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# Statistical Analysis Plan

## A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ACE-083 in Patients with Charcot-Marie-Tooth Disease Types 1 and X

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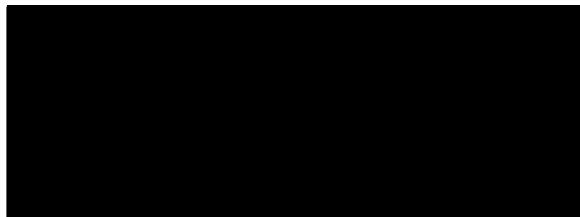
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The undersigned have approved this Statistical Analysis Plan Version 3 for use in this study.

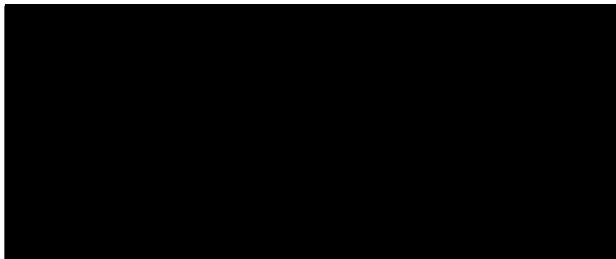
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## 1. INTRODUCTION

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical techniques to be used to analyze data for study protocol A083-03. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock.

## 2. STUDY OBJECTIVES

### 2.1. Primary Objective

#### Part 1

- To evaluate the safety and tolerability of ACE-083 in patients with Charcot-Marie-Tooth (CMT) disease types 1 and X (CMT1 and CMTX)

#### Part 2

- To determine whether treatment with ACE-083 vs. placebo increases total muscle volume of the injected muscle in patients with CMT1 and CMTX

### 2.2. Secondary Objectives

#### Part 1

- To determine the recommended dose level(s) of ACE-083 for Part 2
- To evaluate changes in muscle volume and intramuscular fat fraction of the injected muscle
- To evaluate changes in strength of the injected muscle
- To estimate the systemic exposure of ACE-083 when administered as a local muscle injection
- To evaluate changes in motor function related to the injected muscle
- To evaluate changes in physician-reported and patient-reported outcome measures

#### Part 2

- To determine whether treatment with ACE-083 vs. placebo decreases intramuscular fat fraction of the injected muscle
- To determine whether treatment with ACE-083 vs. placebo increases strength of the injected muscle
- To determine whether treatment with ACE-083 vs. placebo improves motor function related to the injected muscle
- To determine whether treatment with ACE-083 vs. placebo improves physician-reported and patient-reported outcome measures
- To evaluate safety and tolerability of ACE-083

- To estimate the systemic exposure of ACE-083 when administered as a local muscle injection

### **2.3. Exploratory Objectives**

#### **Part 1**

- To evaluate changes in gait parameters
- To evaluate changes in biomarkers

#### **Part 2**

- To evaluate changes in biomarkers
- To evaluate changes in tibialis anterior (TA) compound muscle action potential (CMAP)
- To evaluate changes in gait, activity level, and fall parameters
- To evaluate changes in motor function via the 100-meter timed test

### 3. OVERALL STUDY DESIGN

This study is a two-part multicenter, phase 2 study to evaluate the safety, tolerability, pharmacodynamics (PD), efficacy, and pharmacokinetics (PK) of ACE-083 in patients with CMT1 and CMTX. Part 1 is non-randomized, open-label, dose-escalation and Part 2 is randomized, double blind, placebo-controlled with an open-label extension.

Patients who participate in Part 1 are not eligible to participate in Part 2.

The total study duration for individual patients in Part 1 will be approximately 6 months, which includes a 1-month screening period, a 3-month treatment period, and a 2-month follow-up period after the last dose. The total study duration for individual patients in Part 2 will be approximately 15 months, which includes a 1-month screening period, a 12-month treatment period (6-month double-blind, placebo-controlled followed by a 6-month open-label extension), and a 2-month follow-up period after the last dose.

#### 3.1. Part 1

Part 1 will consist of up to 3 cohorts of patients and will evaluate multiple ascending dose levels of ACE-083 in the tibialis anterior (TA). Patients in each cohort will be enrolled in a 1-month screening period before beginning treatment.

Table 1 below outlines the planned doses to be administered.

**Table 1: Planned Doses to be Administered for Part 1**

Cohort	Dosing Days	Muscle	Planned Dose Level	Type of Administration	ACE-083 n
1	1, 22, 43, 64, and 85	Tibialis Anterior	150 mg	Bilateral	6
2	1, 22, 43, 64, and 85	Tibialis Anterior	200 mg	Bilateral	6
3	1, 22, 43, 64, and 85	Tibialis Anterior	240 mg	Bilateral	6
<b>Total Number of Patients (Planned)</b>					<b>18</b>

Periodic reviews of selected blinded safety and imaging data will be reviewed by the Safety Review Team (SRT) in accordance with the SRT Guidelines.

#### 3.2. Part 2

Prior to the initiation of Part 2, a review of the safety and efficacy data from Part 1 will be done in order to determine the recommended dose level. Up to 40 patients will be enrolled and randomized (1:1 ratio) to receive either ACE-083 (n=20) or placebo (n=20) bilaterally. Patients will receive study drug once every three weeks for approximately 6 months (9 doses). If a patient discontinues the study for reasons other than a safety issue related to investigational study drug and the patient had not completed the Day 43 visit, the patient may be replaced. The replacement patient will receive the same treatment as the patient replaced.

Patients who complete the double-blind treatment period will immediately roll over to open-label treatment with ACE-083. All patients will receive ACE-083 administered at the same dose as in the double-blind period. They will receive bilateral injections, once every three weeks for approximately 6 months (8 doses). In Part 2, the SRT will periodically review the blinded safety data.

A stratified randomization schedule will be prepared under the direction of the Sponsor with the stratification factor of “CMT disease type” (values are CMT1 and CMTX). Because Part 2 is multicenter, an Interactive Response Technology (IRT) system will be used to randomize patients sequentially across clinical sites.

Similar to Part 1, periodic reviews of selected blinded safety and imaging data will be reviewed. Further details concerning the frequency and timing of SRT reviews of Part 2 data are described in the SRT Guidelines.

## 4. STATISTICAL METHODS

### 4.1. General Method

#### 4.1.1. Sample Size Determination

There was no formal sample size calculation for Part 1. Six patients in each cohort will provide sufficient data to evaluate safety and a preliminary assessment of changes in muscle volume and muscle strength.

The sample size calculation for Part 2 is based upon the percent change from baseline in total muscle volume of the injected TA muscle 3 weeks after the last dose. A 10% difference between ACE-083-treated and placebo groups in the percent change in total muscle volume from baseline is considered to be clinically meaningful. The standard deviation (SD) is assumed to be approximately 10% for each group, based on preliminary MRI data for the ACE-083-treated side from the initial TA cohort in Part 1 of the Phase 2 study in FSHD patients.

Assuming a 2-sided type I error rate of 0.10, a 10% difference in percent change from baseline between ACE-083-treated and placebo groups in total muscle volume, a standard deviation of 10% for each group, and a 1:1 randomization, 90% power is achieved with a total sample size of 36 (18 active, 18 placebo), based on a standard t-test.

In addition, this sample size also provides 90% power to detect a 10% difference in 6-minute walk test distance, based on a similar estimated SD of 10% (based off of available data from Part 1 of the Phase 2 study in FSHD patients as well as data from Part 1 of this study, 3-weeks post last dose) and a 2-sided type 1 error rate of 0.10.

In order to account for dropouts (up to 10%), 40 patients will be randomized to study treatment for each muscle (20 active, 20 placebo) to ensure that at least 18 patients per treatment group complete the double-blind treatment period.

#### 4.1.2. Computing Environment

The analysis of clinical data from both Parts 1 and 2 will be performed under the direction of the Acceleron Pharma Biostatistics Department, using SAS® (version 9.4 or higher) and R.

#### 4.1.3. Treatment Description

Treatment descriptions as well as abbreviations used in tables, listings, and figures are described below:

##### Part 1

Unless otherwise stated, tables and figures will be presented as shown below:

Part 1 – Tibialis Anterior

ACE-083 150 mg	ACE-083 200 mg	ACE-083 240 mg	Overall
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Listings will contain only the treatment groups shown with no “Overall” group.

**Part 2**

Unless otherwise stated, tables and figures will be presented using one or more of the following as shown below, depending on what is being summarized/analyzed.

Part 2 – Double-blind period

Placebo	ACE-083	Overall
---------	---------	---------

Part 2 – Open-label period – by treatment group sequence

ACE-083→ACE-083	Placebo→ACE-083
-----------------	-----------------

Part 2 – Open-label period – Pooled across treatment group sequence

ACE-083
---------

Listings will contain the treatment groups shown above however, there will be no “Overall” group.

**4.1.4. Definitions of Baseline****Part 1 and Part 2 (Double-blind Phase)**

Baseline is defined to be the last non-missing assessment prior to the first dose of study drug administration. Theoretically, this could be either the Screening assessment or the Day 1 assessment depending on the parameter.

The first dose date will serve as the reference from which the non-missing pre-treatment values would be identified. For patients that are randomized (applicable to patients participating in Part 2) but do not receive any study drug administration, the date of randomization will be the baseline reference.

## Part 2 (Open-label Extension)

For assessments performed in the open-label extension the baseline is defined to be the Day 190 assessment.

### 4.1.5. Data Handling Conventions

Unless otherwise stated or indicated:

- Individual data for all patients will be presented in data listings, sorted by “Study Part” (Part 1 or Part 2), “Treatment Group”, and “Patient Number”;
- For any parameter analyzed, only observations from visits and/or time points planned in the protocol will be used in descriptive statistics. An exception to this rule is for a baseline assessment. Should an unscheduled assessment be taken after the scheduled baseline assessment but before the first dose of study medication, then the unscheduled assessment may be used as the baseline;
- For variables where the Day 1 assessment is defined as the baseline, should an individual patient have a Day 1 assessment after having received their first dose, then an unscheduled assessment may be used as the baseline, provided that the unscheduled assessment was done prior to first dose.
- Should a patient be assigned to the wrong CMT-type stratum (e.g. a CMT1 patient assigned to the CMTX stratum or a CMTX patient assigned to the CMT1 stratum), the patient’s true CMT-type (CMT1 or CMTX) will be used in statistical models where CMT-type is used as a covariate.
- With the exception of what is described in the preceding bullet, unscheduled assessments will not be collectively summarized in summary tables or figures; however, these data will appear in individual patient listings.
- For adverse events where the assessment of “Relationship to study drug” is missing, it will be assumed that the adverse event is “Probably Related” to study drug.
- For selected pharmacodynamic and efficacy data, tests of statistical hypotheses and estimation using the end-of-treatment visit or the Day 190 visit (Part 2 double-blind component), multiple imputation for missing data will be performed. Additional techniques for handling missing data may also be considered and evaluated.
- If a patient has a Day 190 assessment performed after having received the Day 190 dose (first dose in the open-label phase), then the Day 190 assessment for that patient will be included in statistical analyses of Day 190 data only if the difference between the Day 190 assessment and the Day 190 dose date is less than or equal to 7 days.
- Descriptive statistics for quantitative parameters will be provided using number of observations (N), mean, standard deviation (SD), standard error of the mean (SEM), median, minimum and maximum;
- Should it be necessary to convert duration in days to duration in months, the duration in days will be divided by 30.417 (365/12) to calculate duration in months.

- Descriptive statistics for qualitative parameters will be provided using frequencies (N) and percentages (%).
- If the result of a continuous variable contains nonnumeric values (e.g. ‘<X’ or ‘>X’), the imputed values used for the descriptive statistics will be determined by considering the following rules:
  - If the value is ‘<X’, the value used will be X/2;
  - If the value is ‘>X’, the value used will be X.
- Concerning the determination of absolute and percent change from baseline for data such as MRI and muscle strength where assessments are reported separately for the left and right sides and the average absolute and/or percent change from baseline is needed, the absolute and/or percent change is determined for the left and right sides separately and then averaged. The “average” represents the “average” absolute (or percent) change from baseline for the left and right sides. For MRI and muscle strength data, should a patient have an MRI and/or strength assessment on one side (i.e. right side) but not the other side at an individual time point, the value for the average absolute (or percent) change from baseline for that patient and time point will be the absolute (or percent) change from the side from which the MRI and/or strength assessment was obtained.

## 4.2. Analysis Population

The analysis populations include the following:

- Full Analysis Set: Part 1 – All patients enrolled in the study receiving at least one dose of ACE-083. Part 2 – All patients randomized who have received at least one dose of study drug (includes placebo);
- Safety Set: All patients enrolled/randomized in the study who have received at least one dose of study drug (includes placebo);
- Per Protocol Set: All patients enrolled/randomized in the study who have received at least one dose of study drug (includes placebo) with no data or study procedural related issues that would otherwise impact the interpretability of the efficacy and/or pharmacodynamic data.

Such issues include but are not necessarily limited to:

- Patients who discontinue the study prior to the Dose 3 Day 43 visit; these patients may have been replaced per protocol
- Patients whose Day 1 MRI or Day 190 MRI was done 7 or more days following study drug administration
- Patients who did not receive the full study drug administration planned per protocol at all injection sites on any or both sides (right or left) for 2 or more consecutive visits for reasons other than dose reductions for the safety of the patient or feasibility concern (i.e., the site intended to administer the full dose but was unable).

- Patients whose Screening cumulative distance walked at 6 minutes is greater than 500 meters or less than 150 meters.

A review of the patient data will be performed and a list of patients to be excluded from the Per Protocol Set along with the reason for exclusion will be completed before the data is locked and unblinded.

Statistical analyses of efficacy and pharmacodynamics data will be performed on the Per Protocol Set (primary analysis population) and the Full Analysis Set (secondary analysis population). Analyses of safety data will be performed on the Safety Set. Should the statistical analysis populations be identical (e.g., Full Analysis Set = Per Protocol Set), statistical analyses will not be duplicated or repeated.

#### **4.3. Subject Disposition**

Individual patient disposition data will be listed.

Frequency counts will be tabulated for disposition data and will include the following:

- Number of patients enrolled [Part 1 only],
- Number of patients randomized [Part 2 only],
- Number (%) of patients completing the study [Part 1 only],
- Number (%) of patients completing the double-blind treatment period [Part 2 only]
  - A patient is said to have completed the double-blind treatment period if the patient completed up to and including the Day 190 visit.
- Number (%) of patients entered into the open-label period [Part 2 only]
- Number (%) of patients completing the open-label treatment period [Part 2 only]
  - A patient is said to have completed the open-label treatment period if the patient completed up to and including the Day 337 visit.
- Number (%) of patients that rollover to the extension study, A083-04
  - Patients that rollover to the extension study consist only of patients participating in Part 2 of this study who complete both the double-blind treatment period AND the open-label treatment period who will not have the Day 393/EOS visit. These patients' final study visit will be the Day 358/ET visit.
- Number (%) of patients that do not rollover to the extension study A083-04
  - Patients that do not rollover to the extension study will have both the Day 358/ET and Day 393/EOS visits completed.
- Number (%) of patients discontinuing from the study prior to completing both the double-blind period and the open label period [Part 2 only]
  - Number (%) of patients that discontinued during the double-blind period
  - Number (%) of patients that discontinued during the open-label period

- Number (%) of patients for primary reason for discontinuation will also be provided [provided there is at least one patient who discontinued].

Summaries will be provided by treatment and overall for each study part (Part 1 and Part 2).

## 4.4. Demographic and Baseline Characteristics

### 4.4.1. Demographics

Individual demographic data will be listed.

Descriptive statistics (N, mean, SD, median, minimum and maximum) will be provided for continuous demographic variables (age, weight, height, and BMI) and frequency counts will be tabulated for categorical demographic variables (gender, race, ethnicity) by treatment and overall for each study part (Part 1 and Part 2). Age will be calculated based on birth date and informed consent date.

### 4.4.2. Baseline Characteristics

Baseline characteristics of the patient population consist of selected items from the CMT disease history, MRI, MRC-MMT, and functional test data. Such data includes the following:

- Age at onset of symptoms (years)
- Age at diagnosis (years)
- Duration since onset of symptoms (years)
  - Duration since onset of symptoms = Age (years) – Age at onset of symptoms (years)
- Duration since diagnosis (years)
  - Duration since diagnosis = Age (years) – Age at diagnosis (years)
- Total muscle volume (mm<sup>3</sup>)
  - See [Section 4.8.1](#) for definition.
- Total muscle mass (g)
  - See [Section 4.8.1](#) for definition.
- Calculated contractile muscle volume (mm<sup>3</sup>)
  - See [Section 4.8.1](#) for definition.
- Calculated contractile muscle mass (g)
  - See [Section 4.8.1](#) for definition.
- Fat fraction (%)
- 6-minute walk distance (m)
- Time to complete 10 meter walk/run (s)

- Number and percent of patients belonging to specified CMT Type (i.e., CMT1, CMTX)
- Number and percent of CMT1 patients belonging to specified CMT1 subtype/gene mutation (e.g., CMT1A, CMT1B)
- Number and percent of CMTX patients belonging to specified CMTX subtype/gene mutation (e.g., CMTX1)
- Number and percent of patients belonging to specific forms of CMT (e.g., demyelinating, axonal, mixed)
- Number and percent of patients with first degree relatives with CMT
- Number and percent of patients who have fallen to the ground in the past 6 months
- Number and percent of patients who have had past history of fractures
- Number and percent of patients who have had past surgery for CMT
- Number and percent of patients who wears any lower limb orthotics/braces
- Number and percent of patients who uses assistive devices
- Number and percent of patients who have a regular (at least once a week) exercise program
  - For those who have a regular exercise program, the type (aerobic, resistance training, or both) and frequency of exercise program (1-2, 3-4, or 5+ times per week) will also be summarized.
- Number and percent of patients who have known nerve conduction velocity
  - For those who have a known nerve conduction velocity, the category ( $< 38$  m/s,  $\geq 38$ ) will also be summarized.
- Number and percent of patients with MRC-MMT grades belonging to the following categories: [3 to 4-], [4 to 4+], [5- to 5]
  - Summaries will be provided for each side (left and right) separately for ankle dorsiflexion, knee extension, and plantar flexion.
  - MRC-MMT grades will also be summarized (frequency with percent) by the weakest grade (left or right) for ankle dorsiflexion, knee extension, and plantar flexion.
  - MRC-MMT SCORE which represents the conversion of the MRC-MMT grade to the decimal version as follows: 5 = 5.0, 5- = 4.67, 4+ = 4.33, 4 = 4.0, 4- = 3.67, 3+ = 3.33, 3 = 3.0, 3- = 2.67, 2+ = 2.33, 2 = 2.0, 2- = 1.67, 1+ = 1.33, 1 = 1.0.
    - This will be determined for each side (left and right) and then averaged. The average will be presented in the summary table. This will be done for ankle dorsiflexion.
- Dose of ACE-083 expressed as (mg/g calculated total muscle mass)
- Dose of ACE-083 expressed as (mg/g calculated contractile muscle mass)

- CMTES2 Score
  - See [Section 4.7.1.4](#) for details on how this score is derived.
- Berg Balance Scale total score
  - See Section 4.7.1.4 for details on how this score is derived.

The table below outlines how to derive the dose of ACE-083 expressed as either mg/g total muscle, or mg/g contractile muscle:

	Dose of ACE-083 Expressed as	
	mg/g Calculated Total Muscle Mass	mg/g Calculated Contractile Muscle Mass
<b>Bilateral Cohorts</b>	<p><u>Step 1:</u> For each side (right and left), compute the following: Dose injected (mg) / (Baseline CCMV {mm<sup>3</sup>} * [1.06/1000] + Baseline CIMFV {mm<sup>3</sup>} * [0.9/1000])</p> <p><u>Step 2:</u> Compute average of the Dose of ACE-083 expressed as mg/g total muscle for each side using the information obtained from Step 1.</p>	<p><u>Step 1:</u> For each side (right and left), compute the following: Dose injected (mg) / (Baseline CCMV {mm<sup>3</sup>} * [1.06/1000])</p> <p><u>Step 2:</u> Compute average of the Dose of ACE-083 expressed as mg/g contractile muscle for each side using the information obtained from Step 1.</p>

CCMV = Calculated contractile muscle volume; CIMFV = Calculated intramuscular fat volume

This data will be summarized using appropriate descriptive statistics.

#### 4.5. Prior and Concomitant Medications/Therapy

Prior and concomitant medications recorded during the study will be listed. These will be coded with the WHO Drug Dictionary (Version 201603 DDE).

Medications will be assigned as prior or concomitant based on the following rules:

- If both the start and stop date exist and are before the first dose date of study drug, the medication will be classified as a prior medication.
- If the start date is on or after the first dose date of study drug, the medication will be classified as a concomitant medication.
- If the start date is before the first dose date of study drug and the stop date is after the first dose date of study drug or the medication is ongoing, the medication will be classified as prior and concomitant.
- If the start date is missing and the stop date is before the first dose of study drug, the medication will be classified as prior.
- If the start date is missing and the stop date is after the first dose of study drug or the medication is ongoing, the medication will be classified as concomitant.
- If the start and stop dates are missing, the medication will be classified as concomitant.

## 4.6. Study Drug Exposure

### 4.6.1. Extent of Exposure

A listing of individual patient dosing data will be provided.

Study drug exposure will be summarized descriptively by cohort (Part 1) and by treatment group for each muscle (Part 2) for the safety population. Such summaries will include the total number of treatment doses, the number and percentage of patients with dose delay and reduction. If no patients experience dose delay and reduction, then no such summaries will be provided.

The total number of doses will be summarized by presenting the number and percentage of patients in each category. Categories refer to the total number of treatment doses. For Part 1, the possible values of the total number of treatment doses are: "1", "2", "3", "4", and "5". For Part 2 (double-blind period), the possible values of the total number of treatment doses over the course of the double-blind treatment period is: "1", "2", "3", "4", "5", "6", "7", "8", or "9". For Part 2 (open-label extension), the possible values of the total number of treatment doses over the course of the open-label extension is: "1", "2", "3", "4", "5", "6", "7", or "8".

The total study drug exposure in weeks will also be summarized and will be derived according to the following formula: Exposure (weeks) = [(Last dose date – First dose date) +21] / 7.

For Part 1, summaries of the total study drug exposure in weeks will be provided by cohort using descriptive statistics. The summary table will include a pooled summary across cohorts within each muscle treated.

For Part 2, summaries of the total study drug exposure in weeks will be provided by treatment group for each muscle treated. This will be done for the double-blind and open-label periods.

## 4.7. Efficacy Data

### 4.7.1. Variables

#### 4.7.1.1. Muscle Strength

Muscle strength variables consist of the following:

- Maximum (of 3 measurements) right ankle dorsiflexion MVIC
  - MVIC = maximum force (from 3 measurements) from the hand-held dynamometer
- Maximum (of 3 measurements) left ankle dorsiflexion MVIC
- (Part 2 only): MRC-MMT SCORE which represents the conversion of the MRC-MMT grade to the decimal version as follows: 5 = 5.0, 5- = 4.67, 4+ = 4.33, 4 = 4.0, 4- = 3.67, 3+ = 3.33, 3 = 3.0, 3- = 2.67, 2+ = 2.33, 2 = 2.0, 2- = 1.67, 1+ = 1.33, 1=1.0

For each of the muscle strength variables listed above, the absolute and percent change from baseline will be determined for each side (left, right) at each time point. In addition, the absolute and percent change from baseline will be determined for the average of the left and right sides at each time point.

#### 4.7.1.2. Motor Function

##### 10-Meter Walk/Run Test

- Time to complete 10-meter walk/run (seconds)

##### 6-Minute Walk Test

- Cumulative distance traveled at 1 minute (meters)
- Cumulative distance traveled at 2 minutes (meters)
- Cumulative distance traveled at 3 minutes (meters)
- Cumulative distance traveled at 4 minutes (meters)
- Cumulative distance traveled at 5 minutes (meters)
- Cumulative distance traveled at 6 minutes (meters)

##### 100-meter timed test (Part 2 open-label period only)

- Time to complete 100-meters (sec.)

##### Gait assessments

- General measures: Stride time (sec.), Stride length A (m), Stride length B (% height), Stride velocity A (m/s), Stride velocity B (height/s), Cadence (steps/min), Step length left (m), Step length right (m)
- Gait cycle phase measures: Swing left (%), Swing right (%), Stance left (%), Stance right (%), Double support initial right (%), Double support terminal left (%), Double support total (%)
- Gait assessment range of motion: Knee ROM left (deg.), Knee ROM right (deg.), Hip ROM left (deg.), Hip ROM right (deg.), Ankle ROM left (deg.), Ankle ROM right (deg.), Peak hip flexion angle in swing left (deg.), Peak hip flexion angle in swing right (deg.), Peak knee flexion angle in swing left (deg.), Peak knee flexion angle in swing right (deg.), Peak ankle flexion angle in swing left (deg.), Peak ankle flexion angle in swing right (deg.)
- Gait assessment foot drop: Mid-swing foot angle left (deg.), Mid-swing foot angle right (deg.)

For gait assessments reported on the left and right sides, the absolute and percent change from baseline will be determined for each side and then averaged. Should a patient have a gait assessment reported for one side (i.e. right side) but not the other side at an individual time point, the value for the average absolute (or percent) change from baseline for that patient and time point will be the absolute (or percent) change from the side from which the gait assessment was obtained.

##### Berg Balance Scale

- Total score from the 14 items on the instrument.

- The 14 items on the instrument are: Sitting to standing, Standing unsupported, Sitting with back unsupported but feet supported on floor or on a stool, Standing to sitting, Transfers, Standing unsupported with eyes closed, Standing unsupported with feet together, Reaching forward with outstretched arm while standing, Pick up object from the floor from a standing position, Turning to look behind over left and right shoulders while standing, Turn 360 degrees, Placing alternate foot on step or stool while standing unsupported, Standing unsupported one foot in front, and Standing on one leg.
- Each item score ranges from 0 to 4. The total score ranges from 0 to 56.

### **Falls (Part 2 double-blind and open-label)**

- Number of falls reported by patients wearing the PAMSys™ device
  - From Week 1 to Week 12 (3 months) [inclusive]
  - From Week 13 (3 months) up to Week 24 (6 months) [inclusive]
  - From Week 1 to Week 24 (6 months) [inclusive]
  - From Week 25 to Week 36 [inclusive]
  - From Week 37 to Week 40 [inclusive]
  - From Week 25 (6 months) to Week 48 (12 months) [inclusive]
  - From Week 1 up to Week 48 (12 months) [inclusive]
- Number of patients who fell at least once
  - From Week 1 to Week 12 (3 months) [inclusive]
  - From Week 13 (3 months) up to Week 24 (6 months) [inclusive]
  - From Week 1 to Week 24 (6 months) [inclusive]
  - From Week 25 to Week 36 [inclusive]
  - From Week 37 to Week 40 [inclusive]
  - From Week 25 (6 months) to Week 48 (12 months) [inclusive]
  - From Week 1 up to Week 48 (12 months) [inclusive]
- Risk of recurrent falls from Week 1 up to Week 24 (6 months)
- Risk of recurrent falls from Week 1 up to Week 48 (12 months)

### **Activity Level (Part 2 double-blind and open-label)**

Activity level is defined as the average number of steps per day as measured by the PAMSys™ device over the patient's study participation, adjusted for overall compliance in using the device to record such activity.

#### **4.7.1.3. Patient Reported Outcome Variables**

##### **Charcot-Marie-Tooth Health Index (CMT-HI)**

- CMT-HI total score
- The 18 subscale scores of the CMT-HI
  - Mobility, Foot and ankle strength, Balance, Activities, Hand and finger function, Shoulder and arm function, Numbness, Pain, Fatigue, Sleep and daytime sleepiness, Emotions, Social Performance, Cognition, Heartburn, Constipation, Hearing, Breathing, and Ability to swallow

#### **4.7.1.4. Physician Reported Outcome Variables**

##### **Charcot-Marie-Tooth Examination Score – Version 2 (CMTES2)**

- This is the sum of the following items from the CMT neuropathy score instrument (Murphy et al., 2011): Sensory symptoms, Motor symptoms (legs), Motor symptoms (arms), Pinprick Sensibility, Vibration, Strength (legs), and Strength (arms)
  - Each individual item is assessed using a rating from 0 to 4 inclusive. The range of CMTES2 scores is from 0 to 28 inclusive.

#### **4.7.2. Analyses**

##### **4.7.2.1. Part 1**

Unless otherwise specified, no imputations for missing data will be performed for Part 1 data.

##### **Muscle Strength [Maximum voluntary isometric contraction {MVIC}]**

Individual MVIC data will be listed.

Descriptive statistics of the raw data as well as the absolute and percent change from baseline will be provided by side treated [left and right]. The average absolute and average percent change from baseline for the left and right sides will also be provided.

Least squares mean estimates of the effect of ACE-083 and corresponding 90% and 95% confidence intervals will be produced for the average percent change data (left and right sides) at 3-weeks post last dose [theoretically the Day 106 assessment] described above using an analysis of covariance (ANCOVA) with BASELINE, COHORT, BASELINE\*COHORT, and CMT-TYPE as covariates where:

- COHORT represents the dose level of ACE-083 administered to the muscle
- BASELINE represents the baseline value (average for the left and right sides)
- BASELINE\*COHORT represents the interaction of the baseline and cohort
- CMT-TYPE refers to the type of patient (e.g. CMT1 or CMTX)

Additional analyses may be performed as appropriate.

## **Motor Function Variables**

Individual motor function data will be listed.

For motor function test variables (e.g. cumulative distance at 6 minutes from the 6-minute walk test, time to complete 10-meter walk/run test, gait parameters, Berg Balance Scale), descriptive statistics of the raw data as well as absolute and percent change from baseline will be provided. With the exception of gait parameters, cumulative distances at 1 to 5 minutes inclusive, and the Berg Balance Scale, least squares mean estimates of the effect of ACE-083 and corresponding 90% and 95% confidence intervals will be produced for the percent change data (as well as absolute change data for 6MWD) at 3 weeks post last dose [theoretically the Day 106/End-of-Treatment assessment] described above using an ANCOVA with BASELINE, COHORT, BASELINE\*COHORT, and CMT-TYPE as covariates where BASELINE refers to the baseline motor function value and the other covariates are defined similarly as for the strength variables above.

Additional analyses may be performed as appropriate.

## **Patient Reported Outcome Variables**

Individual CMT-HI data will be listed.

For CMT-HI total score and subscale scores, descriptive statistics of the raw data as well as absolute change from baseline will be provided.

Least square mean estimates of the effect of ACE-083 and corresponding 90% and 95% confidence intervals will be produced for the absolute change data at 3 weeks post last dose [theoretically the Day 106/End-of-Treatment assessment] described above using an ANCOVA with BASELINE, COHORT, BASELINE\*COHORT, and CMT-TYPE as covariates where BASELINE refers to the baseline patient reported outcome variable (i.e. CMT-HI total score or CMT-HI subscale score) and the other covariates are defined similarly as for the strength variables above.

Additional analyses may be performed as appropriate.

## **Physician Reported Outcome Variables**

Individual data from the CMTES2 will be listed.

For CMTES2, descriptive statistics of the raw data as well as the absolute and percent change from baseline will be provided.

Least square mean estimates of the effect of ACE-083 and corresponding 90% and 95% confidence intervals will be produced for the absolute change data at 3 weeks post last dose [theoretically the Day 106/End-of-Treatment assessment] described above using an ANCOVA with BASELINE, COHORT, BASELINE\*COHORT, and CMT-TYPE as covariates where BASELINE represents the baseline CMTES2 and the other covariates are defined similarly as for the strength variables above.

Additional analyses may be performed as appropriate.

#### 4.7.2.2. Part 2

##### 4.7.2.2.1. Double-Blind Period

###### Muscle Strength (MVIC)

Individual MVIC data will be listed.

Descriptive statistics of the raw data as well as the absolute and percent change from baseline will be provided by side treated [left and right]. The average absolute and average percent change from baseline for the left and right sides will also be provided.

A plot of the mean ( $\pm$  SEM) of the average percent change from baseline for the left and right sides by scheduled day and treatment group will also be provided.

An ANCOVA model will be fitted in order to assess the effect of ACE-083 on the average percent change from baseline for the left and right side at Day 190 with the following covariates: TREATMENT, MRC-MMT DECIMAL SCORE, BASELINE, CMT-TYPE where:

- TREATMENT represents the treatment group (ACE-083 or placebo)
- MRC-MMT DECIMAL SCORE represents the conversion of the screening MRC-MMT grade to the decimal version as follows: 5 = 5.0, 5- = 4.67, 4+ = 4.33, 4 = 4.0, 4- = 3.67, 3+ = 3.33, 3 = 3.0, 3- = 2.67, 2+ = 2.33, 2 = 2.0, 2- = 1.67, 1+ = 1.33, 1=1.0
  - This quantity will be the average from the left and right sides and will be computed for each individual patient.
- BASELINE represents the baseline MVIC (average of left and right sides)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)

The effect of ACE-083 versus placebo will be estimated using the ANCOVA model described above and tested using a 0.1 significance level (2-sided). The least-square mean estimate along with the corresponding 90% confidence interval will be provided. In addition, the 95% confidence interval will also be provided. A bar chart of the least squares mean  $\pm$  SEM of the percent change from baseline will be provided.

If the Day 190 MVIC assessment has no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in Section 4.11.1.

A mixed model repeated measures (MMRM) analysis will be performed to assess the sensitivity to the ANCOVA analysis described above. An unstructured covariance structure will be used to model the within-patient covariance across visits. Other covariance structures will be considered if the unstructured covariance fails to converge. The covariates to be included consist of all of the covariates described above for the ANCOVA with the addition of the following additional covariates: VISIT where VISIT represents the scheduled visit day post first dose of MRI assessment and TREATMENT\*VISIT.

Similar to what was described for the ANCOVA analysis above, if missing data is present, a standard multiple imputation with the above MMRM model will be used for analysis as described in [Section 4.11.1](#).

The findings from the ANCOVA model described above will be considered primary.

Additional analyses may be performed as appropriate.

### **MRC-MMT Decimal Score**

Descriptive statistics will be provided for raw and percent change from baseline for the MRC-MMT decimal score for ankle dorsiflexion for each side where the MRC-MMT decimal score represents the conversion of the MRC-MMT grade to the decimal version as follows: 5 = 5.0, 5- = 4.67, 4+ = 4.33, 4 = 4.0, 4- = 3.67, 3+ = 3.33, 3 = 3.0, 3- = 2.67, 2+ = 2.33, 2 = 2.0, 2- = 1.67, 1+ = 1.33, 1=1.0. The average percent change from baseline for the left and right sides will also be provided.

An ANCOVA model will be fitted in order to assess the effect of ACE-083 on the average Day 190 absolute change in the MRC-MMT decimal score for ankle dorsiflexion with placebo. The ANCOVA model will contain the following covariates: TREATMENT, BASELINE MRC-MMT DECIMAL SCORE, and CMT-TYPE where BASELINE MRC-MMT DECIMAL SCORE represents the MRC-MMT decimal score for ankle dorsiflexion (average of right and left sides) and the other covariates are defined similarly as described for MVIC. A bar chart of the least squares mean  $\pm$  SEM of the percent change from baseline will be provided.

No imputations will be performed for missing data.

Additional analyses may be performed as appropriate.

### **10-Meter Walk/Run Test**

Individual data will be listed.

Descriptive statistics of raw data as well as absolute and percent change from baseline will be provided by treatment group for each scheduled time. A plot of mean  $\pm$  SEM will also be provided for the percent change from baseline for each treatment group.

An ANCOVA model will also be fitted in order to assess the effect of ACE-083 on the Day 190 percent change in the time to complete the 10-meter walk/run test from baseline data. Covariates to be included in the model are TREATMENT, HEIGHT, CMT-TYPE and BASELINE where BASELINE represents the baseline time to complete the 10-meter walk/run, HEIGHT represents the height of the patient in centimeters, and each of the other covariates are defined similarly as what was described for MVIC.

The effect of ACE-083 on the Day 190 percent change in the time to complete the 10-meter walk/run test from baseline versus placebo will be estimated using the ANCOVA model described above and tested using a 0.1 significance level (2-sided). The least-square mean estimate along with the corresponding 90% confidence interval will be provided. In addition, the 95% confidence interval will also be provided as well as a bar chart of the least squares mean estimates ( $\pm$  SEM) for each of the treatment groups.

If the Day 190 10-meter walk/run test has no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#)

A mixed model repeated measures (MMRM) analysis will be performed to assess the sensitivity to the ANCOVA analysis described above. An unstructured covariance structure will be used to model the within-patient covariance across visits. Other covariance structures will be considered if the unstructured covariance fails. The covariates to be included consist of all of the covariates described above for the ANCOVA with the addition of the following additional covariates: VISIT where VISIT represents the scheduled visit day post first dose of MRI assessment and TREATMENT\*VISIT.

Similar to what was described for the ANCOVA analysis above, if missing data is present, a standard multiple imputation with the above MMRM model will be used for analysis as described in Section 4.11.1.

The findings from the ANCOVA model described above will be considered primary.

The analyses described above will also be done for the absolute change from baseline.

The analyses described above will also be repeated for the Full Analysis Set.

Additional analyses may be performed as appropriate.

## 6-Minute Walk Test

Individual data will be listed.

Descriptive statistics of raw data as well as changes from baseline (absolute and percent change) will be provided by treatment group by scheduled time separately for cumulative distance recorded at 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, and 6 minutes. A plot of mean  $\pm$  SEM for the cumulative distance recorded at 6 minutes will also be provided for the percent change from baseline for each treatment group.

An ANCOVA model will be fitted in order to assess the effect of ACE-083 on the Day 190 percent change in the cumulative distance recorded at 6 minutes. Covariates to be included in the model are TREATMENT, HEIGHT, CMT-TYPE, and BASELINE where HEIGHT refers to the height of the patient (cm) and BASELINE represents the baseline distance walked in 6 minutes and each of the other covariates are defined the same as what was described for MVIC.

The effect of ACE-083 on the Day 190 percent change in the cumulative distance recorded at 6 minutes from baseline versus placebo will be estimated using the ANCOVA model described above and tested using a 0.1 significance level (2-sided). The least-square mean estimate along with the corresponding 90% confidence interval will be provided. In addition, the 95% confidence interval will also be provided as well as a bar chart of the least squares mean estimates ( $\pm$  SEM) for each of the treatment groups.

An ANCOVA model will also be fitted in order to assess the effect of ACE-083 on the Day 190 absolute change in the cumulative distance recorded at 6 minutes from baseline data. Covariates to be included in the model are TREATMENT, HEIGHT, CMT-TYPE, and BASELINE where HEIGHT refers to the height of the patient (cm) and BASELINE represents the baseline distance

walked in 6 minutes and each of the other covariates are defined the same as what was described for MVIC.

The effect of ACE-083 on the Day 190 absolute change in the cumulative distance recorded at 6 minutes from baseline versus placebo will be estimated using the ANCOVA model described above and tested using a 0.1 significance level (2-sided). The least-square mean estimate along with the corresponding 90% confidence interval will be provided. In addition, the 95% confidence interval will also be provided as well as a bar chart of the least squares mean estimates ( $\pm$  SEM) for each of the treatment groups.

If the Day 190 cumulative distance recorded at 6 minutes has no missing data, then the ANCOVA models described above will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA models will be used for analysis as described in [Section 4.11.1](#).

A mixed model repeated measures (MMRM) analysis will be performed to assess the sensitivity to the ANCOVA analyses described above. An unstructured covariance structure will be used to model the within-patient covariance across visits. Other covariance structures will be considered if the unstructured covariance fails. The covariates to be included consist of all of the covariates described above for the ANCOVA with the addition of the following additional covariates: VISIT where VISIT represents the scheduled visit day post first dose of MRI assessment and TREATMENT\*VISIT.

Similar to what was described for the ANCOVA analyses above, if missing data is present, a standard multiple imputation with the above MMRM model will be used for analysis as described in Section 4.11.1.

The findings from the ANCOVA model described above will be considered primary.

The analyses described above will also be done for the absolute change from baseline.

The analyses described above will also be repeated for the Full Analysis Set.

Additional analyses may be performed as appropriate.

### **Berg Balance Scale**

Individual data will be listed.

Descriptive statistics of raw data as well as changes from baseline (absolute and percent change) will be provided by treatment group and scheduled time.

An ANCOVA model will be fitted in order to assess the effect of ACE-083 on the Day 190 absolute change in the Berg Balance Score from baseline. Covariates to be included are TREATMENT, CMT-TYPE, and BASELINE where BASELINE refers to the baseline Berg Balance Score and the other covariates are defined similarly as for MVIC.

The effect of ACE-083 on the Day 190 absolute change in the Berg Balance Scale versus placebo will be estimated using the ANCOVA model described above and tested using a 0.1 significance level (2-sided). The least-square mean estimate along with the corresponding 90% confidence interval will be provided. In addition, the 95% confidence interval will also be provided as well as a bar chart of the least squares means estimates ( $\pm$  SEM) for each of the treatment groups.

If the Day 190 Berg balance assessment has no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

The statistical analyses described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

Additional analyses may be performed as appropriate.

### **Falls**

Individual data on the number and type of falls recorded in 4-week time intervals along with details on the timing and classification of the individual falls recorded, type of assistance, and information related to input (whether the fall was recorded by device detection or recorded by the individual patient) will be provided in a listing.

The number of falls, as well as the number of patients who fell at least once occurring from Week 1 to Week 24 (6 months) will be summarized by treatment group. Summaries will be provided for the additional subintervals between Weeks 1 and 24 as outlined in [Section 4.7.1.2](#). A record of “Near-fall” will not be counted as a “Fall”.

The hazard ratio of recurring falls between ACE-083 and placebo between Weeks 1 and 24 will be estimated using the Andersen-Gill recurrent events model with the following covariates: TREATMENT, CMT-TYPE, and ankle dorsiflexion MRC-MMT decimal score where the covariates are defined similarly as what was described for MVIC. The point estimate, p-value and 90% confidence interval for the hazard ratio for TREATMENT will be provided.

Additional methods for the statistical analysis of the recurring event of falls may be considered and performed as appropriate (e.g. negative binomial regression with similar covariates as listed for the Andersen-Gill recurrent events model described above).

No imputations will be performed for missing data.

The statistical analyses described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

Additional analyses may be performed as appropriate.

### **CMT-HI**

Individual CMT-HI scored data (total score and each of the subscale scores) will be listed.

Descriptive statistics for the total CMT-HI score as well as for each subscale score will be provided by treatment group and scheduled time for raw data and absolute change from baseline. A line graph of the mean  $\pm$  SEM will also be provided for the absolute change from baseline by treatment for each scheduled time.

Least square mean estimates of the effect of ACE-083 and corresponding 90% and 95% confidence intervals will be produced for the Day 190 absolute change data described above using an ANCOVA model with BASELINE, CMT-TYPE, and TREATMENT as covariates

where BASELINE, CMT-TYPE, and TREATMENT are defined similarly as described above for other analyses.

Similar analyses will be done for each of the individual subscale scores.

In addition, a bar chart of the Day 190 least squares mean absolute change estimates ( $\pm$  SEM) will be provided for the following CMT-HI parameters: CMT-HI total score, CMT-HI mobility, CMT-HI activities, CMT-HI pain, and CMT-HI balance.

If the Day 190 CMT-HI has no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

A mixed model repeated measures (MMRM) analysis will be performed to assess the sensitivity to the ANCOVA analyses described above. An unstructured covariance structure will be used to model the within-patient covariance across visits. Other covariance structures will be considered if the unstructured covariance fails. The covariates to be included consist of all of the covariates described above for the ANCOVA with the addition of the following additional covariates: VISIT where VISIT represents the scheduled visit day post first dose of MRI assessment and TREATMENT\*VISIT.

Similar to what was described for the ANCOVA analysis above, if missing data is present, a standard multiple imputation with the above MMRM model will be used for analysis as described in [Section 4.11.1](#).

The findings from the ANCOVA model described above will be considered primary.

Additional analyses may be performed as appropriate.

## **CMTES2**

Individual data will be listed.

Descriptive statistics for the CMTES2 score will be provided by treatment group for raw data and changes from baseline (absolute and percent change). In addition, a line graph of the mean  $\pm$  SEM will also be provided for the absolute change from baseline by treatment for each scheduled time.

Least square mean estimates of the effect of ACE-083 and corresponding 90% and 95% confidence intervals will be produced for the Day 190 absolute change data described above using an ANCOVA model with CMT-TYPE, BASELINE, and TREATMENT as covariates where BASELINE refers to the baseline CMTES2 score and CMT-TYPE and TREATMENT are defined similarly as described above for other analyses. In addition, a bar chart of the least squares mean estimates ( $\pm$  SEM) for each treatment group will be provided.

If the Day 190 CMTES2 assessment has no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

The statistical analyses described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

Additional analyses may be performed as appropriate.

### **Gait**

Individual data will be listed.

Descriptive statistics of the raw data and change from baseline (percent and absolute change) will be provided for each type of measurement recorded (i.e. “General measures”, “Gait cycle phase measures”, “Gait assessment range of motion”, and “Gait assessment foot drop”) by cohort and scheduled time (for Part 1) and by treatment group and scheduled time (for Part 2).

Descriptive statistics for the average absolute and average percent change from baseline for the left and right sides will also be provided.

Least square mean estimates of the effect of ACE-083 and corresponding 90% and 95% confidence intervals will be produced for the Day 190 average absolute change from baseline for the left and right sides for the mid-swing foot angle using an ANCOVA model with CMT-TYPE, BASELINE, and TREATMENT as covariates where BASELINE refers to the baseline average mid-swing foot angle for the left and right sides and CMT-TYPE and TREATMENT are defined similarly as described above for other analyses. In addition, a bar chart of the least squares mean estimates ( $\pm$  SEM) for each treatment group will be provided.

The statistical analysis described above will be done on the Per Protocol Set and will be considered primary. The analyses will also be repeated for the Full Analysis Set.

No imputations will be performed for missing data.

Additional analyses may be performed as appropriate.

### **Activity Level**

Individual data will be listed.

Exploratory analyses may be performed as appropriate.

No imputations will be performed for missing data.

#### **4.7.2.2.2. Open-Label Extension**

##### **Muscle Strength (MVIC)**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

Descriptive statistics will be provided for raw data and changes (percent and absolute change) from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time for each side treated as well as the average from the left and right sides.

Additional analyses may be performed as appropriate.

##### **MRC-MMT Decimal Score**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

Descriptive statistics will be provided for raw data and changes (percent and absolute change) from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time for each side treated as well as the average from the left and right sides.

Additional analyses may be performed as appropriate.

### **10-Meter Walk/Run Test**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

For the time to complete the 10-meter walk/run, descriptive statistics will be provided for raw data and changes (percent and absolute change) from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time.

Additional analyses may be performed as appropriate.

### **6-Minute Walk Test**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

For the cumulative distance recorded at 6 minutes, descriptive statistics will be provided for raw data and changes (percent and absolute change) from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time.

Additional analyses may be performed as appropriate.

### **Berg Balance**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

Descriptive statistics will be provided for raw data and changes (absolute and percent change) from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time.

Additional analyses may be performed as appropriate.

### **Falls**

Individual data on the number and type of falls recorded in 4-week time intervals along with details on the timing and classification of the individual falls recorded, per day, type of assistance, and information related to input (whether the fall was recorded by device detection or recorded by the individual patient) will be provided in a listing. This data will be included with the data collected in the double-blind placebo-controlled phase.

The number of falls as well as the number of patients who fell at least once occurring from Week 25 up to Week 48 inclusive will be summarized by treatment, including separate summaries for subintervals as outlined in [Section 4.7.1.2](#). A record of “Near-fall” will not be counted as a “Fall”.

Additional analyses may be performed as appropriate.

**CMT-HI**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

For the total CMT-HI and subgroup scores, descriptive statistics will be provided for raw data and absolute change from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time.

Additional analyses may be performed as appropriate.

**CMTES2**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

For the CMTES2 score, descriptive statistics will be provided for raw data and absolute change from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time.

Additional analyses may be performed as appropriate.

**Gait**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

For each type of measurement recorded (i.e. “General measures”, “Gait cycle phase measures”, “Gait assessment range of motion”, and “Gait assessment foot drop”), descriptive statistics will be provided for raw data as well as absolute and percent changes from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time. Descriptive statistics of the average absolute and average percent change from baseline for the left and right sides will also be provided.

Additional analyses may be performed as appropriate.

**Activity Level**

Individual data will be listed.

Exploratory analyses may be performed as appropriate.

No imputations will be performed for missing data.

**4.7.2.2.3. Open-Label vs. Double-Blind Placebo-Controlled Period****MVIC**

The effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the average absolute and/or percent changes [depending on the parameter] observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Possible covariates to be included into the model are SEQUENCE, MRC-MMT SCORE, CMT-TYPE and BASELINE where:

- SEQUENCE represents the treatment sequence from double blind to open-label (ACE-083 → ACE-083 or Placebo → ACE-083)
- MRC-MMT SCORE represents the conversion of the screening MRC-MMT grade to the decimal version as follows: 5 = 5.0, 5- = 4.67, 4+ = 4.33, 4 = 4.0, 4- = 3.67, 3+ = 3.33, 3 = 3.0, 3- = 2.67, 2+ = 2.33, 2 = 2.0, 2- = 1.67, 1+ = 1.33, 1 = 1.0
- CMT TYPE refers to the type of CMT (e.g. CMT1 or CMTX)
- BASELINE represents the baseline value from the double-blind phase

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

If the Day 358 and/or Day 190 assessments have no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

In addition, a line graph of the mean ± SEM of the percent change from baseline will be provided by sequence for each scheduled time.

Additional analyses may be performed as appropriate.

### **MRC-MMT Decimal Score**

The effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the average absolute change [depending on the parameter] observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Possible covariates to be included into the model are SEQUENCE, MRC-MMT SCORE, CMT-TYPE and BASELINE where:

- SEQUENCE represents the treatment sequence from double blind to open-label (ACE-083 → ACE-083 or Placebo → ACE-083)
- MRC-MMT SCORE represents the conversion of the screening MRC-MMT grade to the decimal version as follows: 5 = 5.0, 5- = 4.67, 4+ = 4.33, 4 = 4.0, 4- = 3.67, 3+ = 3.33, 3 = 3.0, 3- = 2.67, 2+ = 2.33, 2 = 2.0, 2- = 1.67, 1+ = 1.33, 1 = 1.0
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)
- BASELINE represents the baseline value from the double-blind phase

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

### 10-Meter Walk/Run Test

The effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the absolute and/or percent changes observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Covariates to be included into the model are SEQUENCE, HEIGHT, CMT-TYPE, and BASELINE where:

- SEQUENCE represents the treatment sequence from double blind to open-label (ACE-083 → ACE-083 or Placebo → ACE-083)
- HEIGHT represents the height of the patient (cm)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)
- BASELINE represents the baseline value of the parameter of interest from the double-blind phase

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

If the Day 358 and/or Day 190 assessments have no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

In addition, a line graph of the mean ± SEM of the percent change from baseline will be provided by sequence for each scheduled time.

Additional analyses may be performed as appropriate.

### 6-Minute Walk Test

The effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the absolute and/or percent changes observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Covariates to be included into the model are SEQUENCE, HEIGHT, CMT-TYPE, and BASELINE where:

- SEQUENCE represents the treatment sequence from double blind to open-label (ACE-083 → ACE-083 or Placebo → ACE-083)
- HEIGHT represents the height of the patient (cm)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)
- BASELINE represents the baseline value of the parameter of interest from the double-blind phase

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

If the Day 358 and/or Day 190 assessments have no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

In addition, a line graph of the mean  $\pm$  SEM of the percent change from baseline will be provided by sequence for each scheduled time.

Additional analyses may be performed as appropriate

### **Berg Balance Scale**

The effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the absolute changes observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Covariates to be included into the model are SEQUENCE, CMT-TYPE, and BASELINE where:

- SEQUENCE represents the treatment sequence from double blind to open-label (ACE-083  $\rightarrow$  ACE-083 or Placebo  $\rightarrow$  ACE-083)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)
- BASELINE represents the baseline value of the parameter of interest from the double-blind phase

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

If the Day 358 and/or Day 190 assessments have no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

The statistical analysis described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

In addition, a line graph of the mean  $\pm$  SEM of the absolute change from baseline will be provided by sequence for each scheduled time.

Additional analyses may be performed as appropriate

### **Falls**

The hazard ratio of recurring falls between ACE-083 and placebo during the entire 12 months (excluding the screening interval) will be estimated using the Andersen-Gill recurrent events model with the following covariates: SEQUENCE, CMT-TYPE, PERIOD, and ankle dorsiflexion MRC-MMT decimal score where SEQUENCE refers to the treatment sequence from double-blind to open-label (ACE-083  $\rightarrow$  ACE-083 or Placebo  $\rightarrow$  ACE-083), and PERIOD

refers to the period of time of observation (“Double-blind”, “Open-label”). The “Double-Blind” period covers Weeks 1 to 24 and the “Open-label” period covers Weeks 25 to 48. The point estimate, p-value and 90% confidence interval for the hazard ratio for SEQUENCE will be provided.

Additional methods for the statistical analysis of the recurring event of falls may be considered and performed as appropriate (e.g. negative binomial regression with similar covariates as listed for the Andersen-Gill recurrent events model described above).

No multiple imputations will be performed for missing data.

The statistical analyses described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

Additional analyses may be performed as appropriate.

### **CMT-HI**

For the total CMT-HI and subgroup scores, the effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the absolute change observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Covariates to be included into the model are SEQUENCE, CMT-TYPE, and BASELINE where:

- SEQUENCE represents the treatment sequence from double blind to open-label (ACE-083 → ACE-083 or Placebo → ACE-083)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)
- BASELINE represents the baseline value of the parameter of interest from the double-blind phase

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

If the Day 358 and/or Day 190 assessments have no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

The statistical analysis described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

In addition, a line graph of the mean ± SEM of the absolute change from baseline will be provided by sequence for each scheduled time.

Additional analyses may be performed as appropriate.

## CMTES2

For the CMTES2 score, the effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the absolute change observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Covariates to be included into the model are SEQUENCE, CMT-TYPE, and BASELINE where:

- SEQUENCE represents the treatment sequence from double-blind to open-label (ACE-083 | ACE-083 or Placebo | ACE-083)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)
- BASELINE represents the baseline value of the parameter of interest from the double-blind phase

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

If the Day 358 and/or Day 190 assessments have no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

The statistical analysis described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

In addition, a line graph of the mean  $\pm$  SEM of the absolute change from baseline will be provided by sequence for each scheduled time.

Additional analyses may be performed as appropriate.

## Gait

For each type of measurement recorded (i.e. “General measures”, “Gait cycle phase measures”, “Gait assessment range of motion”, and “Gait assessment foot drop”), the effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the absolute change observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) by descriptive statistics. This will also be done for the average absolute change from baseline for assessments performed on the left and right sides.

The effect of ACE-083 on the average absolute change for mid-swing foot angle administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase by comparing the average absolute change observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Covariates to be included into the model are SEQUENCE, CMT-TYPE, and BASELINE where baseline represents the baseline from the double-blind phase and SEQUENCE and CMT-TYPE are defined similarly as for MVIC.

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

A line graph of the mean  $\pm$  SEM will be provided by sequence for each scheduled time for the average absolute change for mid-swing foot angle.

Additional analyses may be performed as appropriate.

### **Activity Level**

Exploratory analyses may be performed as appropriate.

#### **4.7.2.3. Other Analyses**

The number and percentage of patients belonging to each of the following criteria will be summarized by treatment group:

- Day 190 percent change in TMV from baseline  $\geq 10\%$
- Day 190 percent change in 6MWD from baseline  $\geq 10\%$
- Day 190 absolute change in 6MWD from baseline  $\geq 30$  m
- Day 190 percent change in time to complete 10mW/R from baseline  $\leq -10\%$
- Day 190 absolute change in time to complete 10mW/R from baseline  $\leq -0.5$  sec.
- Day 190 absolute change in CMT-HI total score from baseline  $\leq -8$
- Day 190 absolute change in CMT-HI mobility subscale score from baseline  $\leq -8$
- Day 190 absolute change in CMT-HI activities subscale score from baseline  $\leq -8$
- Day 190 absolute change in ankle dorsiflexion MRC-MMT decimal score  $\geq 0.16$
- Percent change in number of falls during Weeks 13 to 24 from the number of falls during Weeks 1 to 12  $\leq -20\%$

For each criterion listed above, Fisher's exact test will be used to compare the proportions of patients belonging to the individual criterion between the two treatment groups using a 0.1 significance level.

## **4.8. Pharmacodynamic Data**

### **4.8.1. Variables**

#### **4.8.1.1. MRI**

MRI variables consist of the following:

Variable	Unit	Formula for derivation or SAS variable name/expression from SDTM FA
Total muscle volume (TMV)	mm <sup>3</sup>	TMV = Contractile muscle tissue volume (SAS variable FASTRESN in SDTM FA where FATESTCD = "MVOL") + Intramuscular fat volume (SAS variable FASTRESN in SDTM FA where FATESTCD="IFATVOL")
Intramuscular fat volume (IMFV)	mm <sup>3</sup>	SAS variable FASTRESN in SDTM FA where FATESTCD="IFATVOL"
Contractile muscle volume (CMV)	mm <sup>3</sup>	SAS variable FASTRESN in SDTM FA where FATESTCD="MVOL"
Fat fraction (FF)	%	SAS variable FASTRESN in SDTM FA where FATESTCD="FATF"
Contractile muscle fraction (CMF)	%	CMF = 100 – FF
Calculated contractile muscle volume (CCMV)	mm <sup>3</sup>	CCMV = TMV * CMF/100
Calculated intramuscular fat volume (CIMFV)	mm <sup>3</sup>	CIMFV = TMV * FF/100
Contractile muscle mass (CMM)	g	CMM = CMV * 1.06/1000
Intramuscular fat mass (IMFM)	g	IMFM = IMFV * 0.9/1000
Total muscle mass (TMM)	g	TMM = CMM + IMFM
Calculated contractile muscle mass (CCMM)	g	CCMM = CCMV * 1.06/1000
Calculated intramuscular fat mass (CIMFM)	g	CIMFM = CIMFV * 0.9/1000
Calculated total muscle mass (CTMM)	g	CTMM = CCMM + CIMFM

#### 4.8.1.2. Biomarkers

Biomarker data include but are not necessarily limited to the following selected laboratory data: CTX and hemoglobin.

#### 4.8.1.3. CMAP of TA

This is an exploratory variable that is collected for Part 2 patients.

#### 4.8.2. Analyses

##### 4.8.2.1. Part 1

#### MRI

Individual MRI data will be listed.

For each MRI variable, the raw data as well as the absolute and percent change from baseline will be summarized by cohort for each scheduled time and side treated [left and right]. The average absolute and percent change [from left and right sides] will also be provided.

For total muscle volume, calculated contractile muscle volume, fat fraction, and calculated intramuscular fat, least squares estimates of the effect of ACE-083 and corresponding 90% and 95% confidence intervals will be produced for the average percent change data at Day 106 [from left and right sides] (absolute change for fat fraction at Day 106) using an ANCOVA with BASELINE, COHORT, and BASELINE\*COHORT as variables where:

- COHORT represents the dose level of ACE-083 administered to the muscle
- BASELINE represents the baseline value of the parameter of interest
- BASELINE\*COHORT represents the interaction of baseline and cohort

Graphical summaries of the mean  $\pm$  SEM will be provided for each cohort and scheduled time.

Additional analyses may be performed as appropriate.

## **Biomarker Data**

Individual biomarker data will be listed.

Biomarker data will be summarized by cohort and scheduled time for raw data and changes from baseline (absolute and/or percent). Graphical displays will also be provided (e.g. plot of mean  $\pm$  SEM).

### **4.8.2.2. Part 2**

#### **4.8.2.2.1. Double-Blind Period**

##### **MRI: Total Muscle Volume (TMV)**

Individual total muscle volume data will be listed.

Descriptive statistics will be provided by treatment group and scheduled time for raw data and changes from baseline (absolute and percent change) for each side [left and right]. The average absolute change and average of the percent change for the left and right sides will also be provided.

The primary pharmacodynamic analysis will consist of an ANCOVA in order to assess the effect of ACE-083 on the Day 190 average percent change from baseline for the left and right sides. Covariates to be included into the model are TREATMENT, BASELINE, and CMT-TYPE where:

- TREATMENT represents the treatment group (ACE-083 or placebo)
- BASELINE represents the baseline total muscle volume (average of left and right sides)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)

The effect of ACE-083 versus placebo will be estimated using the ANCOVA model described above and tested using a 0.1 significance level (2-sided). The least-square mean estimate along

with the corresponding 90% confidence interval will be provided. In addition, the 95% confidence interval will also be provided.

If the Day 190 TMV has no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

A mixed model repeated measures (MMRM) analysis will be performed to assess the sensitivity to the ANCOVA analysis described above. An unstructured covariance structure will be used to model the within-patient covariance across visits. Other covariance structures will be considered if the unstructured covariance fails. The covariates to be included consist of all of the covariates described above for the ANCOVA with the addition of the following additional covariates: VISIT where VISIT represents the scheduled visit day post first dose of MRI assessment and TREATMENT\*VISIT.

Similar to what was described for the ANCOVA analysis above, if missing data is present, a standard multiple imputation with the above MMRM model will be used for analysis as described in Section 4.11.1.

The statistical analyses described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

In addition, a line graph of the mean  $\pm$  SEM of the percent change from baseline will be provided by treatment for each scheduled time.

Additional analyses may be performed as appropriate.

### **MRI: Calculated Contractile Muscle Volume (CCMV), Fat Fraction (FF), and Calculated Intramuscular Fat (CIMV)**

Individual data will be listed.

Descriptive statistics will be provided by treatment group and scheduled time for raw data and changes from baseline (absolute and percent change) for each side [left and right]. The average absolute and average of the percent change for the left and right sides will also be provided.

An ANCOVA model will be fitted in order to assess the effect of ACE-083 on the Day 190 average of left and right side percent change (absolute change for FF) from baseline. Covariates to be included in the model are TREATMENT, BASELINE, and CMT-TYPE where:

- TREATMENT represents the treatment group (ACE-083 or placebo)
- BASELINE represents the baseline parameter of interest (average of left and right sides)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)

For each of the selected MRI parameters, the effect of ACE-083 on the Day 190 average percent change (absolute change for FF) from baseline will be estimated using the ANCOVA model described above and tested using a 0.1 significance level (2-sided). The least-square mean estimate along with the corresponding 90% confidence interval will be provided. In addition, the

95% confidence interval will also be provided as well as a bar chart of the least squares mean estimates ( $\pm$  SEM) for each of the treatment groups.

If the Day 190 selected MRI parameter has no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

A mixed model repeated measures (MMRM) analysis will be performed to assess the sensitivity to the ANCOVA analysis described above. An unstructured covariance structure will be used to model the within-patient covariance across visits. Other covariance structures will be considered if the unstructured covariance fails. The covariates to be included consist of all of the covariates described above for the ANCOVA with the addition of the following additional covariates: VISIT where VISIT represents the scheduled visit day post first dose of MRI assessment and TREATMENT\*VISIT.

Similar to what was described for the ANCOVA analysis above, if missing data is present, a standard multiple imputation with the above MMRM model will be used for analysis as described in [Section 4.11.1](#).

The statistical analyses described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

In addition, a line graph of the mean  $\pm$  SEM of the percent change from baseline will be provided by treatment for each scheduled time. For fat fraction, the line graph to be generated will consist of the mean  $\pm$  SEM of the absolute change from baseline by treatment for each scheduled time.

Additional analyses may be performed as appropriate.

### **MRI: Other Parameters**

Individual data will be listed. The listing of such data will be collated with the other MRI data.

Descriptive statistics will be provided for raw data and changes (percent and absolute change) from baseline by treatment for each scheduled time for each side treated [left and right]. The average absolute change and average of the percent change for the left and right sides will also be provided.

Additional analyses may be performed as appropriate.

### **Biomarker Data**

Individual biomarker data will be listed.

Biomarker data will be summarized by treatment group and scheduled time for raw data and changes from baseline (absolute and/or percent). Graphical displays will also be provided (e.g. plot of mean  $\pm$  SEM).

### **CMAP for TA**

Individual CMAP for TA data will be listed.

CMAP data will be summarized by treatment group and scheduled time for raw data and changes from baseline (absolute and/or percent).

Additional analyses may be performed as appropriate.

#### **4.8.2.2. Open-Label Extension**

##### **MRI: TMV**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

Descriptive statistics will be provided for raw data and changes (percent and absolute change) from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time and side treated as well as the average absolute change and average percent change from baseline for the left and right sides.

Additional analyses may be performed as appropriate.

##### **MRI: CCMV, FF, and CIMF**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

Descriptive statistics will be provided for raw data and changes (percent and absolute change) from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time and side treated as well as the average absolute change and average percent change from baseline for the left and right sides.

Additional analyses may be performed as appropriate.

##### **MRI: Other Parameters**

Individual data will be listed. The listing of such data will be collated with the data collected in the double-blind, placebo-controlled phase.

Descriptive statistics will be provided for raw data and changes (percent and absolute change) from the start of the open-label extension (Day 190) will be provided by treatment for each scheduled time and side treated as well as the average absolute change and average percent change from baseline for the left and right sides.

Additional analyses may be performed as appropriate.

##### **Biomarker Data**

Individual biomarker data will be listed and will be collated with data from the double-blind period.

Descriptive statistics of raw data and changes from baseline will be summarized by treatment sequence and scheduled time. Pooled summaries across treatment sequences will also be provided. Such summaries may be accompanied by a plot of mean  $\pm$  SEM.

Additional analyses may be performed as appropriate.

#### 4.8.2.2.3. Open-Label vs. Double-Blind Placebo-Controlled Period

##### **MRI: TMV**

The effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the average percent change (left and right side) observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Covariates to be included into the model are SEQUENCE, CMT-TYPE, and BASELINE where:

- SEQUENCE represents the treatment sequence from double blind to open-label (ACE-083 → ACE-083 or Placebo → ACE-083)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)
- BASELINE represents the baseline TMV from the double-blind period

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

If the Day 358 and/or Day 190 assessments have no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

The statistical analysis described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

In addition, a line graph of the mean ± SEM of the percent change from baseline will be provided by sequence for each scheduled time.

Additional analyses may be performed as appropriate.

##### **MRI: CCMV, FF, and CIMF**

The effect of ACE-083 administered during the open-label extension compared to the treatment administered in the double-blind placebo-controlled phase will be examined for those receiving ACE-083 during the double-blind phase and separately for those receiving placebo during the double-blind phase by comparing the average percent change (left and right side) observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months) using an ANCOVA model.

Covariates to be included into the model are SEQUENCE, CMT-TYPE, and BASELINE where:

- SEQUENCE represents the treatment sequence from double blind to open-label (ACE-083 → ACE-083 or Placebo → ACE-083)
- CMT-TYPE refers to the type of CMT (e.g. CMT1 or CMTX)
- BASELINE represents the baseline TMV from the double-blind period

Least squares estimates of the SEQUENCE effect and 90% confidence intervals will be provided.

If the Day 358 and/or Day 190 assessments have no missing data, then the above ANCOVA model will be used for analysis. If missing data is present, a standard multiple imputation with the above ANCOVA model will be used for analysis as described in [Section 4.11.1](#).

The statistical analysis described above will be done on the Per Protocol Set and will be considered primary. The analyses described above will also be repeated for the Full Analysis Set.

In addition, a line graph of the mean  $\pm$  SEM of the percent change from baseline will be provided by treatment sequence for each scheduled time. For fat fraction, the line graph to be generated will consist of the mean  $\pm$  SEM of the absolute change from baseline by treatment sequence for each scheduled time.

Additional analyses may be performed as appropriate.

### **MRI: Other Parameters**

Descriptive statistics will be provided by sequence where sequence represents the treatment sequence from double-blind to open-label (ACE-083  $\rightarrow$  ACE-083 or Placebo  $\rightarrow$  ACE-083) for the comparison of the percent change observed between Day 190 and pre-first treatment baseline (1<sup>st</sup> 6 months) and Day 358 versus Day 190 (2<sup>nd</sup> 6 months).

Additional analyses may be performed as appropriate.

## **4.9. Subgroup Analyses**

Subgroup analyses will be performed for selected efficacy and pharmacodynamics data from the double-blind period of Part 2.

Subgroups consist of the following:

- Ankle Dorsiflexion MRC-MMT Grade {weaker of two sides at Screening}: (3 to 4-; 4 to 4+)
- Ankle Dorsiflexion Screening MRC-MMT Grade of 4- to 4+ on both left and right sides
- Plantar Flexion MRC-MMT Grade {weaker of two sides at Screening}: (4- to 4+; 5- to 5)
- Knee Extension MRC-MMT Grade {weaker of two sides at Screening}: (3+ to 4+; 5- to 5)
- MRC-MMT Grade {weaker of two sides at Screening} for plantar flexion and knee extension
  - Levels are “Both 5- to 5” and “Not both 5- to 5”.
  - “Both 5- to 5” means that the MRC-MMT grade {weaker of two sides} for both plantar flexion and knee extension must both be between 5- and 5.

- “Not both 5- to 5+” means that the MRC-MMT grade {weaker of two sides} for any or both plantar flexion and knee extension should not both be between 5- and 5+. For example, a patient with plantar flexion MRC-MMT grade {weaker of two sides} of a 5- and knee extension MRC-MMT grade {weaker of two sides} of 4 would be classified as “Not both 5- to 5+”.
- Baseline Fat Fraction (%): (< median;  $\geq$  median)
- CMT type: (CMT1, CMTX)
- CMT gene mutation: (CMT1A, not CMT1A)
- Usage of Braces (Yes; No)
  - This information is contained in the individual patient’s CMT disease history
- Dose per Calculated Contractile Muscle Mass (mg/g): (< median;  $\geq$  median)
- Exercise Program: (resistance; no resistance)
  - The “resistance” subgroup includes patients who responded “Yes” to the question “Does the patient have a regular (at least once a week) exercise program?” and reported “Resistance training” as a type of exercise program.
  - The “no resistance” subgroup includes patients who responded “Yes” to the question “Does the patient have a regular (at least once a week) exercise program?” and did not report “Resistance training” as a type of exercise program.
- Baseline CMT-HI Total Score: (< median;  $\geq$  median)
- Activity level (steps/d): (< median;  $\geq$  median)
  - This is defined as the average number of steps per day as measured by the PAMSys™ device over the patient’s study participation in the Part 2 double-blind period, adjusted for overall compliance in using the device to record such activity.
- ADA (ADA +; ADA-)
  - ADA+ means that the patient had positive ADA for ACE-083 at least once during the double-blind period of Part 2
  - ADA- means that the patient did not have positive ADA for ACE-083 at least once during the double-blind period of Part 2

Subgroup analyses will be performed for the following parameters:

- Day 190 average percent change in total muscle volume from baseline
- Day 190 average percent change in calculated contractile muscle volume from baseline
- Day 190 average absolute change in fat fraction from baseline
- Day 190 average percent change in fat fraction from baseline
- Day 190 average percent change in ankle dorsiflexion MVIC from baseline

- Day 190 average absolute change in ankle dorsiflexion MMT-MRC decimal score from baseline
- Day 190 percent change in 6MWD from baseline
- Day 190 percent change in time to complete 10mW/R from baseline
- Day 190 absolute change in CMT-HI total score from baseline
- Day 190 absolute change in CMT-HI foot/ankle strength subscale score from baseline
- Day 190 absolute change in CMT-HI balance subscale score from baseline
- Day 190 absolute change in CMT-HI fatigue subscale score from baseline
- Day 190 absolute change in CMT-HI mobility subscale score from baseline
- Day 190 absolute change in CMT-HI activities subscale score from baseline
- Fall risk reduction during double-blind period

Subgroup analyses will be performed using similar ANCOVA models described in previous sections for each subgroup category provided that the sample size is at least 4. Because of the reduced sample size within each subgroup category, it is not planned to include CMT-TYPE into such models. For each subgroup category, the treatment effect will be estimated and tested using a 0.1 (two-sided) significance level with the corresponding 90% confidence interval. Bar charts of the least squares mean estimates ( $\pm$  SEM) for each of the treatment groups will be provided.

For purposes of this study, findings of subgroup analyses are considered to yield hypothesis generating statements for future study. It is not planned to control the overall type-1 error.

Additional analyses may be performed as appropriate.

Data from multiple imputations described in [Section 4.7.2.2.1](#) will be used.

## 4.10. Safety Data

### 4.10.1. Adverse Events

Adverse events (AEs) will be coded using MedDRA Version 19.1.

All AEs will be listed and will include but not necessarily be limited to the following: verbatim term, MedDRA preferred term, treatment group, severity, relationship to study medication, action taken with respect to study medication, and whether or not the AE is treatment-emergent although not necessarily in that order.

Treatment-emergent AEs (TEAEs) are defined those AEs that start or worsen in intensity on or after the first study drug administration up to the end of the follow-up period (Day 141 [Part 1] / Day 393 [Part 2]). AEs classified as TEAEs will be summarized. Planned summaries include the following (for each muscle group unless otherwise specified):

- Overall summary of TEAEs by treatment group
- Summary of TEAEs by MedDRA System Organ Class and Preferred Term for each treatment group – Number of Patients

- Summary of TEAEs by MedDRA System Organ Class and Preferred Term for each treatment group – Number of Events
- Summary of TEAEs by MedDRA Preferred Term for each treatment group – Number of Patients
- Summary of TEAEs by MedDRA Preferred Term for each treatment group – Number of Events
- Summary of CTCAE Grade 3 or Higher TEAEs by MedDRA System Organ Class and Preferred Term for each treatment group – Number of Patients
- Summary of CTCAE Grade 3 or Higher TEAEs by MedDRA System Organ Class and Preferred Term for each treatment group – Number of Events
- Summary of CTCAE Grade 3 or Higher TEAEs by MedDRA Preferred Term for each treatment group – Number of Patients
- Summary of CTCAE Grade 3 or Higher TEAEs by MedDRA Preferred Term for each treatment group – Number of Events
- Summary of TEAEs possibly or probably related to study drug by MedDRA System Organ Class and Preferred Term for each treatment group – Number of Patients
- Summary of TEAEs possibly or probably related to study drug by MedDRA System Organ Class and Preferred Term for each treatment group – Number of Events
- Summary of TEAEs possibly or probably related to study drug by MedDRA Preferred Term for each treatment group – Number of Patients
- Summary of TEAEs possibly or probably related to study drug by MedDRA Preferred Term for each treatment group – Number of Events
- Summary of TEAEs by MedDRA Preferred Term by CTCAE Grade and Relationship to Drug for each treatment group – Number of Patients
- Summary of TEAEs by MedDRA Preferred Term by CTCAE Grade and Relationship to Drug for each treatment group – Number of Events
- Summary of Serious Adverse Events – Number of Patients

#### 4.10.2. Clinical Laboratory Evaluations

Individual clinical laboratory data will be listed.

The following table lists the planned clinical laboratory assessments:

Type of Assessment	Details
Hematology	Hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell (WBC) count, and WBC differential
Chemistry	AST, ALT, lactate dehydrogenase (LDH) and isoenzymes 1-5, gamma-glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), creatinine, creatine kinase (CK), myoglobin, aldolase, sodium, potassium, glucose, albumin, total bilirubin
Urine	Urinalysis by dipstick analysis (pH, specific gravity, protein, myoglobin, glucose, ketones, blood, leukocyte esterase, and nitrite)

In addition to the tests listed below, a urine pregnancy test is performed on all females of childbearing potential according to scheduled times listed in the protocol.

Descriptive statistics of raw data and change from baseline data will be provided by treatment group for each scheduled time.

Plots of mean  $\pm$  SEM will be provided for raw data and change from baseline data for the following selected laboratory data: hemoglobin, glucose, aldolase, blood urea nitrogen (BUN), creatinine kinase (CK), creatinine, and myoglobin.

Additional analyses may be performed as appropriate.

#### Vital Signs

Individual vital sign data will be listed.

Vital sign parameters consist of weight, heart rate, systolic and diastolic blood pressure.

Descriptive statistics will be provided for raw data and absolute change from baseline by scheduled time for each treatment group. Post-dose recheck values will not be used for calculation of descriptive statistics.

Additional analyses may be performed as appropriate.

#### Electrocardiogram

Individual twelve-lead electrocardiogram (ECG) data will be listed and consists of the following: heart rate, PR, QRS, QT, and QTcB (Bazett correction).

Descriptive statistics will be provided for raw data and absolute change from baseline by scheduled time for each treatment group. Post-dose recheck values will not be used for calculation of descriptive statistics.

Additional analyses may be performed as appropriate.

#### 4.10.3. Anti-Drug Antibodies

Individual anti-drug antibody (ADA) data will be listed.

The frequency and percentage of ADA responses will be summarized by treatment group and scheduled time.

The frequency and percentage of all patients testing positive for ADA at any point during the study (i.e. ADA prevalence) will be summarized by treatment group. This will include summaries of the prevalence ADA confirmed as “Anti-ACE-083” or “Anti-FST315”. In addition, for ACE-083 ADA, a summary of the prevalence of ACE-083 ADA and titer summary (median, minimum, and maximum value) will be provided by scheduled visit and antibody follow-up visit (as applicable).

Additional analyses may be performed as appropriate.

#### **4.10.4. Other Safety Data**

Not applicable.

### **4.11. Missing Data Handling**

#### **4.11.1. Efficacy and Pharmacodynamic Data**

Statistical analyses of selected efficacy and pharmacodynamics data will make use of standard multiple imputation (MI). For missing data points, the monotonic or fully conditional specification (FCS) regression is used to fill in the missing data points depending on the missing data pattern (monotone or arbitrary) in the order of time points using values calculated at the previous time points. This analysis involves the following steps:

1. The missing data are filled “m” times (e.g. m = 20) in order to generate “m” complete datasets using the monotonic or FCS regression model.
2. Each of the “m” complete datasets are analyzed using the analysis methods specified in [Section 4.7.2.2](#) or [Section 4.8.2.2](#)
3. The results from the “m” complete datasets are combined for the inference.

The above assumes that any missing data are Missing At Random (MAR). The seeds to be used to perform the multiple imputations are listed in [Section 6](#).

#### **4.11.2. Safety Data**

As a general principle, no imputation of missing data will be done unless otherwise specified. Exceptions are the start and stop dates of AEs with rules listed below. The imputed dates will be used to determine whether an AE is/is not treatment emergent. Listings of the AEs will present the actual partial dates; imputed dates will not be shown.

##### **4.11.2.1. Missing Dates for Adverse Event**

Imputing partial AE start dates:

- a. If the year is unknown, the date will not be imputed and will be assigned a missing value.
- b. If the month is unknown, then:

1. If the year matches the first dose date, then impute the month and day of the first dose date.
2. Otherwise, assign January.
- c. If the day is unknown, then:
  3. If the month and year match the first AE stop month and year and AE stop day is not missing, then impute the start day as the stop day.
  4. Otherwise impute start day using the last day of the start month.

Imputing partial AE stop dates:

- a. If the year is unknown, the date will not be imputed and will be assigned a missing value.
- b. If the month is unknown, then assign December or date of last participation in the study, whichever is earlier.
- c. If the day is unknown, then assign the last day of the month.

## 4.12. Pharmacokinetic Data

Pharmacokinetic data will be summarized under the direction of the Acceleron Clinical Pharmacologist and summaries will be outlined in a separate analysis plan.

## 5. MODIFICATIONS FROM THE STATISTICAL SECTION OF THE PROTOCOL

The following modifications from the statistical section of the protocol have been implemented in the statistical analysis plan:

- For statistical analyses where confidence intervals for the least-squares mean are provided, the 95% confidence interval will be provided in addition to the 90% confidence interval.
- The “Safety Population” is now called the “Safety Set”.
- The “Per Protocol Set” definition was redefined to be what is listed in this document..
- The last observation carried forward approach is not being performed in the statistical analyses. Standard multiple imputation will be performed to assess the impact of missing data on the observed data.
- For statistical analyses of data to compare the effects of ACE-083 administered in the open-label extension versus the treatment received in the double-blind period of Part 2, the 90% confidence interval will be provided in place of the 95% confidence interval.

## 6. PROGRAMMING SPECIFICATIONS

### Seed to Use for Multiple Imputations of Missing Data

The seed to be used for multiple imputations of ankle dorsiflexion MVIC data is 1111.

The seed to be used for multiple imputations of functional data is 2222.

The seed to be used for multiple imputations of Berg balance data is 3333.

The seed to be used for multiple imputations of CMT-HI data is 4444.

The seed to be used for multiple imputations of CMTES2 data is 5555.

The seed to be used for multiple imputations of MRI data is 6666.

### Representation of Scheduled Times in Listings

Because data for this study comes from multiple sources, such information will be standardized in the listings.

The standardization is outlined below:

Lab (MRL), CMT-HI, eCRF (long)	eCRF (short)	MRI	Mapping for Tables and Listings	Plots
Screening Day -28 to Day -7	SCN		S1D-28	-28
Dose 1 Day 1	DOSE1D1	DAY 1	D1D1	1
Dose 1 Day 2	DOSE1D2		D1D2	2
Dose 1 Day 8	DOSE1D8		D1D8	8
Dose 2 Day 22	DOSE2D22		D2D22	22
Dose 3 Day 43	DOSE3D43	DAY 43	D3D43	43
Dose 4 Day 64	DOSE4D64		D4D64	64
Dose 5 Day 85	DOSE5D85		D5D85	85
Follow-Up Day 106/ET <sup>a</sup>	ET	DAY 106	F1D106_ET	106
Dose 6 Day 106 <sup>b</sup>	DOSE6D106	DAY 106	D6D106	106
Dose 7 Day 127 <sup>b</sup>	DOSE7D127		D7D127	127
Follow-Up Day 141 <sup>a</sup>	FUP	DAY 141	F2D141	141
Dose 8 Day 148 <sup>b</sup>	DOSE8D148		D8D148	148
Dose 9 Day 169 <sup>b</sup>	DOSE9D169		D9D169	169
Dose 10 Day 190 <sup>b</sup>	DOSE10D190	DAY 190	D10D190	190
Dose 11 Day 211 <sup>b</sup>	DOSE11D211		D11D211	211
Dose 12 Day 232 <sup>b</sup>	DOSE12D232		D12D232	232
Dose 13 Day 253 <sup>b</sup>	DOSE13D253		D13D253	253
Dose 14 Day 274 <sup>b</sup>	DOSE14D274		D14D274	274

Lab (MRL), CMT-HI, eCRF (long)	eCRF (short)	MRI	Mapping for Tables and Listings	Plots
Dose 15 Day 295 <sup>b</sup>	DOSE15D295	DAY 295	D15D295	295
Dose 16 Day 316 <sup>b</sup>	DOSE16D316		D16D316	316
Dose 17 Day 337 <sup>b</sup>	DOSE17D337		D17D337	337
Day 358/ET <sup>b</sup>	ET	DAY 358	F1D358_ET	358
Follow-Up Day 393 <sup>b</sup>	FUP	DAY 393	F2D393	393

<sup>a</sup> Applies to Part 1; <sup>b</sup> Applies to Part 2

### Partial Date of Birth Entries

In the event that a patient does not have a complete date of birth present in the clinical database, the date of birth will be interpolated as follows:

- If the date of birth contains the month and year of birth but no value of day (i.e. day is missing or has value “UNK”), the value of day will be imputed to the 1st for purposes of any calculations that involve the complete birthdate of the patient (i.e. age).
- If the date of birth only contains the year but no value of month and day (i.e. “UNK-UNK-yyyy”), the birthdate will be imputed to “01-Jan-yyyy” where “yyyy” refers to the year that is reported for that patient for purposes of any calculations that involve the complete birthdate of the patient (i.e. age).

### Classification of AEs as TEAEs

In general, the start of reporting of adverse events for an individual patient starts after receiving the first dose of study drug. However:

- If both the AE start and stop date exist and are before the first dose date of study drug, the AE will be classified as a pre-treatment AE and not considered treatment emergent.
- If the AE start date is on or after the first dose date of study drug, the AE will be considered a TEAE.
- If the AE start date is before the first dose date of study drug and the AE stop date is after the first dose of study drug and the AE worsened in intensity, the AE will be considered a TEAE.
- If the AE start date is missing and the stop date is before the first dose of study drug, the AE will be not be considered a TEAE.
- If the AE start date is missing and the stop date is after the first dose of study drug, the AE will be considered a TEAE.
- If the AE start and stop dates are missing, the AE will be considered a TEAE.

### Patients that Discontinue Early

For patients that discontinue early, end-of-treatment and follow-up assessments will be completed and analyzed as such.

**7. APPENDICES**

## APPENDIX 1. SCHEDULE OF EVENTS

## Part 1

	Screening Period	Treatment Period						Follow-Up Period	
		Day 1 <sup>1</sup>		Day 8 <sup>1</sup> (±1d)	Day 22 <sup>1</sup> (±3d)	Day 43 <sup>1</sup> (±3d)	Day 64 <sup>1</sup> (±3d)	Day 85 <sup>1</sup> (±3d)	Day 106/ET <sup>2</sup> (±3d)
	Day -28 to Day -7								
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Urine pregnancy test <sup>3</sup>		X		X	X	X	X		
Medical history	X	X							
MRT assessment (MRC) <sup>15</sup>	X								
Genetic testing <sup>17</sup>	X								
Physical examination <sup>4</sup>	X	X		X		X		X	
Injection site examination <sup>5</sup>			X	X	X	X	X	X	
Vital signs <sup>6</sup>	X	X	X	X	X	X	X	X	
Hematology <sup>7</sup>	X	X		X	X	X	X	X	
Chemistry <sup>7</sup>	X	X		X	X	X	X	X	
Urinalysis <sup>7</sup>	X	X			X	X		X	
Biomarkers <sup>7</sup>	X	X		X	X	X		X	X
Anti-drug antibody			X	X	X	X	X	X	X <sup>8</sup>
Serum PK <sup>9</sup>		0, 1, 2, 4, 6 h	X	X	X	X	0, 1, 2, 4, 6 h	X	X
ECG (12 lead)		X							
Bilateral MRI <sup>10</sup>		X			X			X	X
Timed function tests <sup>11</sup>	X	X		X	X	X	X	X	X
Balance and gait tests <sup>12</sup>	X	X			X			X	X
Strength test <sup>13</sup>	X	X	X	X	X	X	X	X	X
CMTES2 <sup>14</sup>	X	X			X			X	X
CMT-HI <sup>14</sup>	X				X			X	X
Monitoring of concomitant medications	X	X	X	X	X	X	X	X	X
Monitoring of adverse events		X	X	X	X	X	X	X	X
Study drug administration <sup>16</sup>		X		X	X	X	X		

<sup>1</sup> Study procedures must be done prior to administration of study drug. Reference the Study Manual for the order of study procedures. Laboratory samples and functional/strength assessments may be collected up to 24 hours prior to administration of study drug. All visit-day windows should be considered relative to the date of the previous dose of ACE-083. Actual visit days (e.g., day 1, day 8, day 22) may be different than planned due to windows on visits and potential dosing delays.

<sup>2</sup> Patients who discontinue prior to the Day 106/ET visit should complete the Day 106/ET visit at the time of discontinuation and return for the remaining follow-up period visit. If an MRI has been completed within 4 weeks of discontinuation, it does not need to be repeated as part of the Day 106/ET visit procedures.

<sup>3</sup> Pregnancy test for women of childbearing potential to be performed and negative result confirmed before dosing.

<sup>4</sup> Full physical examination (skin, head, eyes, ears, nose, throat and neck, lymph nodes, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological), at screening and Day 106/ET; limited physical examination (skin, cardiovascular, respiratory, musculoskeletal, and neurological assessments) for Days 1, 22, 64.

<sup>5</sup> Injection site examination including but not limited to evaluating erythema, pain, bruising, bleeding, and other signs of discomfort or skin reaction to be completed at least 30 minutes after injection.

<sup>6</sup> Vital signs (weight, heart rate, systolic and diastolic blood pressure) must be taken prior to administration of study drug on dosing days. Height is collected only at screening.

<sup>7</sup> Including but not limited to: insulin-like growth factor-1 (IGF-1), serum C-terminal collagen crosslinks (CTX)

<sup>8</sup> If a patient has a positive ADA result at Day 141, the patient will be asked to return to the clinical site for additional follow-up approximately every 3 months until a negative or stable result is obtained.

<sup>9</sup> PK samples on dosing day have a ±15 minute window for post-dose sample collection. Pre-dose samples may be collected up to 4 hours prior to dosing.

<sup>10</sup> MRI assessments should be completed within 5 days prior to the scheduled dose administration, with the exception of the Day 1 MRI which may be completed within 14 days prior to Day 1 visit. MRI assessments during the follow-up period (Day 106/ET and Day 141) have a ± 5 day window.

<sup>11</sup> 10-meter walk/run, 6-minute walk. Tests may be performed within 3 days prior to Day 1 visit.

<sup>12</sup> Gait parameters, Berg balance scale. Tests may be performed within 3 days prior to Day 1 visit.

<sup>13</sup> Maximum voluntary isometric contraction testing will be conducted using a handheld dynamometer. Both sides will be tested (right and left).

<sup>14</sup> CMTES2 to be assessed by investigator; CMT-HI to be completed by patient

<sup>15</sup> Includes knee extension, ankle dorsiflexion, and ankle plantarflexion

<sup>16</sup> Study drug administration should occur within 21 days (± 3 days) of the previous dose.

<sup>17</sup> To be performed at screening if patient has not already had testing performed previously.

## Part 2

	Screening	Double-Blind, Placebo-Controlled										Open-Label				ET <sup>1</sup>	EOS	
		1	2	3	4	5	6	7	8	9	10	11, 12, 13, 14	15	16	17			
Dose(s)	-	1 <sup>2</sup>	8 (±1d)	22 <sup>1</sup> (±1d)	43 <sup>1</sup> (±3d)	64 <sup>1</sup> (±3d)	85 <sup>1</sup> (±3d)	106 <sup>1</sup> (±3d)	127 <sup>1</sup> (±3d)	148 <sup>1</sup> (±3d)	169 <sup>1</sup> (±3d)	190 <sup>1</sup> (±3d)	(211, 232, 253, 274) <sup>1</sup> (±3d)	295 <sup>1</sup> (±3d)	316 <sup>1</sup> (±3d)	337 <sup>1</sup> (±3d)	358 (±3d)	393 (±3d)
Informed consent	X																	
Inclusion/exclusion criteria	X																	
Urine pregnancy test <sup>3</sup>		X		X	X	X	X	X	X	X	X	X	X	X	X			
Medical history	X	X																
MMT assessment (MRC) <sup>4</sup>	X											X		X		X	X	
Genetic testing <sup>5</sup>	X																	
Full physical examination <sup>6</sup>	X								X			X		X		X	X	
Limited physical examination <sup>7</sup>		X		X		X			X	X	X		X		X	X		
Injection site examination <sup>8</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs <sup>9</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology <sup>10</sup>	X	X		X	X	X	X	X		X		X	X	X	X	X	X	
Chemistry <sup>10</sup>	X	X		X	X	X	X	X		X		X	X	X	X	X	X	
Urinalysis <sup>10</sup>	X	X			X	X	X	X		X		X	X	X		X	X	
Biomarkers <sup>11</sup>	X	X		X	X	X	X	X		X		X	X	X	X	X	X	
Anti-drug antibody		X	X	X	X	X	X	X		X		X	X	X	X	X	X <sup>12</sup>	
Serum PK <sup>13</sup>		0, 1, 2, 4, 6 h	X				0, 1, 2, 4, 6 h					X		X		X	X	
ECG (12 lead)	X	4 h <sup>14</sup>					4 h <sup>14</sup>											
Bilateral MRI <sup>15</sup>		X			X			X				X		X		X	X	
Timed function tests <sup>16</sup>	X	X		X	X	X	X	X		X		X	X	X	X	X	X	
Balance and gait tests <sup>17</sup>	X	X						X			X		X			X	X	
Strength tests <sup>18</sup>	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	
CMTES2 <sup>19</sup>	X	X						X			X		X		X	X	X	
CMT-HI <sup>19</sup>	X				X			X			X		X		X	X	X	
CMAP of tibialis anterior	X										X						X	

	Screening	Double-Blind, Placebo-Controlled										Open-Label				ET <sup>1</sup>	EOS	
		1	2	3	4	5	6	7	8	9	10	11, 12, 13, 14	15	16	17			
Dose(s)	-	1 <sup>2</sup>	8 (±1d)	22 <sup>1</sup> (±1d)	43 <sup>1</sup> (±3d)	64 <sup>1</sup> (±3d)	85 <sup>1</sup> (±3d)	106 <sup>1</sup> (±3d)	127 <sup>1</sup> (±3d)	148 <sup>1</sup> (±3d)	169 <sup>1</sup> (±3d)	190 <sup>1</sup> (±3d)	(211, 232, 253, 274) <sup>1</sup> (±3d)	295 <sup>1</sup> (±3d)	316 <sup>1</sup> (±3d)	337 <sup>1</sup> (±3d)	358 (±3d)	393 (±3d)
Monitoring of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Monitoring of adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization <sup>20</sup>		X																
Distribution of PAMSys™ Device <sup>21</sup>	X																	
Study drug administration <sup>22</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

<sup>1</sup> Study procedures must be done prior to administration of study drug. Reference the Study Manual for the order of study procedures. Laboratory samples and functional/strength assessments may be collected up to 24 hours prior to administration of study drug. All visit-day windows should be considered relative to the date of the previous dose of ACE-083. Actual visit days (e.g., Day 1, Day 8, Day 22) may be different than planned due to windows on visits and potential dosing delays.

<sup>2</sup> Patients who discontinue prior to the Day 358/ET visit should complete the Day 358/ET visit at the time of discontinuation and return for the remaining follow-up period visit. If an MRI has been completed within 4 weeks of discontinuation, it does not need to be repeated as part of the Day 358/ET visit procedures.

<sup>3</sup> Pregnancy test for women of childbearing potential to be performed and negative result confirmed before dosing.

<sup>4</sup> Includes knee extension, ankle dorsiflexion, and ankle plantarflexion.

<sup>5</sup> To be performed at screening if patient has not already had testing performed previously.

<sup>6</sup> Full physical examination includes skin, head, eyes, nose, throat and neck, lymph nodes, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological.

<sup>7</sup> Limited physical examination includes skin, cardiovascular, respiratory, musculoskeletal and neurological assessments.

<sup>8</sup> Injection site examination including but not limited to evaluating erythema, pain, bruising, bleeding, and other signs of discomfort or skin reaction to be completed at least 30 minutes after injection.

<sup>9</sup> Vital signs (weight, heart rate, systolic and diastolic blood pressure) must be taken prior to administration of study drug on dosing days. Height is collected only at screening.

<sup>10</sup> Tests defined in Appendix 2, Table 7.

<sup>11</sup> Including but not limited to: insulin-like growth factor-1 (IGF-1) and serum C-terminal collagen crosslinks (CTX).

<sup>12</sup> If a patient has a positive ADA result at Day 393/EOS, the patient will be asked to return to the clinical site for additional follow-up approximately every 3 months until a negative or stable result is obtained.

<sup>13</sup> PK samples on dosing day have a ±15 minute window for post-dose sample collection. Pre-dose samples may be collected up to 4 hours prior to dosing.

<sup>14</sup> ECG is to be conducted within 1 hour of the 4h PK sample.

<sup>15</sup> MRI assessments should be completed within 5 days prior to the scheduled dose administration, with the exception of the Day 1 MRI which may be completed within 14 days prior to Day 1 visit. MRI assessments during the follow-up period (Day 358/ET and Day 393/EOS) have a ± 5 day window.

<sup>16</sup> 10-meter walk/run, 6-minute walk. Tests may be performed within 3 days prior to Day 1 visit.

<sup>17</sup> Gait parameters, Berg balance scale. Tests may be performed within 3 days prior to Day 1 visit.

<sup>18</sup> Maximum voluntary isometric contraction testing will be conducted using a handheld dynamometer. Both sides will be tested (right and left).

<sup>19</sup> CMTES2 to be assessed by investigator; CMT-HI to be completed by patient

<sup>20</sup> Randomization should occur within 24 hours of Day 1 dose.

<sup>21</sup> PAMSys™ device is a physical activity monitoring system that will be worn by the patient for the duration of the study.

<sup>22</sup> Study drug administration should occur within 21 days (± 3 days) of the previous dose.