory status. The LLN (lower limit of normal) and ULN (upper limit of normal) provided by the laboratories will be used as the criteria for PCS. For each parameter, the denominator is the number of patients with non-PCS or missing baseline assessment and with at least one post baseline assessment; and the numerator is the number of patients with non-PCS or missing baseline assessment and with at least one post baseline PCS value including repeated and unscheduled measurements (subset of the denominator). Assessment at the Follow-up Visit will also be included in the summary.

Clinical laboratory values will be listed. Values outside the Laboratory's normal ranges will be flagged. Unscheduled laboratory values will be flagged. Potentially clinically significant abnormal values will be flagged.

8.5. Vital Signs

Vital signs, which include heart rate and blood pressure measured at resting condition (i.e. after the patient sits or has been supine for at least 3 minutes), and height, weight and ulna length will be obtained at Screening, Day 1, End of Weeks 1, 2, 4 and 8 visits, and at the Follow-Up Visit.

Descriptive statistics of absolute values and changes from baseline of vital sign parameters will be presented at each assessment time point (BMI only at screening) overall and by treatment, dose level, and ambulatory status. Baseline is defined as the last assessment taken prior to study drug dosing. Repeat measurements will be used to replace the original values in the calculation of descriptive statistics.

The number and percentage of patients with PCS vital signs will be presented by overall and by treatment, dose level, and ambulatory status using the criteria specified in Table 2. For each parameter, the denominator is the number of patients with non-PCS or missing baseline assessment and with at least one post baseline assessment; and the numerator is the number of

patients with non-PCS or missing baseline assessment and with at least one post baseline PCS value including repeated and unscheduled measurements (subset of the denominator). Assessment at Follow-up Visit will also be included in the summary.

Oral temperature will be taken at Screening and will be presented in a listing.

Individual vital signs will be listed with dose level, patient ID, and assessment time. Values outside the normal ranges will be flagged. Table 2 below lists vital sign normal rages.

Table 2: Criteria of Clinically Significant Vital Signs

Vital Sign Parameter	Flag	PCS Criteria
Systolic Blood Pressure (mmHg)	High	≥ 160 mmHg
	Low	≤ 80 mmHg
Diastolic Blood Pressure (mmHg)	High	≥100 mmHg
	Low	≤ 50 mmHg
Pulse (beat/min)	High	>120 beat/min
	Low	≤50 beat/min
Temperature (°C)	High	≥ 38 °C
	Low	< 35 °C

8.6. Electrocardiogram

A 12-lead ECG, including ECG parameters of RR, PR, QRS, and QT intervals as well as significant findings will be obtained at Screening, Day 1, End of Week 2 visit, End of Week 8 visit, and at the Follow-Up Visit.

Descriptive statistics of absolute value and change from baseline of ECG parameters (PR interval, RR interval, QRS duration, QT interval, QTc interval [Bazett's and Fridericia's], Ventricular Heart Rate) will be presented at each assessment time overall and by treatment, dose level, and ambulatory status. Baseline is defined as the last assessment taken prior to study drug dosing. Repeat measurements will be used to replace the original values in the calculation of descriptive statistics.

The number and percentage of patients with PCS ECGs will be presented overall and by treatment, dose level, and ambulatory status. ECG parameters are regarded as PCS if the value meets the criterion shown in Table 3. For each parameter, the denominator is the number of patients with non-PCS or missing baseline assessment and with at least one post baseline value; and the numerator is the number of patients with non-PCS or missing baseline assessment and with at least one post baseline PCS value including repeated and unscheduled measurements (subset of the denominator). Assessment at Follow-up Visit will also be included in the summary.

12-lead ECG parameters (PR interval, QRS duration, QT interval, QTc interval [Bazett's and Fridericia's], Ventricular Heart Rate, and RR interval), will be listed with dose level, patient ID,

visit and assessment date and time. PCS ECG values will be flagged. ECG findings and interpretations will be listed as well.

Table 3: Criteria of Clinically Significant ECG

ECG Variable	Units	Normal Lower/Upper (L/U) Limit	PCS High Values
QRS Interval	msec	80 (U)	≥ 120
PR Interval	msec	200 (U)	≥ 240
QTcB Interval	msec	Males: 450 (U) Females: 460 (U)	> 500
QTcF Interval	msec	Males: 450 (U) Females: 460 (U)	> 500
Ventricular Heart Rate	bpm	50 (L)	> 100

8.7. Physical Examination

A routine physical examination will be performed at Screening, and an abbreviated physical examination (consisting of an examination of general appearance, skin, lungs, cardiovascular and abdomen) will be performed at the Follow-Up Visit.

Clinically significant findings in physical examinations will be reported and summarized as Medical History or Adverse Events, as appropriate.

8.8. Neurological Examinations

A neurological examination will be administered at Screening and at the Follow-Up Visit as described in the Study Manual.

Number and percentage of normal and abnormal results in neurological examination will be provided by visit for each category described on CRF. Shift table will also be provided.

Individual neurological examination results will be listed for each test chronologically by patient ID, visit, and the actual assessment date and time.

8.9. Beck Depression Inventory (BDI®)

The BDI will be assessed at all study visits as described in the Study Manual. This study uses a FastScreen version which is composed of 7 questions. When the test is scored, a value of 0 to 3 is assigned for each answer and then the total score is compared to the following key to determine the depression severity:

- 0–3: indicates minimal depression
- 4–8: indicates mild depression
- 9–12: indicates moderate depression

- 13–21: indicates severe depression

Number and percentage of subjects by depression severity as derived from the above method will be provided by visit. Shift table will also be provided. A list will be provided with the actual assessment date and answers to all questions.

8.10. Study Termination Status

Number and percentage of patients who complete and prematurely discontinue planned study dosing will be presented together with reasons for premature discontinuation in the disposition table. The disposition listing will present the same information and the date of completion or premature discontinuation.

9. PHARMACOKINETIC ANALYSES

9.1. Pharmacokinetic Analyses

PK analysis will be based on the PKS. For each patient, the following PK parameters and time to reach steady-state will be calculated, whenever possible, based on the plasma concentrations of CK-2127107 and its metabolites (if applicable) using non-compartmental PK methods:

C_{max}	Maximum observed plasma concentration
C_{trough}	Pre-dose plasma concentration
AUC_{0-12}	Area under the plasma concentration-time curve from zero to 12 hours

Since the PK samples were collected only up to Hour 6, the pre-dose sample will be used as the sample collected at Hour 12 to calculate AUC_{0-12}.

9.2. Statistical Analyses of Pharmacokinetic Data

Descriptive statistics in terms of mean, standard deviation (SD), geometric mean, coefficient of variation (CV), median, and range will be provided for concentrations at all planned sampling time points and all PK parameters by dose level, ambulatory status, weight, adolescent (12 to < 18 years old) and adult (≥ 18 years old) patients, and SMA type (SMA Type II vs. SMA Types III and IV), if data permits. Individual or mean concentrations over time will be graphically displayed. The least square difference of natural log-transformed C_{max}, C_{trough} and AUC_{0-12} at the end of Weeks 2 and 8 between adolescence (12 to < 18 years old) and adult (≥ 18 years old) patients and the associated 90% confidence interval (CI) will be examined using analysis of variance (ANOVA) model including terms of dose, age group, gender, and ambulatory status, using adult patients as the reference, respectively. Back-transformation will provide point estimates and conventional 90% CIs for the geometric mean ratio of C_{max}, C_{trough} and AUC_{0-12} between adolescent and adult patients. Similar method will be used to examine the differences in C_{max} between ambulatory and non-ambulatory patients, controlling for dose, age, and gender, using ambulatory status as the reference. Graphs with PK parameters by dose will be provided for adolescent and adult patients.

10. COMPUTER METHODS

Statistical analyses will be performed using Version 9.4 (or newer) of SAS®. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in USA and other countries. ® indicates USA registration.

11. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

No deviations from the protocol-specific statistical methods are planned.

12. STATISTICAL CODES

The following code will be used as the prototype of the codes that will be used for the final analysis of the study. The final version of the statistical codes to be used will be determined prior to the database lock and will be documented in the specification document for the statistical report of the study.

The ambulatory status is to be removed from the model for PD parameter Timed Up and Go (TUG) test and 6-Minute Walk Test (6-MWT).

1. The SAS code to produce estimates of the effect of the three active dose levels (150 mg BID, 450 mg BID, 150 and 450 mg BID pooled) and placebo, and the difference between the three active dose levels and placebo:

   For continuous PD parameters:

```
PROC MIXED data=work METHOD=REML;
       class <Patient> <Visit> <Dose level> <Ambulatory Status>;
       model <PD Parameter> = <Visit> <Dose level> <Interaction between Visit
       and Dose level> <Ambulatory Status> <Baseline Value of PD Parameter>/
       ddfm=kenwardroger;
       repeated <visit>/subject=<Patient> type=un;
       lsmeans <Interaction between Visit and Dose level> /diff cl;
       lsmestimate <Interaction between Visit and Dose level> followed by
       appropriate syntax for 150 and 450 pooled and difference between 150 and
       450 pooled and placebo /e cl elsm;
       ods output LSMEstimates = lsme LSMeans=lsm Diffs=diffs;
run;

Note: Covariate <Ambulatory Status> will be removed for timed up and go and 6-
minute walk.
```

   For categorical PD parameters:

```
PROC GENMOD data=work;
       class <Patient> <Visit> <Dose level> <Ambulatory Status>;
       model <PD Parameter> = <Visit> <Dose level> <Interaction between Visit
       and Dose level> <Ambulatory Status> /
       dist=binomial link=logit;
       repeated subject=<Patient> type=un;
       lsmeans <Interaction between Visit and Dose level> cl diff;
       lsmestimate <Interaction between Visit and Dose level> followed by
       appropriate syntax for 150 and 450 pooled and difference between 150 and
       450 pooled and placebo /e cl elsm;
       ods output LSMEstimates = lsme LSMeans=lsm Diffs=diffs;
run;
```

2. The SAS code to produce the estimates of the effect of the three active dose levels (150 mg BID, 450 mg BID, 150 and 450 mg BID pooled) and placebo, and the difference between the three active dose levels and placebo by ambulatory status:

   For continuous PD parameters:

```
       PROC MIXED data=work METHOD=REML; by <Ambulatory Status>;
       class <Patient> <Visit> <Dose level>;
       model <PD Parameter> = <Visit> <Dose level> <Interaction between Visit
       and Dose level> <Baseline Value of PD Parameter>/
       ddfm=kenwardroger;
       repeated <visit>/subject=<Patient type=un;
```

```
        lsmeans <Interaction between Visit and Dose level>/diff cl;
        lsmestimate <Interaction between Visit and Dose level> followed by
        appropriate syntax for 150 and 450 pooled and difference between 150 and
        450 pooled and placebo /e cl elsm;
        ods output LSMEstimates = lsme LSMeans=lsm Diffs=diffs;run;
```

Note: By <Ambulatory Status> analysis will not be performed for timed up and go and 6-minute walk.

For categorical PD parameters:

```
        PROC GENMOD data=work; by <Ambulatory Status>;
        class <Patient> <Visit> <Dose level>;
        model <PD Parameter> = <Visit> <Dose level> <Interaction between Visit
        and Dose level> / dist=binomial link=logit;
        repeated subject=<Patient> type=un;
        lsmeans <Interaction between Visit and Dose level> /cl diff;
        lsmestimate <Interaction between Visit and Dose level> followed by
        appropriate syntax for 150 and 450 pooled and difference between 150 and
        450 pooled and placebo /e cl elsm;ods output LSMEstimates = lsme
        LSMeans=lsm Diffs=diffs;
run;
```

3. The SAS code to produce the estimate of the slope of the three active dose levels and placebo, and the difference between the three active dose levels and placebo:

```
PROC MIXED data=work METHOD=REML;
        class <Patient> <Dose level> <Ambulatory Status>;
        model <Change from Baseline of PD Parameter> = <Days from First Dose>
        <Dose level> <Interaction between Days from First Dose and Dose level>
        <Ambulatory Status> <Baseline Value of PD Parameter> / ddfm=kenwardroger
        noint;

        random <Days from First Dose>/subject=<Patient> type=un;

        Estimate 'slope for placebo' <Days from First Dose> 1 <Interaction
        between Days from First Dose and Dose level> 1/cl e;

        Estimate 'slope for 150mg bid' <Days from First Dose> 1 <Interaction
        between Days from First Dose and Dose level> 0 1/cl e;

        Estimate 'slope for 450mg bid' <Days from First Dose> 1 <Interaction
        between Days from First Dose and Dose level> 0 0 1/cl e;

        Estimate 'slope for 150 and 450 pooled' <Days from First Dose> 1
        <Interaction between Days from First Dose and Dose level> 0 &prop1
        &prop2/cl e;

        Estimate 'slope difference (150mg bid – placebo)' <Interaction between
        Days from First Dose and Dose level> -1 1/cl e;

        Estimate 'slope difference (450mg bid – placebo)' <Interaction between
        Days from First Dose and Dose level> -1 0 1/cl e;

        Estimate 'slope difference (150 and 450 pooled – placebo)' <Interaction
        between Days from First Dose and Dose level> -1 &prop1 &prop2/cl e;

        ods output Estimates = est solutionF=sf;
run;
```

Note: Covariate <Ambulatory Status> will be removed for timed up and go and 6-minute walk.

4. The SAS code to produce of the slope of the three active dose levels and the difference between the three active dose levels and placebo by ambulatory status:

```
PROC MIXED data=work METHOD=REML; by <Ambulatory Status>
class <Patient> <Dose level>;
model <Change from Baseline of PD Parameter> = <Days from First Dose>
<Dose level> <Interaction between Days from First Dose and Dose level>
<Baseline Value of PD Parameter>/ddfm=kenwardroger noint;

random <Days from First Dose>/subject=<Patient> type=un;

Estimate 'slope for placebo' <Days from First Dose> 1 <Interaction
between Days from First Dose and Dose level> 1 /cl e;

Estimate 'slope for 150mg bid' <Days from First Dose> 1 <Interaction
between Days from First Dose and Dose level> 0 1 /cl e;

Estimate 'slope for 450mg bid' <Days from First Dose> 1 <Interaction
between Days from First Dose and Dose level> 0 0 1/cl e;

Estimate 'slope for 150 and 450 pooled' <Days from First Dose> 1
<Interaction between Days from First Dose and Dose level> 0 &prop1
&prop2/cl e;

Estimate 'slope difference (150mg bid – placebo)' <Interaction between
Days from First Dose and Dose level> -1 1/cl e;

Estimate 'slope difference (450mg bid – placebo)' <Interaction between
Days from First Dose and Dose level> -1 0 1/cl e;

Estimate 'slope difference (150 and 450 pooled – placebo)' <Interaction
between Days from First Dose and Dose level> -1 &prop1 &prop2/cl e;

ods output Estimates = est solutionF=sf;
run;

Note: By <Ambulatory Status> analysis will not be performed for timed up and go
and 6-minute walk.
```

5. The SAS code to produce the estimates of concentration:

   For continuous PD parameters:

```
PROC MIXED data=work METHOD=REML;
class <Patient> <Visit> <Ambulatory Status>;
model <PD Parameter> = <Visit> <Concentration> <Interaction between Visit
and Concentration> <Ambulatory Status> <Baseline Value of PD Parameter>/
ddfm=kenwardroger;
repeated <visit>/subject=<Patient type=un;
ods output solutionF=sf;
run;

Note: Covariate <Ambulatory Status> will be removed for timed up and go and 6-
minute walk.
```

6. The SAS code to produce the estimates of concentration bin:

   For continuous PD parameters:

```
PROC MIXED data=work;
class <Patient> <Visit> <Ambulatory Status> <Concentration bin>;
```

```
        model <PD Parameter> = <Visit> <Concentration bin> <Interaction between
        Visit and Concentration bin> <Ambulatory Status> <Baseline Value of PD
        Parameter>/ddfm=kenwardroger;
        repeated <visit>/subject=<Patient type=un;
        lsmeans <Interaction between Visit and Concentration bin>/diff cl;
        ods output lsmeans=lsm diffs=diff;
run;
```

Note: Covariate <Ambulatory Status> will be removed for timed up and go and 6-minute walk.

13. REFERENCES

1. Swoboda, K.J., et al., *SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy.* PLoS One, 2010. **5**(8): p. e12140.

APPENDIX A. ANALYSIS VISIT WINDOWS

Analysis Visit Windows for Pulmonary Function Tests, Muscle Strength, Hammersmith Functional Motor Scale-Expanded (HFMS-E), Revised Upper Limb Module (RULM), Vital Signs and BDI Fast Screen

Visit	Scheduled Day	Lower Bound	Upper Bound
Screening	<1	<1	<1
Day 1	1	1	1
Week 1	8	2	11
Week 2	15	12	21
Week 4	29	22	42
Week 8	57	43	70
Follow-Up	85	71	Above 71

Analysis Visit Windows for Timed Up and Go Test and 6-Minute Walk Test

Visit	Scheduled Day	Lower Bound	Upper Bound
Screening	<1	<1	<1
Day 1	1	1	1
Week 4	29	2	42
Week 8	57	43	70
Follow-Up	85	71	Above 71

Analysis Visit Windows for Global Assessments

Visit	Scheduled Day	Lower Bound	Upper Bound
Week 2	15	12	21
Week 8	57	43	70
Follow-Up	85	71	Above 71

Analysis Visit Windows for SMA-HI

Visit	Scheduled Day	Lower Bound	Upper Bound
Day 1	1	1	1
Week 8	57	43	70

Analysis Visit Windows for Clinical Safety Labs and 12-lead ECG

Visit	Scheduled Day	Lower Bound	Upper Bound
Screening	<1	<1	<1
Day 1	1	1	1
Week 2	15	2	35
Week 8	57	36	70
Follow-Up	85	71	Above 71

Analysis Visit Windows for Pharmacokinetics

Visit	Scheduled Day	Lower Bound	Upper Bound
Day 1	1	1	1
Week 1	8	2	11
Week 2	15	12	21
Week 4	29	22	42
Week 8	57	43	70