Official Title: 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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Protocol A083-03

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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ORIGINAL PROTOCOL DATE: 27 October 2016

AMENDMENT 01 DATE: 01 March 2018

AMENDMENT 02 DATE: 23 October 2018

AMENDMENT 03 DATE: 09 January 2019

Signature Page

Acceleron Pharma Approval

Signature: [redacted] **Date:** 10 Jan 2019

Name (print): [redacted]

Investigator Agreement: I have read the protocol and agree to conduct the study as outlined in the protocol. The study will be conducted in accordance to current United States Food and Drug Administration (FDA) regulations, International Council of Harmonization (ICH) Guidelines, Good Clinical Practices (GCP), the Declaration of Helsinki, and local ethical and legal requirements.

Signature: _____ **Date:** _____

Name (print): _____

Institution Name and Address:

_____

_____

_____

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Medical Monitor	[redacted]	[redacted]
Pharmacovigilance	[redacted]	[redacted]
Pharmacovigilance	Medpace Clinical Safety	Medpace SAE Hotline-USA Tel: 866-336-0930 or 800-730-5779 ext. 2999 Fax: 866-336-5320 medpace-safetynotification@medpace.com Medpace SAE Hotline-Europe Tel: 49 89 89 55 718 44 Fax: 49 89 89 55 718 104 medpace-safetynotification@medpace.com

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ALS	Amyotrophic lateral sclerosis
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
CK	Creatine kinase
CMAP	Compound muscle action potential
CMT	Charcot-Marie-Tooth
CMT-HI	Charcot-Marie-Tooth health index
CMTES2	Charcot-Marie-Tooth examination score version 2
CRF	Case report form
CRO	Contract research organization
CTX	C-terminal collagen crosslinks
DLT	Dose limiting toxicity
ECG	Electrocardiogram
EMG	Electromyography
FDA	Food and Drug Administration
FST	Follistatin
GCP	Good clinical practice
GDF8	Growth and differentiation factor 8
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent ethics committee
IGF-1	Insulin-like growth factor-1
IgG2	Immunoglobulin G2
IM	Intramuscular
IP	Investigational product
IRB	Institutional review board

Abbreviation or Specialist Term	Explanation
MMT	Manual muscle testing
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MVIC	Maximum voluntary isometric contraction
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PD	Pharmacodynamic
PK	Pharmacokinetic
QoL	Quality of life
RF	Rectus femoris
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SRM	Standardized response mean
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
TA	Tibialis anterior
TGF-β	Transforming growth factor beta
ULN	Upper limit of normal

4. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Acceleron Pharma Inc., 128 Sidney Street, Cambridge, MA 02139

Name of Investigational Product: ACE-083

Name of Active Ingredient: ACE-083 is a recombinant fusion protein consisting of a modified form of human follistatin linked to a human IgG2 Fc domain.

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

Study Centers: Approximately 20 centers

Phase of Development: 2

Objectives

Part 1

Primary:

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

Secondary:

- To determine the recommended dose level of ACE-083 for Part 2
- To evaluate change in muscle volume and intramuscular fat fraction of the injected muscle
- To evaluate change 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

Exploratory:

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

Part 2

Primary:

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

Secondary:

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

Exploratory:

- 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

Endpoints

Part 1

Primary:

- Presence and nature of adverse events (AE) including injection site reactions and changes in clinical laboratory parameters

Secondary:

- Percent change from baseline in muscle volume of injected muscle by magnetic resonance imaging (MRI)
- Percent and absolute change from baseline in intramuscular fat fraction of injected muscle by MRI
- Percent change from baseline in strength measurements by maximum voluntary isometric contraction of ankle dorsiflexion measured by quantitative muscle testing
- Pharmacokinetic (PK) parameters for ACE-083 serum concentrations over time

- Percent change from baseline in functional assessments: 10-meter walk/run, 6-minute walk test, Berg balance scale
- Percent and absolute change from baseline in CMT examination score version 2 (CMTES2) and CMT-health index (CMT-HI)

Exploratory:

- Percent and absolute change from baseline in gait parameters
- Percent and absolute change from baseline in biomarkers

Part 2

Primary:

- Percent change from baseline in muscle volume of injected muscle by MRI

Secondary:

- Percent and absolute change from baseline in intramuscular fat fraction of the injected muscle by MRI
- Percent change from baseline in strength measurements by maximum voluntary isometric contraction of ankle dorsiflexion measured by quantitative muscle testing
- Percent change from baseline in functional assessments: 10-meter walk/run, 6-minute walk test, Berg balance scale
- Percent and absolute change from baseline in CMTES2 and CMT-HI
- Presence and nature of AEs including injection site reactions and changes in clinical laboratory parameters
- Pharmacokinetic parameters for ACE-083 serum concentrations over time

Exploratory:

- Percent and absolute change from baseline in biomarkers
- Percent and absolute change from baseline in TA CMAP amplitude
- Percent and absolute change from baseline in gait parameters
- Activity level and falls (PamSys™ wearable device)
- Percent change from baseline in the 100-meter timed test

Methodology

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

placebo-controlled. Patients who have signed the informed consent form (ICF) and meet the eligibility criteria will be enrolled into the study.

Study Design

Part 1: N=Up to 18 (non-randomized, open-label, dose-escalation)

Cohort	ACE-083 Dose per Muscle[a]	ACE-083 n
1	150 mg	6
2	TBD up to 200 mg[b]	6
3	TBD up to 250 mg[b]	6

Part 2: N=Up to 40 (6-month, randomized, double-blind, placebo-controlled, with 6-month open-label extension)

	6-month placebo controlled		6-month open-label extension
ACE-083 Dose per Muscle[a]	ACE-083 n	Placebo n	ACE-083 n
TBD up to 250 mg[b]	20	20	40

[a] Administered bilaterally by injection into the tibialis anterior muscle once every 3 weeks
[b] Dose level to be based on recommendations from the Safety Review Team (SRT)

Part 1 (non-randomized, open-label, dose-escalation)

Part 1 will consist of up to 3 cohorts of 6 patients each and will evaluate multiple ascending dose levels of ACE-083 administered bilaterally once every 3 weeks for up to 5 doses in the tibialis anterior (TA) muscle. Patients in each cohort will be enrolled in a 4-week screening period before beginning treatment.

For Cohort 1, the dose level will be 150 mg/muscle administered bilaterally.

For Cohort 2, the dose level will be based on review of safety data and recommendations made by the Safety Review Team (SRT). The planned dose level for Cohort 2 is 200 mg/muscle administered bilaterally.

For Cohort 3, the decision to enroll patients and the dose level will be based on recommendations of the SRT following review of safety and, as necessary, imaging data for prior cohorts. The maximum possible dose level for Cohort is 250 mg/muscle administered bilaterally.

Part 2 (randomized, double-blind, placebo-controlled)

Prior to the initiation of Part 2, a review of safety and efficacy data from Part 1 will be conducted by the SRT to determine the recommended dose level (maximum 250 mg/muscle). A total of up to 40 new patients may be enrolled and randomized (1:1 randomization) to receive either ACE-083 (n=20) or placebo (n=20) bilaterally by injection into both TA muscles. Patients will receive blinded study drug once every 3 weeks for approximately 6 months (9 doses).

Patients who complete the double-blind treatment period, will immediately roll over to open-label treatment with ACE-083, receiving the same dose of active drug, bilaterally in the TA muscle, once every 3 weeks for approximately 6-months (8 doses). In Part 2, the SRT will periodically review blinded safety data for each muscle treated.

Number of Patients (planned)

Up to 18 patients will be enrolled in Part 1 of the study (dose-escalation, non-randomized, open-label) and up to 40 patients (20 active, 20 placebo) will be enrolled in Part 2 (randomized, double-blind, placebo-controlled, with open-label extension) for a total of up to 58 patients. Up to 40 patients participating in the double-blind treatment period of Part 2 will participate in the open-label extension all of which (including those on placebo during the double-blind treatment period) will receive the same dose of ACE-083 administered during the double-blind treatment period.

Diagnosis and Main Criteria for Eligibility

Inclusion Criteria:

1. Age ≥ 18 years
2. Diagnosis of CMT1 or CMTX confirmed by:
   a. Clinical presentation and electrodiagnostics
   b. Genetically-confirmed CMT1 or CMTX (Appendix 3) for the patient or first-degree relative
3. Part 1:
   a. Six-minute walk distance (6MWD) of at least 150 meters (without a brace or walker)
   b. Independent ambulation for at least 10 meters, without a brace
   c. Left and right ankle plantar flexion MRC grade 4+ to 5, inclusive

   Part 2:
   a. 6MWD ≥ 150 and ≤ 500 meters (without a brace or walker); a maximum of 20% of enrolled patients with 6MWD ≥ 450 meters will be included
   b. Left and right ankle plantar flexion MRC grade 4- to 5, inclusive

4. Left and right ankle dorsiflexion Medical Research Council (MRC) manual muscle testing (MMT) grade 3 to 4+, inclusive (Appendix 4). No more than 12 of the 40 enrolled subjects may have a grade of 3 or 3+ on one or both sides.
5. Females of childbearing potential (defined as sexually mature women who have not undergone hysterectomy or bilateral oophorectomy, or are not naturally postmenopausal ≥ 24 consecutive months) must have negative urine pregnancy test prior to enrollment and use highly effective birth control methods (abstinence, oral contraceptives, barrier method with spermicide, or surgical sterilization) during study participation and for 8 weeks following the last dose of ACE-083. Hormonal birth control use must be stable for at least 14 days prior to Day 1. Males must agree to use a condom during any sexual contact with females of childbearing potential while participating in the study and for 8 weeks following the last dose of ACE-083, even if he has undergone a successful vasectomy. Patients must be counseled concerning measures to be used to prevent pregnancy prior to the first dose of ACE-083.
6. Ability to adhere to the study visit schedule/procedures, and to understand and comply with protocol requirements
7. Signed written informed consent

Exclusion Criteria:

1. Current/active malignancy (e.g., remission less than 5 years' duration), with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or ≤ 2 squamous cell carcinomas of the skin
2. Symptomatic cardiopulmonary disease, significant functional impairment, significant orthopedic or neuropathic pain, or other co-morbidities that in the opinion of the investigator would limit a patient's ability to complete strength and/or functional assessments on study
3. Type 1 or type 2 diabetes mellitus
4. Thyroid disorder unless condition is stable with no change in treatment for at least 4 weeks before the first dose and no expected change for duration of study
5. Renal impairment (serum creatinine ≥ 2 times the upper limit of normal [ULN])
6. Aspartate transaminase (AST) and/or alanine transaminase (ALT) ≥ 3 times ULN
7. Increased risk of bleeding (i.e., due to hemophilia, platelet disorders, or use of any anticoagulation/platelet modifying therapies up to 2 weeks prior to Study Day 1 and for duration of study; single agent low dose aspirin [≤ 100 mg daily] is permitted)
8. Severe deformity or ankle fixation that would sufficiently limit passive range of motion to affect assessment of dorsiflexion strength
9. Major surgery within 4 weeks prior to Study Day 1

10. Chronic pharmacologic doses of systemic corticosteroids (≥ 2 weeks) within 4 weeks before Study Day 1 and for duration of study; intra-articular/topical/inhaled/intranasal physiologic doses of systemic corticosteroids are permitted
11. Androgens, growth hormone, insulin or oral hormone replacement therapy within 6 months before Study Day 1 and for duration of study; topical physiologic androgen replacement is permitted
12. Any change in medications potentially affecting muscle strength or function within 4 weeks of Study Day 1 and for duration of study (e.g., creatinine, CoQ10, systemic beta-adrenergic agonists)
13. Previous exposure to any investigational agent potentially affecting muscle volume, muscle strength, or muscle or nerve function within 5 half-lives of last dose plus an additional 8-week washout period (or 12 weeks prior to Study Day 1 if half-life is unknown)
14. Any previous or current exposure to ACE-083
15. Significant change in physical activity or exercise (e.g., significant increase or decrease in intensity or frequency) within 8 weeks before Study Day 1 or inability to maintain the baseline level of physical activity throughout the study
16. Any condition that would prevent MRI scanning or compromise the ability to obtain a clear and interpretable scan of the lower leg, as applicable (e.g., knee/hip replacement metallic implants)
17. Known active substance abuse, including alcohol
18. History of sensitivity to protein pharmaceuticals
19. Female that is lactating/breast-feeding

Investigational Product, Dosage, and Mode of Administration

ACE-083 drug product is provided as a lyophilized powder contained in stoppered and sealed glass vials. After reconstitution with 1.2 mL of sterile water, the ACE-083 drug product solution for injection has a concentration of 50 mg/mL. The nominal strength of each vial is 50 mg of ACE-083.

Using electromyography (EMG) or ultrasound guidance, each dose of ACE-083 will be administered into the non-tendinous portion of the TA as a series of up to 4 equal-volume injections. The use of EMG or ultrasound guidance will ensure that viable muscle is present at the injection site. If the degree of atrophy or fibro-fatty infiltration poses administration challenges, injections of ACE-083 should be distributed approximately 2 cm apart into viable muscle. Injection site locations as well as measures to avoid adjacent nerves and blood vessels and prevent intravascular injection are outlined in the Investigational Product (IP) Handling Guide.

The maximum absolute dose and schedule for both Parts 1 and 2 is 250 mg/muscle administered bilaterally by injection into the left and right TA muscles every 3 weeks for up to 5 doses (actual dose levels to be based on recommendations of the SRT).

Individual Dose Modification Rules

For an adverse event (AE, including injection site reaction) of grade 3 or higher, regardless of relationship to study drug, treatment will be paused and the patient will be monitored weekly. At the discretion of the investigator, dosing may resume upon resolution of the AE to ≤ grade 1 or baseline and may be reduced to the previously tolerated dose (i.e. from 240 to 200 mg or from 200 to 150 mg). Dose will not be reduced to below 100 mg (Part 1) or 150 mg (Part 2).

Duration of Treatment

Study duration for a patient enrolled in Part 1 will be approximately 24 weeks, including a 4-week screening period, a 12-week treatment period, and an 8-week follow-up period after the last dose. Study duration for a patient enrolled in Part 2 will be approximately 15 months, including a 4-week screening period, a 12-month treatment period (6-month double-blind, placebo controlled and a 6-month open-label extension), and an 8-week follow-up period after the last dose. If a patient has a positive anti-drug antibody (ADA) result at the last visit, the patient will be asked to return for additional ADA testing approximately every 3 months, until a negative result is obtained or the result is considered to be stabilized.

Reference Therapy, Dosage, and Mode of Administration

The placebo (control agent) to be used in Part 2 of this study will be sterile normal saline (0.9% sodium chloride for injection). Sterile normal saline will be supplied by the investigational site's pharmacist. The manufacturer's directions for saline storage and handling are to be followed, as are standard clinical practices for ensuring sterility. Saline-filled syringes will be prepared by unblinded study personnel and provided to blinded study personnel for administration.

Placebo will be administered using EMG or ultrasound guidance into the non-tendinous portion of the TA as a series of up to 4 equal-volume injections. If the degree of atrophy or fibro-fatty infiltration poses administration challenges, injections of placebo should be distributed approximately 2 cm apart into viable muscle. Injection site locations as well as measures to avoid adjacent nerves and blood vessels and prevent intravascular injection are outlined in the IP Handling Guide.

Safety Assessment:

Dose-Limiting Toxicity (DLT) Definition:

- A serious adverse event (SAE), possibly or probably related to study drug

OR

- An adverse event (AE), injection site reaction, laboratory parameter abnormality, or vital sign abnormality, possibly or probably related to study drug, and either grade ≥ 3 (National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE], current version) or grade ≥ 2 and considered clinically significant.

Part 1 Dose Escalation Stopping Rules (under SRT review):

Dosing at current levels will continue unless the following condition occurs:

- ≥ 2 DLTs of the same character in a cohort

Safety Review Team:

An SRT, comprised at minimum of a principal investigator, medical monitor, and an independent neuromuscular specialist, will meet to review safety and, as needed, imaging data, for each cohort. The review will include all collected safety data (and, as necessary, imaging data) when at least 4 patients in a cohort have completed at least their Day 22 visit. For both parts of the study, the SRT safety data will include, but not be limited to, AEs, laboratory results (including hematology, chemistry, and urinalysis) and vital signs data to assess for DLTs and overall safety. The SRT may request review of additional data collected in currently enrolled patients.

Based on review of relevant data, the SRT will make one or more of the following recommendations:

- Continue enrollment of remaining patients in the current cohort at the current dose level
- Open next cohort in Part 1 or open Part 2 of the study at a recommended dose (higher or lower dose level)
- Discontinue one or more cohorts in Part 1, or the study as a whole

SRT recommendations for dose escalation in Part 1 will be based in part upon the dose escalation stopping rules. If a stopping rule is met, a lower intermediate dose may be recommended or the previous dose level will be considered the maximally tolerated dose (MTD). The SRT may also recommend no further enrollment in the presence of AEs that do not meet dose stopping rules if the nature of these AEs is deemed a significant risk to patients in a given cohort.

For Part 2, the SRT will periodically review blinded preliminary safety data. Further details on the role of the SRT during Part 2 are included in the SRT Guidelines.

Assessments for Evaluation:

Safety: AEs, injection site reactions, concomitant medications, clinical laboratory tests (including hematology, chemistry, and ADA), urinalysis, vital signs, physical examination findings

Pharmacokinetics: ACE-083 serum concentrations

Pharmacodynamics:

Muscle assessments: Muscle volume and intramuscular fat fraction of TA by MRI; CMAP of TA

Biomarkers: including but not limited to: insulin-like growth factor-1 (IGF-1), serum C-terminal collagen crosslinks (CTX)

Efficacy:

Muscle strength: Muscle strength (maximum voluntary isometric contraction [MVIC]) of ankle dorsiflexion measured by quantitative muscle testing (by handheld dynamometer)

Motor function tests: 10-meter walk/run, 6-minute walk test, 100-meter timed test (Part 2 open label), gait, activity and fall parameters, Berg balance scale

Physician-reported functional rating scale: CMTES2

Patient-reported health-related quality of life (QoL): CMT-HI

Statistical Methods:

Sample Size Calculation:

Part 1

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

Part 2

The sample size calculation for Part 2 is based upon the expected percent change from baseline in total muscle volume of the injected TA 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 estimated to be approximately 10% for each group based on preliminary MRI data for the ACE-083-treated side of the TA muscle from Part 1 of the Phase 2 study in FSHD patients.

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

In addition, this sample size provides 90% power to detect a 10% difference in 6MWD, based on an assumed estimated SD of 10% (based off of available data from Part 1 of the Phase 2 study in FSHD patients as well as available data from Part 1 of this study) and a 2-sided type 1 error rate of 0.1.

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

Analysis Populations:

Full Analysis Set: Part 1: All patients enrolled in the study and who have received at least one dose of study drug; Part 2: All patients randomized in the study

Safety Population: All patients enrolled/randomized in the study who have received at least one dose of study drug (including placebo)

Per Protocol Set: All patients enrolled/randomized in the study, who have received at least one dose of study drug (including placebo) with no CSR-reportable protocol violations and at least one post-baseline MRI evaluation

Pharmacokinetic Population: All patients who have received at least one dose of study drug and have sufficient PK samples collected and assayed for PK analysis

Statistical Analysis:

Details regarding the final data analysis will be described in a separate statistical analysis plan.

Part 1

Safety: Unless otherwise specified, safety data will be summarized using descriptive statistics and individual safety data will be listed. AEs will be coded using the Medical Dictionary for Regulatory Activities. Incidence of treatment-emergent AEs will be presented by system organ class and preferred term. AE incidence rates will be described by cohort with and without regard to causality. The frequency of occurrence of overall toxicity, categorized by toxicity grades (NCI-CTCAE, current version) will be summarized. Change from baseline in clinical laboratory parameters and vital signs will be summarized across time. Shift tables will be presented for selected laboratory parameters and vital signs. Physical examination results will be presented in listings.

Efficacy: Individual efficacy data will be listed. For muscle strength (as assessed by handheld dynamometer), the MVIC will be derived for each side and the average MVIC [from the left and right sides] will be determined for each individual patient and scheduled time. For the MVIC value for each side treated as well as the average from the left and right sides, CMTES2 score, CMT-HI total score and selected subscale scores, and motor function test assessments, raw data and changes from baseline (percent and absolute change) for the injected muscle will be summarized for each scheduled time using descriptive statistics. For each efficacy variable, a repeated measures analysis of covariance (ANCOVA) model will be fitted and least squares estimates of the effect of ACE-083 and the corresponding 90% confidence intervals will be provided for the percent change from baseline. For muscle strength parameters, the change from the screening to baseline value will serve as the control for each cohort and will be summarized together with post-baseline data.

Pharmacokinetic: Listings of individual patient serum ACE-083 concentrations, actual blood sampling times, and PK parameters including graphs of concentration versus time will be prepared by dose level. PK parameters of ACE-083 will be determined using the standard non-compartmental method. Descriptive statistics of PK parameters will be summarized by treatment group.

Pharmacodynamic: Individual pharmacodynamic data (e.g., muscle volume, intramuscular fat fraction, and biomarker data) will be listed. For individual pharmacodynamic data that are measured on the left and right side (e.g., MRI), the average of the left and right side assessments will also be listed and summarized. This will also be done for Part 2. Descriptive statistics (raw data and change from baseline [percent and absolute change]) will be provided by treatment group and scheduled time. For muscle volume and intramuscular fat fraction, estimates of the effect of ACE-083 and corresponding 90% confidence intervals will be provided. For biomarker data (e.g., IGF-1 and CTX), raw data and changes from baseline (percent and absolute change) will be summarized by treatment group and scheduled time.

Part 2

Pharmacodynamic: Individual pharmacodynamic parameter data will be listed.

The primary pharmacodynamic parameter will be the percent change in total muscle volume (average of left and right side) 3 weeks after the last dose of the double-blind treatment period (Day 190) from the corresponding baseline. A mixed model will be used to assess the treatment effect (ACE-083 vs. placebo) using a 2-sided 0.10 significance level. If data from the end of treatment visit are missing, the last observation will be carried forward. Additional techniques for handling missing data will also be evaluated as sensitivity analyses to the last observation carried forward approach.

Least squares estimates of the effect of ACE-083 and the corresponding 90% confidence interval will be produced. Descriptive statistics for the percent change in total muscle volume from baseline will be provided for each treated side as well as the average of the left and right side by treatment for each scheduled time.

For secondary pharmacodynamic parameters, descriptive statistics will be provided by treatment and scheduled time. In addition, a mixed model will be used to assess the treatment effect using a 2-sided 0.10 significance level for the following secondary pharmacodynamic variables: percent change from baseline for the average of the left and right side at 3 weeks after the last dose of the double-blind treatment period (Day 190) for muscle volume and intramuscular fat fraction as well as derived variables such as contractile muscle fraction and contractile muscle volume. Least squares estimates of the effect of ACE-083 and corresponding 90% confidence interval will be provided.

For biomarker data (e.g., IGF-1 and CTX) as well as TA CMAP amplitude, raw data and changes from baseline (percent and absolute change) will be summarized by treatment group and scheduled time.

Safety: Same as in Part 1

Efficacy: Individual efficacy data will be listed. For muscle strength, the MVIC value will be derived for each side and the average MVIC value [from the left and right sides] will be determined for each individual patient and scheduled time. For the MVIC value for each side treated as well as the average from the left and right sides, CMTES2 score, CMT-HI total score and selected subscale scores, and motor function test assessments, raw data and the absolute and percent change from baseline will be summarized by treatment for each scheduled time using descriptive statistics. In addition, a mixed model will be used to assess the treatment effect (ACE-083 vs. placebo) using a 2-sided 0.10 significance level for the percent change from baseline. Least squares estimates of the treatment effect and corresponding 90% confidence intervals will be provided.

Pharmacokinetic: Same as in Part 1

Anti-drug antibody data (Parts 1 and 2):

The results of ADA testing for ACE-083 versus time as well as results following further characterization of positive ADA samples will also be presented. Exploratory analyses will be

performed on the potential effect of ADA on ACE-083 PK exposure if ADA tests are determined to be positive.

Part 1 and Part 2 Pooled Analysis: If applicable, similar analyses will be performed for pooled Part 1 and 2 data for patients at the same dose level. Pooling by the estimated local dose of ACE-083 in the injected muscle (i.e., mg ACE-083/g muscle) may also be performed.

5. INTRODUCTION

5.1. Background

ACE-083 is a recombinant fusion protein consisting of a modified form of human follistatin (FST) linked to a human IgG2 Fc domain. FST is a member of the transforming growth factor (TGF)-β superfamily, a large family of structurally related cytokine-like proteins and cell surface receptors that play pivotal roles in the development, differentiation, and maturation of virtually all cells and tissues.[1] FST has been shown to be a potent activin antagonist through its role as a natural ligand trap, functioning as a key regulator of activin activity in body tissues.[2] Growth and differentiation factor 8 (GDF8), also known as myostatin, is a powerful negative regulator of skeletal muscle development and growth.[3] Inhibition of the modulating effects of both activin and myostatin on skeletal muscle growth has been identified as a promising therapeutic approach for degenerative diseases of skeletal muscle.[4] Unlike myostatin, in which the expression and site of action is primarily restricted to skeletal muscle, activin is produced in many different tissues and mediates a wide range of biologic processes in animals and humans, throughout all stages of development.[5] The challenge for therapeutic intervention in muscle diseases, therefore, has been in the selective inhibition of activin/myostatin activity only in the target tissue (i.e., skeletal muscle) in order to prevent or minimize undesirable off-target effects due to broad systemic inhibition of activin. ACE-083 has been engineered and developed as a locally-active ligand trap of activin and myostatin in addition to other ligands. The properties of ACE-083 are such that, when administered by IM injection, the drug remains primarily within the injected muscle(s) to increase mass and strength of the particular muscle(s).

As described in the ACE-083 Investigator's Brochure (IB), a number of nonclinical pharmacology studies have been conducted with ACE-083 to define the ligand-binding properties of the molecule and assess its anabolic effects on skeletal muscle in normal animals and in a mouse model of muscle disease. Preclinical studies in normal mice and rats have demonstrated increased muscle mass as a result of increased fiber hypertrophy and not hyperplasia. This ACE-083-induced muscle hypertrophy has also been shown to translate to functional improvement in muscle strength in normal mice. ACE-083 has also been evaluated in a well-established mouse model of human Duchenne muscular dystrophy as representative of a degenerative muscle disorder as well as the SOD1 mouse model of human amyotrophic lateral sclerosis (ALS), representative of a neurogenic disorder. ACE-083 treatment in both mouse models resulted in significant increases in the mass and peak strength of the injected muscle. These studies provide evidence that local inhibition of activin/myostatin by ACE-083 can increase muscle mass even in animals with a degenerative skeletal muscle disease.

In addition, Study A083-01, a Phase 1, double-bind, placebo-controlled, dose-ranging study designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of local muscle injections of ACE-083 in healthy postmenopausal women has been completed. Forty -two subjects have received ACE-083 at dose levels of 50 to 200 mg administered as single or multiple injections into either the right rectus femoris or right tibialis anterior muscle. ACE-083 was generally safe and well tolerated in this study with no serious adverse events or grade ≥ 3 AEs reported. A significant dose-dependent change in volume of the injected muscle has been seen in the treated versus placebo group.

5.2. Study Rationale

Hereditary motor sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth (CMT) disease, is the most common form of hereditary neuropathy with a prevalence of 1 in 2500 individuals or about 125,000 people.[6] A specific mutation in one of several myelin genes results in defects in myelin structure, maintenance, and formation. Duplication of the *PMP22* gene causes CMT1A, the most common type of CMT, accounting for approximately 40 percent of cases. X-linked forms of CMT are the second most common form of CMT and account for approximately 10 to 15 percent of cases.[7]

Patients with CMT typically present with both motor and sensory nerve manifestations, distal leg weakness, foot deformities (pes cavus, hammer toes), and sensory deficits. Involvement of the hands may also follow as the patient progresses. Weakness in the lower leg manifests as "foot drop" and patients have difficulty lifting their toes during ambulation. As this weakness progresses, patients begin to lose mobility and are at increased risk for falls and injury.

To date, treatment of CMT has been restricted to symptomatic interventions. Although some clinical and pharmacological trials have been performed, the results have not been encouraging.[8] Patients will commonly wear braces and/or use assistive devices such as canes and walkers to preserve mobility but each of these orthopedic interventions is associated with practical as well as social limitations. Surgery has been shown to successfully treat deformities of the foot as well as foot drop but it is a more invasive option and not always an appropriate intervention in every case. In some patients, exercise is the recommended therapy but it is still uncertain whether exercise should be considered safe for the general CMT population and, if so, how the frequency, timing, and type of exercise should be selected for each patient.[9]

In our Phase 1 study, local injection of ACE-083 into the tibialis anterior (TA) of healthy volunteers led to a dose-dependent increase in TA muscle volume. Because CMT disease selectively impacts muscles in the lower leg innervated by longer nerve fibers, including the TA, a locally acting agent such as ACE-083 can be can be used to selectively target atrophied muscle that is contributing to functional limitations. In CMT patients with lower limb weakness and atrophy of the TA, an increase in TA muscle volume has the potential to increase strength and function associated with ankle dorsiflexion, which could improve a patient's mobility and ultimately their quality of life.

6. OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Part 1

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of ACE-083 in patients with CMT1 and CMTX	• Presence and nature of AEs including injection site reactions and changes in clinical laboratory parameters
Secondary	
• To determine the recommended dose level of ACE-083 for Part 2	• Recommendation from SRT
• To evaluate change in muscle volume and intramuscular fat fraction of the injected muscle	• Percent change from baseline in muscle volume of injected muscle • Percent and absolute change from baseline in intramuscular fat fraction of injected muscle
• To evaluate change in strength of the injected muscle	• Percent change from baseline in strength measurements by maximum voluntary isometric contraction of ankle dorsiflexion measured by quantitative muscle testing
• To estimate the systemic exposure of ACE-083 when administered as a local muscle injection	• PK parameters for ACE-083 serum concentrations over time
• To evaluate changes in motor function related to the injected muscle	• Percent change from baseline in functional assessments
• To evaluate changes in physician-reported and patient-reported outcome measures	• Percent and absolute change from baseline in CMTES2 and CMT-HI
Exploratory	
• To evaluate changes in gait parameters	• Percent and absolute change from baseline in gait parameters
• To evaluate changes in biomarkers	• Percent and absolute change from baseline in biomarkers

Objectives	Endpoints
Primary	
• To determine whether treatment with ACE-083 vs placebo increases muscle volume of the injected muscle in patients with CMT1 and CMTX	• Percent change from baseline in muscle volume of injected muscle by MRI
Secondary	
• To determine whether treatment with ACE-083 vs placebo decreases intramuscular fat fraction of the injected muscle	• Percent and absolute change from baseline in intramuscular fat fraction of the injected muscle by MRI
• To determine whether treatment with ACE-083 vs placebo increases strength of the injected muscle	• Percent change from baseline in strength measurements by maximum voluntary isometric contraction of ankle dorsiflexion measured by quantitative muscle testing
• To determine whether treatment with ACE-083 vs placebo improves motor function related to the injected muscle	• Percent change from baseline in functional assessments
• To determine whether treatment with ACE-083 vs placebo improves physician-reported and patient-reported outcome measures	• Percent and absolute change from baseline in CMTES2 and CMT-HI
• To evaluate the safety and tolerability of ACE-083	• Presence and nature of AEs including injection site reactions and changes in clinical laboratory parameters
• To estimate the systemic exposure of ACE-083 when administered as a local muscle injection	• PK parameters for ACE-083 serum concentrations over time
Exploratory	
• To evaluate changes in biomarkers	• Percent and absolute change from baseline in biomarkers
• To evaluate changes in TA compound muscle action potential (CMAP)	• Percent and absolute change from baseline in TA CMAP amplitude
• To evaluate changes in gait, activity level and fall parameters	• Percent and absolute change from baseline in gait parameters
• To evaluate changes in motor function via the 100-meter timed test	• Activity level and falls (PamSys™ wearable device)
	• Percent change from baseline in the 100-meter timed test

7. STUDY DESIGN

7.1. Overview of Study Design

Study A083-03 is a multicenter, Phase 2 study to evaluate the safety, tolerability, pharmacodynamics (PD), efficacy, and pharmacokinetics (PK) of ACE-083 in patients with CMT1 and CMTX, to be conducted in two parts. Part 1 is non-randomized, open-label, and dose-escalation; Part 2 is randomized, double-blind, and placebo-controlled. Patients who have signed the informed consent form (ICF) and meet the eligibility criteria will be enrolled into the study.

Duration of Treatment

Study duration for a patient enrolled in Part 1 will be approximately 24 weeks, including a 4-week screening period, a 12-week treatment period, and an 8-week follow-up period after the last dose. Study duration for a patient enrolled in Part 2 will be approximately 15 months, including a 4-week screening period, a 12-month treatment period (6-month double-blind, placebo controlled and a 6-month open-label extension), and an 8-week follow-up period after the last dose.

If a patient has a positive anti-drug antibody (ADA) result after the last visit, the patient will be asked to return for additional ADA testing approximately every 3 months, until a negative result is obtained or the result is considered to be stabilized.

Part 1 (non-randomized, open-label, dose-escalation)

Part 1 will consist of up to 3 cohorts of 6 patients each and will evaluate multiple ascending dose levels of ACE-083 administered bilaterally once every 3 weeks for up to 5 doses in the tibialis anterior (TA) muscle. Patients in each cohort will be enrolled in a 4-week screening period before beginning treatment.

For Cohort 1, the dose level will be 150 mg/muscle administered bilaterally.

For Cohort 2, the dose level will be based on review of safety data and recommendations made by the Safety Review Team (SRT). The planned dose level for Cohort 2 is 200 mg/muscle administered bilaterally.

For Cohort 3, the decision to enroll patients and the dose level will be based on recommendations of the SRT following review of safety and, as necessary, imaging data for prior cohorts. The maximum possible dose level for Cohort is 250 mg/muscle administered bilaterally.

The SRT will provide recommendations to the sponsor regarding the conduct of the current or subsequent cohorts in the study (e.g., dose level) as described in Section 7.2 below.

Part 2 (randomized, double-blind, placebo-controlled)

Prior to the initiation of Part 2, a review of safety and efficacy data from Part 1 will be conducted by the SRT to determine the recommended dose level (maximum 250 mg/muscle). A total of up to 40 new patients may be enrolled and randomized (1:1 randomization) to receive either

ACE-083 (n=20) or placebo (n=20) bilaterally by injection into both TA muscles. Patients will receive blinded study drug once every 3 weeks for approximately 6 months (9 doses).

Patients who complete the double-blind treatment period will immediately roll over to open-label treatment of ACE-083, receiving the same dose of active drug, bilaterally in the TA muscle, once every 3 weeks for approximately 6 months (8 doses). In Part 2, the SRT will periodically review blinded safety data for each muscle treated.

7.2. Justification for Dose Level

ACE-083 was administered into either the rectus femoris (RF) or TA muscle of healthy post-menopausal women in the Phase 1 Study A083-01 at absolute dose levels per muscle of up to 200 mg (RF) or 150 mg (TA) as either a single dose or repeated dose every 3 weeks. The estimated ACE-083 (mg/g muscle) within the muscle was calculated using the dose administered to each patient and the size of each patient's RF muscle as measured by baseline MRI. The highest dose of ACE-083 evaluated (200 mg x 2 doses for RF; 150 mg x 2 doses for TA) produced a mean increase from baseline in muscle volume of 14.5% and 8.9% for RF and TA, respectively, at 3 weeks following the last dose. These dose levels were considered safe and generally well tolerated.

A starting dose level of 150 mg/muscle is considered appropriate and safe based on the Phase 1 clinical trial results. This starting dose level will protect patient safety and also ensure that the initial exposures achieved within the muscle have the potential to impact efficacy endpoints. All subsequent dose levels (higher or lower) will be determined following review of study data and recommendations from the SRT. A maximum absolute dose level of 250 mg/muscle following dose escalation has been chosen based on administration feasibility and volume constraints.

7.3. Benefit/Risk Assessment

Information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of ACE-083 is provided in the IB.

8. STUDY POPULATION

8.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

Inclusion Criteria:

1. Age ≥ 18 years
2. Diagnosis of CMT1 or CMTX confirmed by:
    a. Clinical presentation and electrodiagnostics
    b. Genetically confirmed CMT1 or CMTX (Appendix 3) for the patient or first-degree relative
3. Part 1:
    a. Six-minute walk distance (6MWD) of at least 150 meters (without a brace or walker)
    b. Independent ambulation for at least 10 meters, without a brace
    c. Left and right ankle plantar flexion MRC grade 4+ to 5, inclusive

    Part 2:
    a. 6MWD ≥ 150 and ≤ 500 meters (without a brace or walker); a maximum of 20% of enrolled patients with 6MWD ≥ 450 meters will be included
    b. Left and right ankle plantar flexion MRC grade 4- to 5, inclusive
4. Left and right ankle dorsiflexion Medical Research Council (MRC) manual muscle testing (MMT) grade 3 to 4+ inclusive (Appendix 4). No more than 12 of the 40 subjects may have a grade of 3 or 3+ on one or both sides.
5. Females of childbearing potential (defined as sexually mature women who have not undergone hysterectomy or bilateral oophorectomy, or are not naturally postmenopausal ≥ 24 consecutive months) must have negative urine pregnancy test prior to enrollment and use highly effective birth control methods (abstinence, oral contraceptives, barrier method with spermicide, or surgical sterilization) during study participation and for 8 weeks following the last dose of ACE-083. Hormonal birth control use must be stable for at least 14 days prior to Day 1. Males must agree to use a condom during any sexual contact with females of childbearing potential while participating in the study and for 8 weeks following the last dose of ACE-083, even if he has undergone a successful vasectomy. Patients must be counseled concerning measures to be used to prevent pregnancy prior to the first dose of ACE-083.
6. Ability to adhere to the study visit schedule/procedures, and to understand and comply with protocol requirements
7. Signed written informed consent

8.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

1. Current active malignancy (e.g., remission less than 5 years duration), with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or ≤ 2 squamous cell carcinomas of the skin
2. Symptomatic cardiopulmonary disease, significant functional impairment, significant orthopedic or neuropathic pain, or other co-morbidities that in the opinion of the investigator would limit a patient's ability to complete strength and/or functional assessments on study
3. Type 1 or type 2 diabetes mellitus
4. Thyroid disorder unless condition is stable with no change in treatment for at least 4 weeks before the first dose and no expected change for duration of study
5. Renal impairment (serum creatinine ≥ 2 times the upper limit of normal [ULN])
6. Aspartate transaminase (AST) and/or alanine transaminase (ALT) ≥ 3 times ULN
7. Increased risk of bleeding (i.e., due to hemophilia, platelet disorders, or use of any anticoagulation/platelet modifying therapies up to 2 weeks prior to Study Day 1 and for duration of study; low dose aspirin [≤ 100 mg daily] is permitted)
8. Severe deformity or ankle fixation that would sufficiently limit passive range of motion to affect assessment of dorsiflexion strength.
9. Major surgery within 4 weeks prior to Study Day 1
10. Chronic pharmacologic doses of systemic corticosteroids (≥ 2 weeks) within 4 weeks before Study Day 1 and for duration of study; intra-articular/topical/inhaled/intranasal physiologic doses of systemic corticosteroids are permitted
11. Androgens, growth hormone, insulin, or oral hormone replacement therapy within 6 months before Study Day 1 and for duration of study; topical physiologic androgen replacement is permitted
12. Any change in medications potentially affecting muscle strength or function within 4 weeks of Study Day 1 and for duration of study (e.g., creatinine, CoQ10, systemic beta adrenergic agonists)
13. Previous exposure to any investigational agent potentially affecting muscle volume, muscle strength, or muscle or nerve function within 5 half-lives of last dose plus an additional 8-week washout period (or 12 weeks prior to Study Day 1 if half-life is unknown)
14. Any previous or current exposure to ACE-083
15. Significant change in physical activity or exercise (e.g., significant increase or decrease in intensity or frequency) within 8 weeks before Study Day 1 or inability to maintain the baseline level of physical activity throughout the study

16. Any condition that would prevent MRI scanning or compromise the ability to obtain a clear and interpretable scan of the lower leg, as applicable (e.g., knee/hip replacement metallic implants)
17. Known active substance abuse, including alcohol
18. History of sensitivity to protein pharmaceuticals
19. Female that is lactating/breast-feeding

8.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 additional times. The interval between rescreenings should be at least 4 weeks after the end of the 4-week screening period (i.e., the earliest re-consent may occur is 8 weeks after the prior consent was signed). Each time a rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number. If a test is repeated within the screening window, the patient does not need to sign a new ICF.

9. DISCONTINUATION/ WITHDRAWAL CRITERIA

The reasons for treatment discontinuation / study withdrawal must be recorded in the patient's case report form (CRF). The investigator must notify the sponsor and medical monitor when a patient has been withdrawn from the study.

All patients who are withdrawn from the study prior to the end of treatment visit should complete the tests and evaluations (excluding the MRI if it has been done within 4 weeks of study withdrawal) scheduled for the end of treatment visit (Day 106/ET for Part 1, Day 358/ET for Part 2) at the time of withdrawal and will be asked to return to the clinic to complete the remaining follow-up visit assessment.

9.1. Discontinuation of Study Treatment

Reasons that may lead to discontinuation of study treatment include:

- Treatment completed
- Adverse event
- Patient request (withdrawal of consent)
- Death
- Lost to follow-up
- Pregnancy
- Protocol deviation
- Study terminated by sponsor[1]

9.2. Withdrawal from the Study

Reasons that may lead to a patient's withdrawal from the study include:

- Study terminated by sponsor[1]
- Patient's request
- Screen failure
- Patient's unwillingness or inability to comply with the protocol
- Death
- Lost to follow-up
- Adverse event

[1] The sponsor may terminate this study or a dose level after consultation with the investigator and the SRT at any time for safety or administrative reasons. The sponsor will terminate the study if the occurrence of SAEs or other findings suggests unacceptable risk to the health of the patients.

9.3. Lost to Follow Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted after three attempts by the study site. Every attempt should be made to collect all data on discontinued patients.

10. TREATMENT OF PATIENTS

10.1. Treatments Administered

Using electromyography (EMG) or ultrasound guidance, each dose of study drug will be administered into the non-tendinous portion of the TA as a series of up to 4 equal-volume injections. The use of EMG or ultrasound guidance will ensure that viable muscle is present at the injection site. If the degree of atrophy or fibro-fatty infiltration poses administration challenges, injections of ACE-083 should be distributed approximately 2 cm apart into viable muscle. Injection site locations as well as measures to avoid adjacent nerves, blood vessels, and prevent intravascular injection are outlined in the IP Handling Guide.

The maximum absolute dose level and schedule, based on SRT review, is 250 mg/muscle administered bilaterally by injection into the left and right TA muscles every 3 weeks for up to 5 doses in Part 1 and up to 17 doses in Part 2.

For Part 2, ACE-083 or placebo (normal saline) will be administered blinded study drug every 3 weeks for approximately 6 months (9 doses). Patients who complete the double-blind treatment period will immediately roll over to open-label treatment with ACE-083, receiving the same dose of active drug, bilaterally in the TA muscle once every 3 weeks for approximately 6 months (8 doses).

The planned dose scheme for Part 1 and 2 is shown in Table 4.

Table 4: Cohort Schedule for Study A083-03

Part 1: N=Up to 18 (non-randomized, open-label, dose-escalation)

Cohort	ACE-083 Dose per Muscle[a]	ACE-083 n
1	150 mg	6
2	TBD up to 200 mg[b]	6
3	TBD up to 250 mg[b]	6

Part 2: N= Up to 40 (6-month, randomized, double-blind, placebo-controlled, with 6-month open-label extension)

	6-month double-blind, placebo controlled		6-month open-label extension
ACE-083 Dose per Muscle[a]	ACE-083 n	Placebo n	ACE-083 n
TBD up to 250 mg[b]	20	20	40

[a] Administered bilaterally by injection into the tibialis anterior muscle once every 3 weeks
[b] Dose level to be based on recommendations from the SRT

10.1.1. Individual Dose Modification Rules

For an adverse event (AE, including injection site reaction) of grade 3 or higher, regardless of relationship to study drug, treatment will be paused and the patient will be monitored weekly. At the discretion of the investigator, dosing may resume upon resolution of the AE to ≤ grade 1 or

baseline and may be reduced to the previously tolerated dose (i.e. from 240 to 200 mg or from 200 to 150 mg). Dose will not be reduced to below 100 mg (Part 1) or 150 mg (Part 2). If dosing does not resume within 6 weeks of the last dose given, the patient will be discontinued from treatment.

10.2. Safety Review Team

Dose-Limiting Toxicity (DLT) Definition:

- An SAE, possibly or probably related to study drug

OR

- An AE, injection site reaction, laboratory parameter abnormality, or vital sign abnormality, possibly or probably related to study drug, and either Grade ≥ 3 (NCI-CTCAE, current version) or Grade ≥ 2 and considered clinically significant

Part 1 Dose Escalation Stopping Rules (under SRT review):

Dosing at current levels will continue unless the following condition occurs:

- ≥ 2 DLTs of the same character in a cohort

Safety Review Team:

An SRT, comprised at minimum of a principal investigator, medical monitor, and an independent neuromuscular specialist, will meet to review safety and, as needed, imaging data, for each cohort. The review will include all collected safety data (and, as necessary imaging data) when at least 4 patients in a cohort have completed at least their Day 22 visit. For both parts of the study, the SRT safety data will include, but not be limited to, AEs, laboratory results (including hematology, chemistry, and urinalysis) and vital signs data to assess for DLTs and overall safety. The SRT may request review of additional data collected in currently enrolled patients.

Based on review of relevant data, the SRT will make one or more of the following recommendations:

- Continue enrollment of remaining patients in the current cohort at the current dose level
- Open next cohort in Part 1 or open Part 2 of the study at a recommended dose (higher or lower dose level)
- Discontinue one or more cohorts in Part 1, or the study as a whole

SRT recommendations for dose escalation in Part 1 will be based in part upon the dose escalation stopping rules. If a stopping rule is met, a lower intermediate dose may be recommended or the previous dose level will be considered the MTD. The SRT may also recommend no further enrollment in the presence of AEs that do not meet dose stopping rules if the nature of these AEs is deemed a significant risk to patients in a given cohort.

For Part 2, the SRT will review blinded preliminary safety data. Further details on the role of the SRT during Part 2 are included in the SRT Guidelines.

10.3. Concomitant Medications

During screening and throughout the study, patients may take stable doses of medications for chronic conditions that are not specifically excluded by the protocol. These medications include:

single agent low dose aspirin (≤ 100 mg daily), intra-articular/topical/inhaled/intranasal physiologic doses of systemic corticosteroids, and topical physiologic androgen replacement. Any change in medications potentially affecting muscle strength or function (e.g., creatinine, CoQ10, or systemic beta adrenergic agonist) is not allowed. If there is an immediate clinical need during the study to prescribe a new medication or a new dosage of an existing medication for either a new or chronic condition, concurrent therapy may be administered at the discretion of the investigator. The investigator may consult the medical monitor regarding what constitutes a stable dose or a chronic condition. Information regarding concomitant medications will be collected beginning at study screening and will include all medications taken within 4 weeks prior to Study Day 1.

Patients are not permitted to take the following: anticoagulation / platelet modifying therapies, systemic corticosteroids, androgens, growth hormone, insulin, or hormone replacement therapy. Additionally, patients must be withdrawn from study treatment if at any time during their participation they receive other investigational compound(s), or start any new experimental or approved therapies related to the treatment of CMT. This withdrawal excludes standard of care procedures and participation in observational research.

10.4. Treatment Compliance

Each dose of study drug will be administered via injections at the clinical site by the study staff and will be documented in the study record. Monitoring for patient compliance with the treatment regimen is therefore unnecessary.

10.5. Randomization and Blinding

Part 1: This is an open-label, dose escalation phase that does not require randomization.

Part 2: Patients who have signed the informed consent and meet all eligibility criteria will be stratified by CMT disease type (CMT1 or CMTX) and then randomized to receive ACE-083 (at a dose level determined by Part 1) or placebo. The randomization scheme will be computer generated and will be prepared by a statistical group designated by the sponsor.

If a patient discontinues the study for reasons other than a safety issue related to ACE-083 and the patient had not completed visit Day 43, the patient may be replaced. The replacement patient will receive the same treatment as the patient replaced. Both the replacement and originally allocated patient numbers will be unique numbers.

Among study personnel, only the pharmacist or his/her designee who prepares the study drug (ACE-083 or placebo), an unblinded clinical monitor designated by the sponsor, and the analytical laboratory will be unblinded to the patient treatment assignments. All other study personnel (including but not limited to investigators, study coordinators, nursing staff, and clinical monitors) and all patients will remain blinded to the study treatment assignments. The sponsor and the sponsor's representatives will also remain blinded to the study treatment assignments.

In the event of a medical emergency for an individual patient in which knowledge of the study drug is critical to the patient's medical management, the investigator may break the blind for that patient. However, prior to breaking the blind, every effort must be made by the investigator to first discuss the need to break the blind with the medical monitor. Further, it must be determined

by the investigator that breaking the treatment blind is necessary information for the medical management of that patient. If the blind is broken prior to Day 190, the patient must be withdrawn from the study and complete the tests and evaluations scheduled for the end of treatment visit (Day 358/ET) and will be expected to return to the clinic to complete the remaining follow-up visit assessments.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

Study drug is either ACE-083 or placebo. ACE-083 is a recombinant fusion protein consisting of a modified form of human follistatin linked to a human IgG2 Fc domain. Placebo will be sterile normal saline (0.9% sodium chloride for injection).

11.2. Study Drug Packaging and Labeling

ACE-083 drug product is provided as a lyophilized powder contained in stoppered and sealed glass vials. Each single-use vial will be reconstituted with sterile water and contains 1.2 mL of ACE-083 solution for injection after reconstitution. ACE-083 drug product solution for injection contains ACE-083 at a nominal concentration of 50 mg/mL. Sterile normal saline for placebo will be supplied by the investigational site's pharmacist.

11.3. Study Drug Storage

ACE-083 should be stored at 2–8°C until use. The manufacturer's directions for saline storage are to be followed, as are standard clinical practices for ensuring sterility.

11.4. Study Drug Preparation

Please refer to the IP Handling Guideline, provided separately, for detailed study drug handling, administration, and storage instructions. The manufacturer's directions for saline handling are to be followed, as are standard clinical practices for ensuring sterility.

11.5. Study Drug Accountability

Accountability for study drug is the responsibility of the investigator. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secured location. The clinical site must maintain accurate records demonstrating dates and amounts of study drug received, to whom it was dispensed (patient-by-patient accounting), and accounts of any study drug accidentally or deliberately destroyed or returned.

Unless otherwise notified, all vials of study drug, both used and unused, must be saved for drug accountability purposes. The used vials may be discarded, per the institution's standard practice, after a drug accountability assessment has been completed by the clinical monitor. At the end of the study, the sponsor will provide direction for the outcome of all unused vials. Following the sponsor's instructions, the investigator must either return all unused vials of study drug to the sponsor or destroy them at the clinical site. In either case, the outcome must be documented on the drug accountability log.

11.6. Study Drug Handling and Disposal

Please refer to the IP Handling Guideline, provided under separate cover, for detailed study drug handling, administration, storage, and disposal instructions.

12. STUDY PROCEDURES

12.1. Written Informed Consent

Patients will be required to sign an independent ethics committee (IEC)/institutional review board (IRB)-approved ICF prior to any study-related procedures, including screening evaluations.

12.2. Study Assessments

For each patient, all study procedures should be conducted according to the Schedule of Events (Appendix 1) and following the study-specific recommendations included in the Study Manual.

12.3. Safety Assessments

Safety assessment include monitoring of adverse events, injection site reactions, concomitant medications, clinical laboratory assessments (including ADA), vital signs, and physical examination findings.

Specifically for ADA, if a patient has a positive ADA result at the last visit, the patient will be asked to return for additional ADA testing approximately every three months, until a negative result is obtained or the result is considered to be stabilized.

Please refer to Appendix 2 for the Clinical Laboratory Assessments that will be performed during this study.

12.4. Efficacy Assessments

Muscle strength: Muscle strength (maximum voluntary isometric contraction) of ankle dorsiflexion measured by quantitative muscle testing (by handheld dynamometer)

Motor function tests: 10-meter walk/run, 6-minute walk test, 100-meter timed test (Part 2 open-label), gait, activity and fall parameters, Berg balance scale

Physician-reported functional rating scale: CMTES2

Patient-reported health-related QoL: CMT-HI

12.5. Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetic assessments: ACE-083 serum concentrations (PK samples for patients taking concomitant medications may be analyzed for changes in cytochrome P450 enzymes.)

Pharmacodynamic assessments

Muscle assessments: Muscle volume and intramuscular fat fraction of TA by MRI; CMAP of TA

Biomarkers: including but not limited to: insulin-like growth factor-1 (IGF-1), serum C-terminal collagen crosslinks (CTX)

13. SAFETY

13.1. Definition of Adverse Events

13.1.1. Adverse Event

For this protocol, an AE is any untoward medical occurrence in a clinical investigational study in which a patient is administered a study drug (i.e., on or after the Dose 1 Day 1 dose), which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug whether or not it is considered related to the study drug.

Abnormal laboratory and other abnormal investigational findings (e.g., physical exam, ECG) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are otherwise considered clinically relevant by the investigator. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In the case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

13.1.1.1. Unexpected Adverse Events

An unexpected AE is an AE that is not described in nature or severity in the IB under the Reference Safety Information.

13.1.1.2. Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present before the screening period that do not worsen in severity or frequency during the study are defined as baseline medical conditions, and are not to be considered AEs.

13.1.1.3. Serious Adverse Event

An SAE is any AE (on or after the Dose 1 Day 1 dose), occurring at any dose, regardless of causality, that:

- Results in death
- Is life-threatening: life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form)
- Requires inpatient hospitalization or prolongation of existing hospitalization; however, a hospitalization for an elective procedure will not be considered a SAE
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event: an important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the

patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

13.1.1.4. Events Not to Be Considered as Serious Adverse Events

Elective hospitalizations to administer or to simplify study treatment or perform procedures are not considered SAEs. Unexpected complications and/or prolongation of elective hospitalization should be recorded as AEs.

13.1.1.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and the investigator identifies as related to the investigational product or procedure. Acceleron follows procedures for the expedited reporting of SUSARs consistent with global regulations and associated guidances.

13.2. Severity

Investigators must evaluate the severity/intensity of AEs according to the CTCAE current version, preferentially using the graded scales. If the severity/intensity of a particular AE is not specifically graded, the investigator should apply the general guidelines for determination of Grade 1 through Grade 5 as listed in the CTCAE v4 cover page (reproduced below), using their best medical judgment:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

13.3. Relationship to Study Drug

Investigators must also assess the causal relationship of each AE to study drug. Factors for the assessment of causal relationship include, but are not limited to, temporal relationship between the AE and the administration of study drug, known side effects of study drug, medical history, concomitant therapy, course of the underlying disease and pertinent study procedures.

Probably: A causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of study drug and there is a reasonable response on withdrawal.

Possibly: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of study drug.

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible.

Not Related: A causal relationship can be definitively excluded and another documented cause of the AE is most plausible.

13.4. Recording Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study. Patients will be evaluated and questioned generally for AEs during the course of the study,. The investigator must report in detail all adverse signs and symptoms which are either volunteered by patients or observed during or following the course of investigational product administration on the appropriate CRF page. All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded as a single diagnosis. All untoward medical occurrences arising after signing of the ICF until a patient is dosed on Dose 1 Day 1 are to be documented on the medical history CRF. All AEs occurring on or after the Dose 1 Day 1 dose through Day 141/End of Study visit (Part 1) or Day 393/End of Study visit (Part 2) are to be reported and documented on the AE CRF.

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the AE CRF. Any clinically relevant changes in laboratory assessments, or other clinical findings as described in Section 13.1 , are considered AEs and must be recorded on the AE CRF. AEs are to be followed for resolution as described in in Section 13.5.

It is important that each AE report include a description of the event, duration (onset and resolution dates), severity, relationship with ACE-083, any other potential causal factors, any treatment given, or other action taken (including dose delay or discontinuation of study drug) and outcome. In addition, SAEs should be identified and the appropriate seriousness criteria documented. AEs categorized as SAEs must also be documented using an SAE Report Form as described in Section 13.4.1.

Specific guidance can be found in the CRF Completion Guidelines provided by the sponsor or designee.

13.4.1. Documentation of Serious Adverse Events

All SAEs that occur after the first study drug administration on Dose 1 Day 1 until Day 141/End of Study visit (Part 1) or Day 393/End of Study visit (Part 2) are to be documented on the AE CRF.

For all SAEs, an SAE Report Form must be completed with as much information as possible and submitted within the time frame described in Section 13.5. When new significant information is obtained as well as when the outcome of an event is known, the investigator should record the

information on a new SAE Report Form. In all instances, the investigator should follow up with patients until the outcome of the SAE is known.

13.5. Reporting Adverse Events

As described in Section 13.4 , all AEs must be recorded in the CRF up until the last follow-up visit. All patients who received at least one dose of study drug, whether they completed the treatment period or not, should complete the end of treatment procedures.

All AEs will be followed until clinical database lock (or resolution if it occurs before database lock). All SAEs will undergo active follow-up until the event(s) have returned to baseline status, have stabilized, or until the investigator and sponsor have agreed that follow-up is no longer necessary. Follow-up data for SAEs obtained after clinical database lock will be incorporated into the study drug safety database. If a patient experiences an SAE that is considered to be related to study treatment at any time after the study, it must be reported to the sponsor.

13.6. Pregnancy

Female patients who are of childbearing potential at the time of consent or who become of childbearing potential during study participation must agree to use a highly effective method of birth control for the duration of the study and for 8 weeks after the last dose of ACE-083.

Male patients and their partners must be using a highly effective method of birth control for the duration of the study and for 8 weeks after last dose of ACE-083.

All pregnancies occurring during the study and up to 8 weeks after the last dose of ACE-083 must be reported immediately to the investigator. The investigator must report all pregnancies to the sponsor within 24 hours of notification. A pregnant female participant must discontinue study drug immediately. Monitoring of the patient should continue until conclusion of the pregnancy.

If the pregnancy ends for any reason before the anticipated date, the investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

13.7. Reporting Serious Adverse Events

If an SAE occurs during the reporting period, the investigator must immediately (i.e., within a maximum 24 hours after becoming aware of the event) inform the contract research organization (CRO) by telephone, fax, or e-mail.

All written reports should be transmitted using the study-specific SAE Report Form, which must be completed by the investigator following specific completion instructions. Names, addresses, telephone and fax numbers for SAE reporting are located on the SAE Report Form and in the completion instructions provided in the Study Manual. When an SAE (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. Reporting procedures and timelines for follow-up information are the same as for the initially reported SAE.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant therapy). In all cases, the information provided in the SAE Report Form must be consistent with the data that are recorded in the corresponding sections of the CRF.

The investigator/reporter must respond to any request for follow-up information or to any question the sponsor or designee may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the sponsor and (as applicable) to allow the sponsor to meet regulatory timelines associated with expedited reporting obligations.

Requests for follow-up will usually be made by the responsible clinical monitor or medical monitor, or in exceptional circumstances, by a pharmacovigilance representative who may contact the investigator directly to obtain clarification on a particularly critical event.

13.7.1. Safety Reporting to Health Authorities, Independent Ethics Committees, Institutional Review Boards, and Investigators

The sponsor will send appropriate safety notifications to health authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving his/her patients to the IEC or IRB that approved the study.

In accordance with ICH GCP guidelines, the sponsor will inform the investigator of "findings that could adversely affect the safety of patients, impact the conduct of the study, or alter the IEC's/IRB's approval/favorable opinion to continue the study."

The sponsor will inform the investigator of AEs that are both serious and unexpected and are considered to be related to study drug (SUSARs). The investigator should place copies of these Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to investigators will be followed.

When specifically required by regulations and guidelines, the sponsor will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports and for filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Union Clinical Trials Directive 2001/20/EC, the sponsor's responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that Directive and with the related Detailed Guidances.

14. STATISTICS

This section outlines the planned statistical analyses. Additional details will be described in a separate statistical analysis plan (SAP).

14.1. Analysis Populations

Full Analysis Set: Part 1: All patients enrolled in the study and have received at least one dose of study drug; Part 2: All patients randomized in the study

Safety Population: All patients enrolled/randomized in the study who have received at least one dose of study drug (including placebo)

Per Protocol Set: All patients enrolled/randomized in the study, who have received at least one dose of study drug (including placebo) with no CSR-reportable protocol violations and at least one post-baseline MRI evaluation

Pharmacokinetic Population: All patients who have received at least one dose of study drug and have sufficient PK samples collected and assayed for PK analysis

14.2. Statistical Analysis Considerations

14.2.1. Patient Demographics and Disposition

Individual patient demographic data will be listed by patient.

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 (sex, 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.

Individual patient disposition data will be listed by patient.

Frequency counts will be tabulated for disposition data and will consist of the number of patients completing the study (Yes / No) along with frequency counts of primary reason for discontinuation (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).

14.2.2. Drug Exposure

Individual study drug administration data will be listed by patient. Descriptive statistics of study drug exposure will be presented.

14.2.3. Efficacy Data

Part 1

Individual efficacy data will be listed. For muscle strength (as assessed by handheld dynamometer), the MVIC value will be derived for each side and the average maximum peak force value [from the left and right sides] will be determined for each individual patient and scheduled time. For the MVIC value for each side treated as well as the average from the left and right sides, CMTES2 score, CMT-HI total score and selected subscale scores, and motor

function test assessments, raw and changes from baseline (percent and absolute change) for the injected muscle will be summarized for each scheduled time using descriptive statistics. For each efficacy variable, a repeated-measures ANCOVA model will be fitted and least square mean estimates of the effect of ACE-083 and the corresponding 90% confidence intervals will be provided for the percent change from baseline. For muscle strength parameters, the change from the screening to baseline value will serve as the control for each cohort and will be summarized together with post-baseline data. Baseline is defined as the last non-missing value prior to dosing. Theoretically, this should be the Day 1 predose value. Other strength measurements will be summarized and reported similarly. Additional analyses may be performed as appropriate.

Analyses described above concerning selected motor function test assessments related to gait will be considered as exploratory.

Part 2

Individual efficacy data will be listed. For muscle strength, the MVIC value and decimal MMT-MRC score will be derived for each side and the average [from the left and right sides] will be determined for each individual patient and scheduled time.

Double-blind, placebo-controlled phase

For the MVIC value and decimal MMT-MRC score for each side treated as well as the average from the left and right sides, CMTES2 score, CMT-HI total score and selected subscale scores, and motor function test assessments, raw data and changes from baseline (percent and absolute change) from baseline will be summarized by treatment for each scheduled time using descriptive statistics. In addition, a mixed model will be fitted to assess the treatment effect (ACE-083 vs. placebo) using a 2-sided 0.10 significance level for the percent change from baseline. Least squares estimates of the treatment effect and corresponding 90% confidence intervals will be provided. In addition, least squares estimates of the treatment effect and corresponding 90% confidence intervals will be provided for patients having dorsiflexion MMT-MRC grade of 4- to 4+ on both sides.

Additional analyses may be performed as appropriate.

Open-label extension

For the MVIC value and decimal MMT-MRC score for each side treated as well as the average from the left and right sides, CMTES2 score, CMT-HI total score and selected subscale scores, and motor function test assessments, raw data and changes (percent and absolute change) from the start of the open-label extension (Day 190) will be summarized by treatment for each scheduled time using descriptive statistics.

Additional analyses may be performed as appropriate.

Open-label extension vs. double-blind placebo-controlled phase

For the MVIC value [average from the left and right sides] decimal MMT-MRC score [average from the left and right sides], CMTES2 score, CMT-HI total score and selected subscale scores, and motor function test assessments, 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 [depending on the parameter] observed between Day 190 and pre-first treatment baseline (1st 6 months) and Day 358 versus Day 190 (2nd 6 months) using a mixed model. Least squares estimates of this effect and 95% confidence intervals will be provided. In addition, least squares estimates of this effect and corresponding 95% confidence intervals will be provided for patients having dorsiflexion MRC-MMT grade of 4- to 4+ on both sides.

Additional analyses may be performed as appropriate.

14.2.4. Pharmacodynamic Data

Part 1

Individual pharmacodynamic data will be listed. For individual pharmacodynamic data that is measured on the left and right side (i.e., MRI), the average of the left and right side assessments will also be listed and summarized.

Descriptive statistics (change from baseline [percent and absolute change]) will be provided by treatment group and scheduled time. In addition, for muscle volume and intramuscular fat fraction, a repeated measures ANCOVA will be fitted to the percent change from baseline data and estimates of the effect of ACE-083 at 3 weeks post last dose and corresponding 90% confidence intervals will be provided.

Additional analyses may be performed as appropriate.

Part 2

Individual pharmacodynamic data will be listed. For individual pharmacodynamic data that is measured on the right and left side (i.e., MRI), the average of the left and right side assessments will also be listed and summarized.

Double-blind, placebo-controlled phase

Descriptive statistics for raw data and changes from baseline (percent and/or absolute change) will be provided for each pharmacodynamic parameter by treatment group for each scheduled time. For pharmacodynamic parameters that are measured on the right and left side (i.e., MRI), the descriptive statistics will include summaries for each side and the average of the right and left sides.

The primary pharmacodynamic parameter will be the percent change in total muscle volume (average of left and right side) 3 weeks after the last dose of the double-blind treatment period (Day 190) from the corresponding baseline. A mixed model will be used to assess the treatment effect (ACE-083 vs. placebo) using a 2-sided, 0.10 significance level. If data from the end of treatment visit are missing, the last observation will be carried forward. Additional techniques for handling missing data will also be evaluated as sensitivity analyses to the last observation carried forward approach. Least squares estimates of the effect of ACE-083 and the corresponding 90% confidence interval will be produced. In addition, least squares estimates of the treatment effect and corresponding 90% confidence intervals will be provided for patients having dorsiflexion MRC-MMT grade of 4- to 4+ on both sides.

For each secondary pharmacodynamic parameter, a mixed model will also be used to assess the treatment effect using a 2-sided 0.10 significance level for the following secondary

pharmacodynamic variables: percent change from baseline for the average of the left and right side at 3 weeks after the last dose of the double-blind treatment period (Day 190) for intramuscular fat fraction as well as derived variables such as contractile muscle fraction and contractile muscle volume. Least squares estimates of the effect of ACE-083 and corresponding 90% confidence interval will be provided. In addition, least squares estimates of the treatment effect and corresponding 90% confidence intervals will be provided for patients having dorsiflexion MRC-MMT grade of 4- to 4+ on both sides.

For biomarker data (e.g., IGF-1 and CTX) and TA CMAP amplitude, raw data and changes from baseline (percent and absolute change) will be summarized by treatment group and scheduled time. Such analyses will be considered exploratory.

Additional analyses may be performed as appropriate.

Open-label extension

Descriptive statistics for the percent change from baseline will be provided for each pharmacodynamic variable by treatment group for each scheduled time. For pharmacodynamic variables that are measured on the right and left side (i.e., MRI), the descriptive statistics will include summaries for each side and the average of the right and left sides.

For each pharmacodynamic variable, raw data and changes (percent and/or absolute change) from the start of the open-label extension (Day 190) will be summarized by treatment for each scheduled time using descriptive statistics.

Additional analyses may be performed as appropriate.

Open-label extension vs. double-blind placebo-controlled phase

For each of the following pharmacodynamic variables, a mixed model will be used to assess the effect ACE-083 administered during the open-label extension [Day 358 vs. Day 190 (2^{nd} 6 months)] compared to the effect of the treatment administered in the double-blind placebo-controlled phase [Day 190 vs. pre-first treatment baseline (1^{st} 6 months)] separately for those receiving placebo during the double-blind phase as well as for those receiving ACE-083 during the double-blind phase:

- Percent change in total muscle volume (average of right and left sides) during the open-label extension vs. double-blind phase
- Percent change in intramuscular fat fraction (average of right and left sides) during the open-label extension vs. double-blind phase
- Percent change in contractile muscle fraction (average of right and left sides) during the open-label extension vs. double-blind phase
- Percent change in contractile muscle volume (average of right and left sides) during the open-label extension vs. double-blind phase

Least squares estimates of this effect and 95% confidence intervals will be provided. In addition, point estimates of this effect and corresponding 95% confidence intervals will be provided for patients having dorsiflexion MRC-MMT grade of 4- to 4+ on both sides.

Additional analyses may be performed as appropriate.

14.2.4.1. Pooled Analyses

If applicable, similar analyses will be performed for pooled Part 1 and 2 data for patients at the same dose level. Pooling by the estimated local dose of ACE-083 in the injected muscle (i.e., mg ACE-083/g muscle) may also be performed. Details of these analyses will be included in the SAP.

14.2.5. Safety Data

Unless otherwise specified, safety data will be summarized using descriptive statistics and individual safety data will be listed. AEs will be coded using the Medical Dictionary for Regulatory Activities. Incidence of treatment-emergent AEs will be presented by system organ class and preferred term. AE incidence rates will be described by cohort with and without regard to causality. The frequency of occurrence of overall toxicity, categorized by toxicity grades (NCI-CTCAE, current version) will be summarized. Change from baseline in clinical laboratory parameters, ECG, and vital signs will be summarized across time. Shift tables will be presented for selected laboratory parameters and vital signs. Physical examination results will be presented in listings.

14.2.6. Pharmacokinetic Data

Individual patient serum ACE-083 concentrations will be listed and summarized by treatment group. Listings will also include dosing times and actual sampling times relative to dosing. Individual and mean concentration data versus time will also be presented graphically. PK parameters of ACE-083 will be determined using the standard non-compartmental method. Individual PK parameters will be listed and will be summarized by treatment group.

14.2.7. Anti-drug Antibody Data

The results of ADA testing for ACE-083 versus time as well as results following further characterization of positive ADA samples will also be presented. Exploratory analysis will be performed on the potential effect of ADA on ACE-083 PK exposure if ADA tests are determined to be positive.

14.3. Determination of Sample Size

There is no formal sample size calculation for Part 1. Six patients in each cohort will provide sufficient data to evaluate safety and preliminary efficacy data.

The sample size calculation for Part 2 is based upon the expected percent change from baseline in total muscle volume of the injected TA 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 SD is estimated to be approximately 10% for each group based on preliminary MRI data for the ACE-083 treated side of the TA muscle from Part 1 of the Phase 2 study in FSHD patients. Assuming a 2-sided type 1 error rate of 0.10, a 10% difference in percent change from baseline between the 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 n=36 patients (18 active, 18 placebo), based on a standard t-test.

In addition, this sample size provides 90% power to detect a 10% difference in 6MWD, based on an assumed 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 (20 active, 20 placebo) to ensure that at least 18 patients per treatment group complete the double-blind treatment period.

14.4. Interim Analysis

For Part 1, periodic reviews of the available safety and tolerability will be done to assist dose escalation decisions. For Part 2, no interim analyses are planned.

14.5. Deviation from Original Analysis Plan

A formal statistical analysis plan for the analysis and presentation of data from this study will be prepared before the database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

15. ETHICS

15.1. Institutional Review Board

The investigator will submit this protocol, any protocol modifications, and the patient ICF to be used in this study to the appropriate IRB/IEC for review and approval. A letter confirming IRB/IEC approval of the protocol and ICF as well as a statement that the IRB/IEC is organized and operates according to GCP and the applicable laws and regulations, must be forwarded to the sponsor prior to the enrollment of patients into the study. A copy of the approved ICF will also be forwarded to the sponsor. Appropriate reports on the progress of the study will be made to the IEC and the sponsor by the principal investigator in accordance with applicable governmental regulations and in agreement with the policy established by the sponsor.

15.2. Ethical Conduct of the Study

The sponsor and the investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

15.3. Patient Information and Consent

Informed written consent is required from each patient prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the study center's IEC, must follow the Protection of Human Patients regulations listed in the Code of Federal Regulations, Title 21, Part 50. The principles of informed consent in the Declaration of Helsinki should be implemented in this clinical study and should comply with local and national regulations. The consent forms must be in a language fully comprehensible to the prospective subject. Information should be given in both oral and written form whenever possible and deemed appropriate by the IEC.

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the patients. It is the responsibility of the investigator to obtain consent and to provide the patient with a copy of the signed and dated ICF. Confirmation of a patient's informed consent must also be documented in the patient's medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IEC and by the sponsor or designee. The ICF must not be altered without the prior agreement of the relevant IEC and the sponsor.

15.4. Patient Data Protection

Prior to any testing under this protocol, including screening tests and evaluations, patients must authorize the release and use of protected health information, as required by local law.

The patient will not be identified by name in the CRF or in any study reports. These reports will be used for research purposes only. The sponsor, its designee, and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient's personal medical data confidential.

16. SOURCE DOCUMENTATION AND INVESTIGATOR FILES

16.1. Study Monitoring

The clinical monitor will arrange to visit the clinical sites at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the clinical sites and their facilities. During these visits, CRFs and other data related to the study will be reviewed and any discrepancies or omissions will be resolved. The clinical monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

16.2. Audits and Inspections

The investigators and clinical sites will permit trial-related monitoring, audits, IEC review, and regulatory inspections as requested by FDA or other health authorities and the sponsor or designee. In addition to CRFs, the clinical site will permit direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.). During and/or after completion of the study, quality assurance officers named by the sponsor or the regulatory authorities may wish to perform on-site audits. The investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

17. QUALITY CONTROL AND QUALITY ASSURANCE

17.1. Data Quality Control and Quality Assurance

17.1.1. Investigator Responsibility

The investigator is responsible for ensuring the study is conducted according to the protocol, Code of Federal Regulations, GCP, and applicable regulatory requirements. The investigator's responsibilities are outlined in these documents and must include the responsibility to obtain a signed informed consent prior to patient participation in the study.

17.1.2. Protocol Modifications

The investigator should not modify the protocol without agreement from the sponsor and prior review or approval by the IEC, unless an emergency situation requires protocol modification to ensure the safety of patients. Any deviations from the protocol should be documented by the investigator or designee.

18. CONFIDENTIALITY

To maintain patient privacy, all CRFs, study drug accountability records, study reports and communications will identify the patient by the assigned patient identification number. The investigator will grant clinical monitor(s) and auditor(s) from the sponsor or designee and regulatory authorities' access to the patient's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available. The patient's medical information will only be released to the extent permitted by the applicable laws and regulations.

All information regarding the investigational product supplied by the sponsor to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

19. PUBLICATION POLICY

All information concerning study drug is considered confidential and shall remain the sole property of the sponsor. The investigator(s) agrees to use this information only in conducting the study and shall not use it for any other purposes without the sponsor's written approval. The investigator(s) agrees not to disclose the sponsor's confidential information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

It is understood by the investigator(s) that the information developed from this clinical study will be used by the sponsor in connection with the development of study drug, and therefore may be disclosed as required to regulatory agencies. To allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between the sponsor and the investigator(s).

20. PROTOCOL AMENDMENTS

Protocol amendments that impact patient safety, change the scope of the investigation, or affect the scientific quality of the study must be approved by the IEC and submitted to the appropriate regulatory authorities before implementation.

In the event that the protocol needs to be modified immediately to eliminate an apparent hazard to a patient, the sponsor will implement the protocol change and subsequently amend the protocol and notify the regulatory authorities and/or the IEC, as appropriate.

21. DATA HANDLING AND RECORDKEEPING

21.1. Case Report Form Completion

CRFs will be completed for each enrolled patient. It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

Investigators will maintain copies of the CRFs at the clinical site. For patients who discontinue or terminate from the study, the CRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate CRF.

21.2. Retention of Records

The investigator will maintain all study records according to ICH GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product, or according to applicable regulatory requirements. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The sponsor must be notified in writing if a custodial change occurs.

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23. APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS

Table 5: Schedule of Events for Part 1: Non-Randomized, Open-Label, Dose Escalation

	Screening Period	Treatment Period						Follow-Up Period	
	Day -28 to Day -7	Dose 1		Dose 2	Dose 3	Dose 4	Dose 5	Day 106/ET[2] (±3d)	Day 141 (±3d)
		Day 1[1]	Day 8 (±1d)	Day 22[1] (±3d)	Day 43[1] (±3d)	Day 64[1] (±3d)	Day 85[1] (±3d)		
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Urine pregnancy test[3]		X		X	X	X	X		
Medical history	X	X							
MRT assessment (MRC)[15]	X								
Genetic testing[17]	X								
Physical examination[4]	X	X		X		X		X	
Injection site examination[5]		X	X	X	X	X	X	X	
Vital signs[6]	X	X	X	X	X	X	X	X	
Hematology[7]	X	X		X	X	X	X	X	
Chemistry[7]	X	X		X	X	X	X	X	
Urinalysis[7]	X	X			X	X		X	
Biomarkers[7]	X	X		X	X	X		X	X
Anti-drug antibody		X	X	X	X	X	X	X	X[8]
Serum PK[9]		0, 1, 2, 4, 6 h	X	X	X	X	0, 1, 2, 4, 6 h	X	X
ECG (12 lead)		X							
Bilateral MRI[10]		X			X			X	X
Timed function tests[11]	X	X		X	X	X	X	X	X
Balance and gait tests[12]	X	X			X			X	X
Strength test[13]	X	X	X	X	X	X	X	X	X
CMTES2[14]	X	X			X			X	X
CMT-HI[14]	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[16]		X		X	X	X	X		

[1] 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. Time of study drug administration is the time of the first injection.

[2] 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.

[3] Pregnancy test for women of childbearing potential to be performed and negative result confirmed before dosing.

[4] 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.

[5] 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.

[6] 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.

[7] Including but not limited to: insulin-like growth factor-1 (IGF-1), serum C-terminal collagen crosslinks (CTX)

[8] 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.

[9] PK samples on dosing day have a ±15 minute window for post-dose sample collection, based on time of first injection. Pre-dose samples may be collected up to 4 hours prior to dosing.

[10] 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.

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

[12] Gait parameters, Berg balance scale. Tests may be performed within 3 days prior to Day 1 visit.

[13] Maximum voluntary isometric contraction testing will be conducted using a handheld dynamometer. Both sides will be tested (right and left).

[14] CMTES2 to be assessed by investigator; CMT-HI to be completed by patient

[15] Includes knee extension, ankle dorsiflexion, and ankle plantarflexion

[16] Study drug administration should occur within 21 days (± 3 days) of the previous dose.

[17] To be performed at screening if patient has not already had testing performed previously.

Table 6: Schedule of Events for Part 2: Randomized, Double-Blind, Placebo-Controlled with Open-Label Extension

	Screening	Double-Blind, Placebo-Controlled										Open-Label					ET[2]	EOS[23]
Dose(s)	--	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11, 12, 13, 14**	**15**	**16**	**17**	--	--
Planned Day(s)	-28 to -7	1[1]	8 (±1d)	22[1] (±1d)	43[1] (±3d)	64[1] (±3d)	85[1] (±3d)	106[1] (±3d)	127[1] (±3d)	148[1] (±3d)	169[1] (±3d)	190[1] (±3d)	(211, 232, 253, 274)[1] (±3d)	295[1] (±3d)	316[1] (±3d)	337[1] (±3d)	358 (±3d)	393 (±3d)
Informed consent	X																	
Inclusion/exclusion criteria	X																	
Urine pregnancy test[3]		X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Medical history	X	X																
MMT assessment (MRC)[4]	X											X		X			X	X
Genetic testing[5]	X																	
Full physical examination[6]	X							X				X		X			X	X
Limited physical examination[7]		X		X		X			X	X	X		X		X	X		
Injection site examination[8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[10]	X	X		X	X	X	X	X		X		X	X	X		X	X	
Chemistry[10]	X	X		X	X	X	X	X		X		X	X	X		X	X	
Urinalysis[10]	X	X			X	X	X	X		X		X	X	X		X	X	
Biomarkers[11]	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[12]
Serum PK[13]		0, 1, 2, 4, 6 h	X				0, 1, 2, 4, 6 h					X		X			X	X
ECG (12 lead)	X	4 h[14]					4 h[14]											
Bilateral MRI[15]		X			X			X				X		X			X	X
Timed function tests[16]	X	X		X	X	X	X	X		X		X	X	X		X	X	X
Balance and gait tests[17]	X	X						X				X		X			X	X
Strength tests[18]	X	X	X	X	X	X	X	X		X		X	X	X		X	X	X
CMTES2[19]	X	X						X				X		X			X	X
CMT-HI[19]	X				X			X		X		X		X			X	X
CMAP of tibialis anterior	X											X					X	

	Screening	Double-Blind, Placebo-Controlled										Open-Label					ET[2]	EOS[23]
Dose(s)	--	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11, 12, 13, 14**	**15**	**16**	**17**	--	--
Planned Day(s)	-28 to -7	1[1]	8 (±1d)	22[1] (±1d)	43[1] (±3d)	64[1] (±3d)	85[1] (±3d)	106[1] (±3d)	127[1] (±3d)	148[1] (±3d)	169[1] (±3d)	190[1] (±3d)	(211, 232, 253, 274)[1] (±3d)	295[1] (±3d)	316[1] (±3d)	337[1] (±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	X
Monitoring of adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[20]		X																
Distribution of PAMSys™ Device[21]	X																	
Study drug administration[22]		X		X	X	X	X	X	X	X	X	X	X	X	X	X		

[1] 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. Time of study drug administration is the time of the first injection.

[2] 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.

[3] Pregnancy test for women of childbearing potential to be performed and negative result confirmed before dosing.

[4] Includes knee extension, ankle dorsiflexion, and ankle plantarflexion.

[5] To be performed at screening if patient has not already had testing performed previously.

[6] Full physical examination includes skin, head, eyes, ears, nose, throat and neck, lymph nodes, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological

[7] Limited physical examination includes skin, cardiovascular, respiratory, musculoskeletal and neurological assessments

[8] 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.

[9] 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.

[10] Tests defined in Appendix 2, Table 7.

[11] Including but not limited to: insulin-like growth factor-1 (IGF-1) and serum C-terminal collagen crosslinks (CTX)

[12] 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.

[13] PK samples on a dosing day have a ±15 minute window for post-dose sample collection, based on the time of the first injection. Pre-dose samples may be collected up to 4 hours prior to dosing.

[14] ECG is to be conducted ±1 hour of the 4h PK sample.

[15] 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.

[16] 10-meter walk/run, 6-minute walk, 100-meter timed test (Part 2, open-label only; starting at the Dose 10 visit and continuing through to the EOS visit at all timepoints noted). Tests may be performed within 3 days prior to Day 1 visit.

[17] Gait parameters, Berg balance scale. Tests may be performed within 3 days prior to Day 1 visit.

[18] Maximum voluntary isometric contraction testing will be conducted using a handheld dynamometer. Both sides will be tested (right and left).

[19] CMTES2 to be assessed by investigator; CMT-HI to be completed by patient

[20] Randomization should occur within 24 hours prior to Day 1 dose.

[21] PamSys™ device is a physical activity monitoring system that will be worn by the patient for the duration of the study.

[22] Study drug administration should occur within 21 days (± 3 days) of the previous dose.

[23] If subjects enroll directly into a separate extension study and will receive additional treatment with ACE-083, they do not need to complete the EOS visit. For these subjects, their final Study Visit in this protocol will be the ET visit.

APPENDIX 2. CLINICAL SAFETY LABORATORY ASSESSMENTS

Table 7: Clinical Safety 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
Urinalysis	Dipstick analysis (pH, specific gravity, protein, myoglobin, glucose, ketones, blood, leukocyte esterase, and nitrite)

APPENDIX 3. CHARCOT-MARIE-TOOTH DISEASE CLASSIFICATION

Classification and Genetics of CMT Disease[10]

Inheritance	Pathophysiology	Type	Example gene associations
Autosomal dominant	Demyelinating	CMT1	*PMP22, MPZ, LITAF/SIMPLE, EGR2, NEFL, FBLN5*
	Axonal	CMT2	*KIF1B, MFN2, RAB7, TRPV4, GARS, NEFL, HSPB1, MPZ, GDAP1, HSPB8, DNM2, AARS, DYNC1H1, LRSAM1, DHTKD1, DNAJB2, HARS, MARS, MT-ATP6, TFG*
	Intermediate	CMTDI	*DNM2, YARS, MPZ, IFN2, GNB4*
Autosomal recessive	Demyelinating	CMT4	*GDAP1, MTMR2, MTMR13 (SBF2), SBF1, SH3TC2, NDRG1, EGR2, PRX, HK1, FGD4, FIG4, SURF1*
	Axonal	CMT2	*LMNA, MED25, GDAP1, MFN2, NEFL, HINT1, TRIM2, IGHMBP2, GAN*
	Intermediate	CMTRI	*GDAP1, KARS, PLEKHG5, COX6A1*
X-linked	Intermediate or axonal	CMTX	*GJB1, AIFM1, PRPS1, PDK3*

APPENDIX 4. MEDICAL RESEARCH COUNCIL MANUAL MUSCLE TESTING GRADING SCALE

Grading Scale for Manual Muscle Testing (MMT)[11,12]

MMT Grade	Description
5	Normal strength
5-	Uncertain muscle weakness
4+	Inability to resist against maximal pressure throughout range of motion
4	Ability to resist against moderate pressure throughout range of motion
4-	Ability to resist against minimal pressure throughout range of motion
3+	Ability to move through full range of motion against gravity and to resist against minimal pressure through partial range of motion, then contraction breaks abruptly
3	Ability to move through full range of motion against gravity
3-	Ability to move through greater than one half range of motion against gravity
2+	Ability to move through less than one half range of motion against gravity
2	Ability to move through full range of motion with gravity eliminated
2-	Ability to move in any arc of motion with gravity eliminated
1	A flicker of movement is seen or felt in the muscle
0	No contraction palpable