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

- 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

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

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.

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.

[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.

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*

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:

- 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

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

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

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

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	

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