Abbreviation or Specialist Term	Explanation
IEC	Independent ethics committee
IGF-1	Insulin-like growth factor-1
IgG2	Immunoglobulin G2
IP	Investigational product
IRB	Institutional review board
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
PUL	Performance of the upper limb
qXw	Every X weeks
QMT	Quantitative muscle testing
QoL	Quality of life
SAE	Serious adverse event
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

- Percent change from baseline in muscle volume of injected muscle by magnetic resonance imaging (MRI)

Secondary:

- Percent and absolute change from baseline in the intramuscular fat fraction of injected muscle by MRI
- Percent change from baseline in strength measurements
- Percent and absolute change from baseline in functional assessments: For tibialis anterior (TA) muscle: 10-meter walk/run, 6-minute walk test, 4-stair climb (subjects from A083-02 only), and 100-meter timed test; for biceps brachii (BB) muscle: mid-level and high level performance of the upper limb (PUL) test
- Absolute change from baseline in FSHD-health index (FSHD-HI, subjects from A083-02) or CMT health index (CMT-HI, subjects from A083-03) total score and subscale scores
- PK parameters of ACE-083 serum concentrations over time

Exploratory:

- Percent and absolute change from baseline in biomarkers.
- Percent and absolute change in PD parameters as a function of ACE-083 exposure

Methodology

Subjects who have signed the informed consent form (ICF) and meet the eligibility criteria will be enrolled into the study. This is an open-label, multicenter, phase 2 extension study to evaluate the safety, tolerability, PK, PD, and efficacy of ACE-083 in subjects with FSHD previously enrolled in Study A083-02 and subjects with CMT1 and CMTX previously enrolled in Study A083-03. This study will be conducted in two Parts: Part 1, which is a loading phase of 6 months' duration, and Part 2, the maintenance phase, which will last up to 24 months.

7. STUDY DESIGN

7.1. Overview of Study Design

This is an open-label, multicenter, phase 2 extension study to evaluate the safety, tolerability, PD, efficacy, and PK of ACE-083 in patients with FSHD previously enrolled in Study A083-02 and patients with CMT1 and CMTX previously enrolled in Study A083-03. This study will be conducted in two Parts: Part 1, consisting of a loading phase of 6 months, and Part 2, consisting of a maintenance phase of 24 months. Subjects who enroll in this study without interruption of treatment following the previous study will enroll directly into Part 2 of this study.

Part 1 is a non-randomized, open-label, loading phase in which subjects will receive bilateral injections of 240 mg/muscle ACE-083 every 4 weeks. Part 1 will include subjects previously treated in Part 1 of Studies A083-02 and A083-03 after a washout period of at least 3 months. Upon completion of this 6-month loading phase, these subjects will then rollover into Part 2 of this study, which is the maintenance phase.

Subjects who complete Part 2 of study A083-02 or A083-03 will enroll directly into Part 2 of this study without interruption. The end-of-treatment visit in the previous study will coincide with the Day 1 visit of this study. Part 2 is an open-label maintenance phase study in which subjects will be randomized to receive bilateral injections of 240 mg/muscle ACE-083 either every 4 weeks or every 8 weeks. A schematic diagram of subject enrollment and disposition is shown in Figure 1.

Duration of Treatment

For subjects enrolled in Part 1 and Part 2 of this study, study duration will be approximately 33 months, including a screening period of up to 1 month, the 6-month Part 1 loading phase, the Part 2 maintenance phase of 24 months, and a 2-month follow-up period.

For subjects who enroll directly into Part 2 of this study from Part 2 of Study A083-02 or A083-03, study duration will be approximately 26 months, including a maintenance phase of 24 months and a 2-month follow-up period. These subjects will sign the Informed Consent Form (ICF) for this study at the end-of-treatment visit for Study A083-02 or Study A083-03 (i.e., Day 1 of this study).

If a subject has a positive anti-drug antibody (ADA) result at the last scheduled follow-up visit, the subject may be asked to return for additional ADA testing approximately every 3 months, until a negative result is obtained or the titer is no longer increasing.

Part 1 (non-randomized, open-label, loading phase with subjects from A083-02 Part 1 and A083-03 part 1)

Part 1 will consist of 3 cohorts of up to 18 subjects each. In this loading phase, 240 mg/muscle ACE-083 will be administered bilaterally q4w for 6 doses (6 months) into either the TA muscle or BB muscle, depending on the muscle injected in the previous study; subjects may not switch muscle cohort upon enrollment in this study. Subjects in each cohort will be enrolled in a screening period of up to 4 weeks before beginning treatment.

Subjects enrolled in Cohorts 1a and 1b will have completed the 3-month, dose escalation, non-randomized, open-label Part 1 of Study A083-02. As part of that study, these subjects will have

previously received injections of up to 240 mg/muscle ACE-083, either unilaterally or bilaterally, q3w for up to 5 doses.

Subjects enrolled in Cohort 1c, will have completed the 3-month, dose escalation, non-randomized, open-label Part 1 of Study A083-03. These subjects will have previously received up to 240 mg/muscle ACE-083 bilaterally by injection into the TA every q3w for up to 5 doses.

Part 2 (randomized, open-label rollover maintenance phase, with subjects from Part 1 A083-04 and A083-02 part 2 and A083-03 part 2)

Part 2 will consist of 6 additional cohorts. Cohorts 2a, 2b, and 2c will receive 240 mg/muscle ACE-083 q4w, and Cohorts 3a, 3b, and 3c will receive 240 mg/muscle ACE-083 q8w. Cohorts are separated and randomized based upon disease (FSHD or CMT) and target muscle (BB or TA).

Subjects who complete Part 1 (loading phase), will immediately rollover into Part 2 (open-label maintenance phase) treatment with ACE-083. The subjects will be randomized into treatment groups to receive 240 mg/muscle ACE-083 bilaterally either q4w or q8w.

Subjects who completed Part 2 of Study A083-02 or Part 2 of Study A083-03 will directly enter into Part 2 (open-label maintenance phase) of this study and will be randomized to receive 240 mg/muscle either q4w or q8w. The first study visit of this study will coincide with the end-of-treatment visit of the previous study (either A083-02 or A083-03).

7.2. Justification for Dose Level

A starting dose of 150 mg/muscle was used in the dose escalation cohorts in Part 1 of Phase 2 Study A083-02 and Part 1 of Phase 2 Study A083-03, with a maximum dose in these studies of 240 mg/muscle unilaterally or bilaterally q3w for 3 months (5 doses). All doses were well-tolerated, including bilateral cohorts. The most common TEAEs in all cohorts were grade 1 injection site reactions, and there were no treatment-related SAEs. Injections of 150 to 240 mg/muscle ACE-083 produced significant, dose-dependent muscle volume increases that were maintained for up to 8 weeks following the last dose.

Based upon these safety and efficacy data, the dose of 240 mg/muscle bilaterally was chosen for Part 2 of the A083-02 and A083-03 studies as well as for this extension study. This study will evaluate if long-term, maintenance phase dosing of 240 mg/muscle q8w and/or q4w can maintain total muscle volume increases and functional improvements reached at the conclusion of the loading phase (q3w or q4w for 6 months). Any changes in the dose level or schedule in this study will be determined following review of study data and recommendations from the SRT. A maximum absolute dose level of 240 mg/muscle has been chosen based in part 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 during the treatment period that occurs in a subject who has received a treatment in this protocol. An AE does not necessarily have a causal relationship with treatment and can be any unfavorable and unintended sign, symptom, or disease (including an abnormal laboratory finding) temporally associated with the use of 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 (after the first dose in this protocol), 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 in a child of a subject that was exposed to study drug prior to conception or during pregnancy
- 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 guidance.

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. Subjects 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 subjects 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 701/End of Study visit 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 until resolution as described in Section 13.5.

It is important that each AE report include a description of the event, duration (onset and resolution dates), severity, relationship to 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 in Part 1 until the End of Study visit in 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 subjects 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 subject 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 subjects 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 subjects 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. Subjects must be counseled about effective contraception at the beginning of this study and every three months thereafter until the EOS Visit.

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 subject must discontinue study drug immediately. Monitoring of the subject 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.

Table 8: Schedule of Events for Part 1: Loading Phase

	Screening	Part 1: Loading Phase*					
Dose	-	L1	L2	L3	L4	L5	L6
Planned Day	-28 to -1	1	29 ± 3d	57 ± 3d	85 ± 3d	113 ± 3d	141 ± 3d
Informed Consent	X						
Inclusion/exclusion criteria	X						
Urine pregnancy test		X		X		X	
Medical History	X						
MMT assessment (MRC)	X	X			X		
Full Physical examination[2]	X						
Limited Physical examination[2]		X			X		
Injection site examination		X	X	X	X	X	X
Vital signs[3]	X	X	X	X	X	X	X
Hematology	X	X		X		X	
Chemistry	X	X		X		X	
Urinalysis		X		X		X	
Biomarkers		X			X		
Anti-drug antibody	X	X		X		X	
Serum PK[6]		0,1, 2, 4, 24 h			0,1, 2, 4, 24 h	X	X
ECG (12 lead)[7]	X	X			X		
Bilateral MRI[4]		X			X		
10MWR, 6MWT, 100mTT (all TA subjects); 4-stair climb (FSHD TA subjects); PUL (FSHD BB subjects)[5]	X	X			X		
QMT assessment (MVIC by hand-held dynamometer)	X	X			X		
FSHD-HI or CMT-HI	X	X			X		
Monitoring of concomitant medications	X	X	X	X	X	X	X
Monitoring of adverse events	X	X	X	X	X	X	X
Study drug administration[1]		X	X	X	X	X	X

* The L before the Dose in this table denotes that these doses occur in the Loading Phase.
[1] Study procedures must be done prior to administration of study drug. Reference the Study Manual for the order of study procedures. All visit-day windows should be considered relative to the date of the previous dose of ACE-083. Actual visit days (e.g. Day 29, Day 57) may be different than planned due to windows on visits and dosing delays.
[2] Full physical examination during the screening period; limited physical examination for Days 1, 85.
[3] Vital signs (weight, heart rate, systolic and diastolic blood pressure) must be taken prior to administration of study drug on dosing days
[4] MRI should be completed within 5 days prior to scheduled dose administration, with the exception of the Day 1 MRI, which may be completed within 14 days prior to the Day 1 visit. If performed on the same day as study drug administration, the subject should receive the MRI first.
[5] These function tests may be performed within 3 days prior to Day 1 visit.
[6] PK samples on dosing day have a ±15 minute window with the exception of the 24 h time point, which has a ± 2 window. Pre-dose samples may be collected up to 4 h prior to dosing.
[7] ECG to be conducted ±1 hour of the 4h PK sample

Table 9: Schedule of Events for Maintenance Phase and Follow-up: q4w dosing arm

	Part 2: Maintenance Phase												Follow-up Visits	
Planned Day(s)	**1** ± 3d	**29** ± 3d	**57** ± 3d	**85** ± d	**113** ± 3d	**141** ± 3d	**169** ± 3d	**197-309** ± 3d	**337** ± 3d	**365-477** ± 3d	**505** ± 3d	**533-645** ± 3d	**ET 673** ± 5d	**EOS 701** ± 5d
Dose number (q4w)	1	2	3	4	5	6	7	8-12	13	14-18	19	20-24		
Study Drug Administration[1]	X	X	X	X	X	X	X	X	X	X	X	X		
Informed consent	X													
Urine pregnancy test	X		X		X		X		X		X		X	
MMT assessment (MRC)	X				X		X		X		X		X	X
Limited physical examination[2]	X				X		X		X		X			X
Injection site examination	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X				X		X		X		X		X	
Chemistry	X				X		X		X		X		X	
Urinalysis	X				X		X		X		X		X	
Biomarkers	X				X		X		X		X		X	X
Anti-drug antibody	X				X		X		X		X		X	X
ECG (12 lead)	X				X		X		X		X		X	
Bilateral MRI [4]	X				X		X		X		X		X	
10MWR, 6MWT, 100mTT (all TA subjects); 4-stair climb (FSHD TA subjects); PUL (FSHD BB subjects) [5]	X				X		X		X		X		X	X
QMT assessment (MVIC by hand-held dynamometer)	X				X		X		X		X		X	X
CMT-HI/FSHD-HI	X				X		X		X		X		X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	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. For subjects who enroll in A083-04 without treatment interruption, the Day 1 Dose 1 (D1D1) visit may coincide with the ET visit of the base study (either A083-032 or A083-03). For these subjects without treatment interruption, the D1D1 procedures shaded in grey may be conducted as part of the ET visit for Study A083-02 or A083-03 and may not need to be repeated for study A083-04.

Visit schedule: All visit-day windows should be considered relative to the date of the previous dose of ACE-083. Actual visit days (e.g. Day 29, Day 57, Day 85) may be different than planned due to windows on visits and potential dosing delays.

[2] Limited physical examination (skin, cardiovascular, respiratory, musculoskeletal, and neurological assessments) only.

[3] Vital signs (weight, heart rate, systolic and diastolic blood pressure) must be taken prior to administration of study drug on dosing days

[4] MRI assessments should be completed within 5 days prior to scheduled dose administration, with the exception of the Day 1 MRI, which may be completed within 14 days prior to the Day 1 visit. If performed on the same day as study drug administration, the subject should receive the MRI first. MRI assessments during the follow-up period have a ± 5-day window.

[5] These function tests may be performed within 3 days prior to Day 1 visit.

Table 10: Schedule of Events for Maintenance Phase and Follow-up: q8w dosing arm

	Part 2: Maintenance Phase												Follow-up Visits	
Planned Day(s)	**1**	**57** ± 5d	**113** ± 5d	**169** ± 5d	**225** ± 5d	**281** ± 5d	**337** ± 5d	**393** ± 5d	**449** ± 5d	**505** ± 5d	**561** ± 5d	**617** ± 5d	**ET 673** ± 5d	**EOS 701** ± 5d
Dose number (q8w)	1	2	3	4	5	6	7	8	9	10	11	12		
Study Drug Administration[1]	X	X	X	X	X	X	X	X	X	X	X	X		
Informed consent	X													
Urine pregnancy test	X	X	X	X			X			X				
MMT assessment (MRC)	X		X	X			X			X			X	X
Limited physical examination[2]	X		X	X			X			X			X	X
Injection site examination	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X		X	X			X			X			X	
Chemistry	X		X	X			X			X			X	
Urinalysis	X		X	X			X			X			X	
Biomarkers	X		X	X			X			X			X	X
Anti-drug antibody	X		X	X			X			X			X	X
ECG (12 lead)	X		X	X			X			X			X	
Bilateral MRI [4]	X		X	X			X			X			X	
10MWR, 6MWT, 100mTT (all TA subjects); 4-stair climb (FSHD TA subjects); PUL (FSHD BB subjects)[5]	X		X	X			X			X			X	X
QMT assessment (MVIC by hand-held dynamometer)	X		X	X			X			X			X	X
CMT-HI/FSHD-HI	X		X	X			X			X			X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	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. For subjects who enroll in A083-04 without treatment interruption, the Day 1 Dose 1 (D1D1) visit may coincide with the ET visit of the base study (either A083-032 or A083-03). For these subjects without treatment interruption, the D1D1 procedures shaded in grey may be conducted as part of the ET visit for Study A083-02 or A083-03 and may not need to be repeated for study A083-04.

Visit schedule: All visit-day windows should be considered relative to the date of the previous dose of ACE-083. Actual visit days (e.g. Day 29, Day 57, Day 113) may be different than planned due to windows on visits and potential dosing delays.

[2] Limited physical examination (skin, cardiovascular, respiratory, musculoskeletal, and neurological assessments) only.

[3] Vital signs (weight, heart rate, systolic and diastolic blood pressure) must be taken prior to administration of study drug on dosing days

[4] MRI assessments should be completed within 5 days prior to scheduled dose administration, with the exception of the Day 1 MRI, which may be completed within 14 days prior to the Day 1 visit. If performed on the same day as study drug administration, the subject should receive the MRI first. MRI assessments during the follow-up period have a ± 5-day window.

[5] These function tests may be performed within 3 days prior to Day 1 visit.

APPENDIX 2. CLINICAL SAFETY LABORATORY ASSESSMENTS

Table 11: 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. MEDICAL RESEARCH COUNCIL MANUAL MUSCLE TESTING GRADING SCALE

Grading Scale for Manual Muscle Testing (MMT)[14,15]

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

For subjects who receive BB treatment, elbow flexion will be tested. In TA-treated subjects, dorsiflexion, plantar flexion, and knee extension measurements will be taken.

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: An Open-Label Extension Study to Evaluate the Long-Term Effects of ACE-083 in Patients with Facioscapulohumeral Muscular Dystrophy (FSHD) Previously Enrolled in Study A083-02 and in Patients with Charcot-Marie Tooth (CMT) Disease Types 1 and X Previously Enrolled in Study A083-03

Study Centers: Up to 30 centers

Phase of Development: 2

Objectives

Primary:

- To evaluate the long-term safety and pharmacodynamic (PD) effects of ACE-083 in patients with facioscapulohumeral muscular dystrophy (FSHD) previously enrolled in Study A083-02 and in patients with Charcot-Marie-Tooth (CMT) disease types 1 and X (CMT1 and CMTX) previously enrolled in Study A083-03.

Secondary:

- To evaluate the safety and PD effects of every 4 week (q4w) dosing in the loading phase, and of q4w and q8w dosing in the maintenance phase.
- To evaluate changes in strength, motor function, and quality of life (patient-reported outcomes) during the maintenance and loading phases of treatment.
- To evaluate the pharmacokinetics (PK) of ACE-083 when administered as a local muscle injection during the maintenance and loading phases of treatment.

Exploratory:

- To evaluate changes in biomarkers
- To evaluate PK/PD relationships.

Endpoints

Primary:

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

Study Design

Figure 1: Schematic Diagram of Subject Enrollment and Disposition

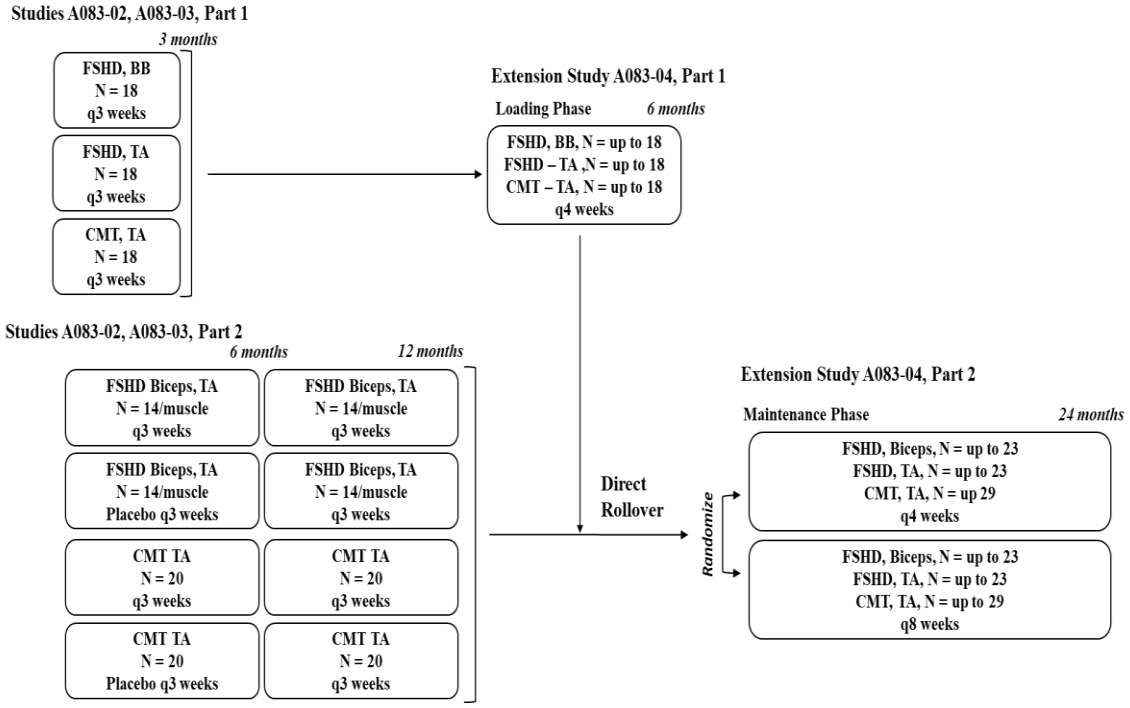

Table 3: Part 1: Loading Phase; N=Up to 54; ACE-083 240 mg/muscle bilaterally q4w

Cohort	Disease	Muscle	N
1a	FSHD	Tibialis anterior (TA)	Up to 18
1b	FSHD	Biceps brachii (BB)	Up to 18
1c	CMT	Tibialis anterior (TA)	Up to 18

Part 1: 6-month, non-randomized, open-label, loading phase for subjects from A083-02 Part 1 and A083-03 Part 1

Part 1 will consist of 3 cohorts of up to 18 subjects each. Subjects enrolled in Cohorts 1a and 1b will have completed Part 1 of Study A083-02; subjects enrolled in Cohort 1c will have completed Part 1 of Study A083-03. In this loading phase, 240 mg/muscle ACE-083 will be administered bilaterally q4w for 6 doses (6 months) into either the TA muscle or the BB muscle, depending on the muscle injected in the previous study; subjects may not switch muscle cohort upon enrollment in this study. Subjects will participate in a screening period of up to 4 weeks before receiving the first dose of ACE-083.

8. STUDY POPULATION

8.1. Inclusion Criteria

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

Inclusion Criteria:

1. Completion of treatment with study drug per protocol and completion of the end of treatment (ET) visit in Study A083-02 or Study A083-03.
2. 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 they have undergone a vasectomy. Subjects must be counseled about contraception prior to the first dose of ACE-083 and every three months thereafter during the study.
3. Ability to adhere to the study visit schedule/procedures and to understand and comply with protocol requirements
4. Signed written informed consent

8.2. Exclusion Criteria

Subjects 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. Co-morbidities, including symptomatic cardiopulmonary disease, significant orthopedic or neuropathic pain, or other conditions that, in the opinion of the investigator, would limit a subject's ability to complete strength and/or functional assessments
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)

14. STATISTICS

14.1. Analysis Populations

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

Safety Population: All subjects enrolled/randomized in the study who have received at least one dose of study drug

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

Pharmacokinetic Population: All subjects 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

This section and sections that follow outline planned statistical analyses and describe sample size considerations. Further details will be provided in a separate statistical analysis plan.

14.2.1. Patient Demographics and Disposition

Individual demographic data will be listed by subject.

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 cohort/treatment regimen and overall for each study part (Part 1 and Part 2). Age will be calculated based on birth date and informed consent date.

Individual disposition data will be listed by subject.

Frequency counts will be tabulated for disposition data and will consist of the number of subjects 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 cohort as well as by treatment regimen and overall for each study part (Part 1 and Part 2).

14.2.2. Drug Exposure

Study drug administration data will be listed by subject. Descriptive statistics of study drug exposure will be presented.

14.2.3. Efficacy Data

The primary analysis population for efficacy data will be the Per Protocol Set. The secondary analysis population will be the Full Analysis Set.

Efficacy parameters consist of the following:

APPENDIX 4. PERFORMANCE OF THE UPPER LIMB