Official Title: 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

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Protocol A083-04

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

SPONSOR: Acceleron Pharma Inc.
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ORIGINAL PROTOCOL DATE: 09 January 2019

Signature Page

Acceleron Pharma Approval

Signature: [redacted] **Date:** 11 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]	Acceleron Pharma Inc. 128 Sidney Street Cambridge, MA 02139 Office Tel: [redacted] Mobile: [redacted] Fax: [redacted] [redacted]
Medpace Medical Monitor	[redacted]	Medpace 5375 Medpace Way Cincinnati, Ohio 45227 Office Tel: [redacted] Mobile: [redacted] Fax: [redacted] [redacted]
Pharmacovigilance	[redacted]	Acceleron Pharma Inc. 128 Sidney Street Cambridge, MA 02139 Office Tel: [redacted] Fax: [redacted] [redacted]
Medpace 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

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

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
BB	Biceps brachii
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
DUX4	Double homeobox protein 4
ECG	Electrocardiogram
EMG	Electromyography
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FST	Follistatin
FSHD	Facioscapulohumeral muscular dystrophy
FSHD-HI	Facioscapulohumeral muscular dystrophy-health index
GCP	Good clinical practice
GDF8	Growth and differentiation factor 8
IB	Investigator’s brochure
ICF	Informed consent form
ICH	International Council on Harmonisation

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

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

- 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.

Study Design

Figure 1: Schematic Diagram of Subject Enrollment and Disposition

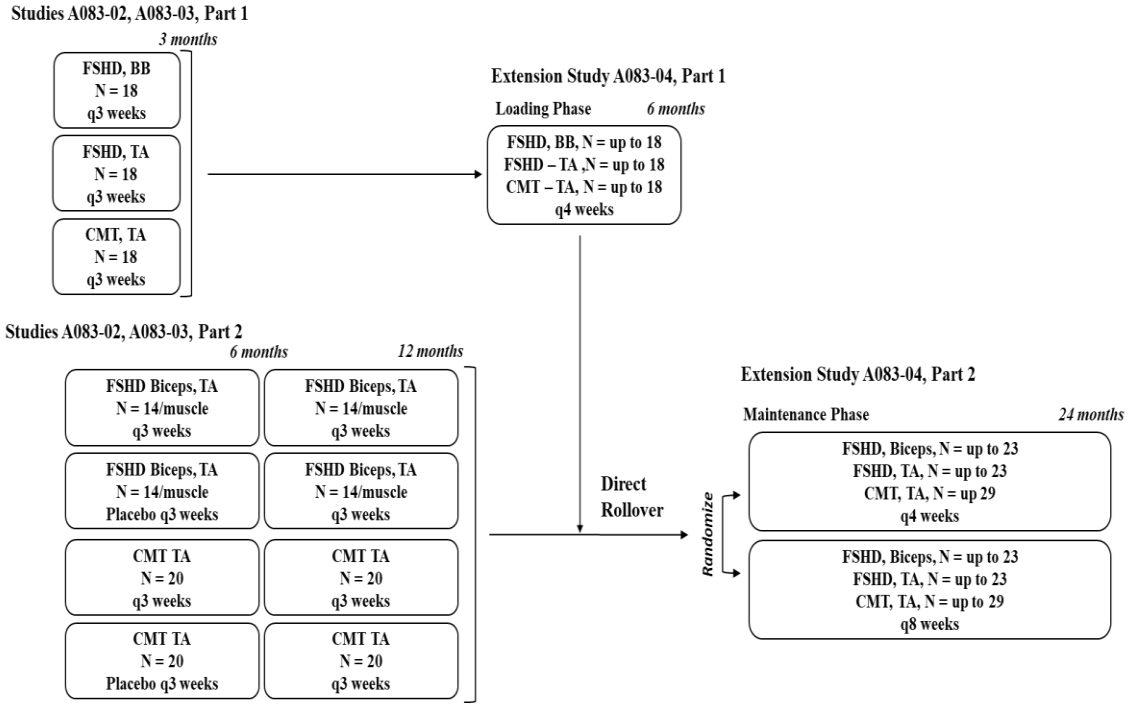

Table 3: Part 1: Loading Phase; N=Up to 54; ACE-083 240 mg/muscle bilaterally q4w

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.

Table 4: Part 2: Maintenance Phase; N=Up to 150; ACE-083 240 mg/muscle bilaterally

Cohort	Disease	Muscle	Dose Interval	N
2a	FSHD	TA	q4w	Up to 23
2b	FSHD	BB	q4w	Up to 23
2c	CMT	TA	q4w	Up to 29
3a	FSHD	TA	q8w	Up to 23
3b	FSHD	BB	q8w	Up to 23
3c	CMT	TA	q8w	Up to 29

Part 2: 24-month randomized, open-label rollover maintenance phase for subjects from A083-02 Part 2, A083-03 Part 2, and A083-04 Part 1

Subjects who complete Part 1 of this study (the loading phase), Part 2 of A083-02, or Part 2 of A083-03 will enroll directly into the Part 2 open-label maintenance phase of treatment with ACE-083. These subjects will be randomized (1:1) to receive ACE-083, 240 mg/muscle bilaterally, either q4w or q8w.

Number of Subjects (planned)

Up to 54 subjects from Study A083-02 Part 1 and Study A083-03 Part 1will be enrolled in Part 1 of the study. A total of up to 150 subjects will be enrolled in Part 2 of the study; Part 2 will be comprised of up to 54 subjects from Part 1 of this study, up to 56 subjects from Part 2 of Study A083-02, and up to 40 subjects from Part 2 of Study A083-03. Total study enrollment will be up to 150 subjects.

Diagnosis and Main Criteria for Eligibility

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 a 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

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. 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)
8. Severe deformity or ankle fixation that would sufficiently limit passive range of motion to affect functional assessments (TA subjects only)
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 other investigational agent (not including ACE-083) 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. 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
15. Any condition that would prevent the use of MRI or compromise the ability to obtain a clear and interpretable image of the treated muscles (e.g., knee/hip replacement metallic implants)
16. Known active substance abuse, including alcohol
17. History of sensitivity to protein pharmaceuticals
18. Female that is pregnant or 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 (64 mg/vial; nominal strength of each vial is 50 mg of ACE-083). After reconstitution with 1.2 mL of sterile water for injection, 1.0 mL will deliver 50 mg ACE-083.

Using electromyography (EMG) or ultrasound guidance, each dose of ACE-083 will be administered into the non-tendinous portion of the TA or BB as a series of 4 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 is 240 mg/muscle (4.8 mL) administered bilaterally by injection into the left and right TA or BB muscles q4w for up to 30 months (30 doses).

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 dose may be reduced. Up to two dose reductions are permitted: from 240 mg/muscle to 200 mg/muscle and from 200 mg/muscle to 150 mg/muscle. Dose will not be reduced below 150 mg/muscle. Dose delay and/or modification may be considered and implemented unilaterally or bilaterally. A maximum of 3 dose delays are allowed for subjects receiving q4w injections of ACE-083; only one dose delay is permitted for subjects in the q8w arm of Part 2 of the study.

Duration of Treatment

Study duration for a subject initially enrolled in Part 1 and then extended to Part 2 will be approximately 33 months, including a 1-month screening period, 6-month Part 1 loading phase, 24-month Part 2 maintenance phase, and 2-month follow-up period.

For subjects who enrolled directly into Part 2 of this study from Part 2 of Studies A083-02 and A083-03, the duration of the study will be approximately 26 months, including a 24-month maintenance phase and a 2-month follow-up period.

If a subject has a positive anti-drug antibody (ADA) result at the last visit, the subject will 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.

Safety Assessment

Safety Review Team:

An SRT, comprised at minimum of a principal investigator, medical monitor, and an independent neuromuscular specialist, will meet periodically (approximately every 3 months for the first six months, and every six months thereafter) to review safety for each cohort. The reviews will include all collected safety data and will begin when at least 10 subjects have received at least 3 doses of ACE-083 in this study. The SRT will review safety data, including AEs, laboratory results, and vital signs, to assess overall safety. The SRT may request review of additional data including PD and efficacy measurements.

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

- Continue ACE-083 administration at the current dose
- Reduce the dose for all subjects within a cohort, or for the study as a whole
- Discontinue one or more cohorts, or the study as a whole

Any changes in the dose level or schedule (e.g., continued treatment with q4w or q8w) in this study will be determined following review of study data and recommendations from the SRT. Further details on the role of the SRT 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 or BB by MRI

Biomarkers: including, but not limited to, serum C-terminal collagen crosslinks (CTX)

Efficacy:

Muscle strength: Quantitative muscle testing using maximum voluntary isometric contraction (MVIC) by hand-held dynamometry and manual muscle testing (MRC grade) of elbow flexion, ankle dorsiflexion, plantar flexion, and/or knee extension

Motor function tests: TA muscle function by 10-meter walk/run, 6-minute walk test, 4-stair climb (subjects from A083-02 only), 100-meter timed test; BB muscle function by PUL test

Patient-reported health-related quality of life (QoL): FSHD-HI (for FSHD patients) or CMT-HI (for CMT patients) total score and subscale scores

Statistical Methods:

Sample Size Calculation:

There was no formal sample size calculation for Part 1 or Part 2 of this study.

The sample size for Part 1 is determined by how many subjects from Part 1 of Studies A083-02 and A083-03 decide to participate in this study. Similarly, the sample size for Part 2 is based upon how many subjects from Part 2 of Studies A083-02 and A083-03 and Part 1 of this study participate in Part 2 of this study.

Non-inferiority of the q8w or q4w maintenance dose regimen during the first 6 months of the maintenance phase for the percent change in total muscle volume relative to the start of the maintenance phase (or equivalently the end of the loading phase – either from Part 2 of phase 2 studies A083-02 and A083-03 or from Part 1 of this study) will be analyzed. Based upon data from Parts 1 of Studies A083-02 and A083-03, it is assumed that the standard deviation is approximately 9. A non-inferiority margin of -5 and a 0.05 significance level is used. If 75 subjects per maintenance regimen participate and the observed mean percent change in total muscle volume at the first 6 months of the maintenance regimen from the start of the maintenance regimen is -2, the probability to conclude that the effect of any single maintenance regimen (q8w or q4w) is non-inferior is approximately 89%. If 65 subjects per maintenance regimen participate and the observed mean percent change is -2, the probability to conclude that the effect of any single maintenance regimen (q8w or q4w) is non-inferior is approximately 85%. If 57 subjects per maintenance regimen participate, the probability is approximately 80%.

Statistical Analysis:

Additional detail concerning the planned statistical analyses outlined below are included in Section 14. STATISTICS and will be described further in a separate statistical analysis plan (SAP).

Part 1

Safety: Unless otherwise specified, safety data will be summarized, by cohort and overall, using descriptive statistics; individual safety data will be listed. AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities and 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.

Pharmacodynamics: Individual PD data (e.g., total muscle volume, contractile muscle volume, intramuscular fat fraction, and biomarker data) will be listed. For individual PD data that are measured bilaterally (e.g., MRI), the average of the left and right side assessments will also be listed and summarized. Descriptive statistics (raw data and change from baseline [percent and

absolute change]) will be provided by cohort and scheduled time where baseline is defined to be the last non-missing assessment done prior to first dose.

For total muscle volume, contractile muscle volume, and intramuscular fat fraction, a mixed model will be fitted to the data and the least squares estimate of the mean difference in the percent change from baseline at 6 months post first dose under the q4w regimen of ACE-083 versus placebo will be determined for each cohort with the corresponding 90% confidence interval, where placebo refers to data from the double-blind component of Part 2 of either study A083-02 or A083-03. This will be compared with the findings from Part 2 of studies A083-02 and A083-03 for the mean difference in the percent change from baseline under the q3w regimen vs placebo.

For biomarker data (e.g. CTX), raw data and changes from baseline (percent and absolute change) will be summarized by cohort and scheduled time.

Efficacy: Individual efficacy data will be listed. For muscle strength, both quantitative muscle testing (QMT) and manual muscle testing (MMT) will be measured for the left and right sides and average of the two sides will be calculated. QMT is based on maximum voluntary isometric contraction (MVIC) using a hand-held dynamometer, and the MMT is based on Medical Research Council (MRC) grade. The MMT-MRC grades will be converted to decimal scores in the following way: 5 = 5.0, 5- = 4.67, 4+ = 4.33, 4 = 4.0, 4- = 3.67, 3+ = 3.33, 3 = 3.0, 3- = 2.67, 2+ = 2.33, 2 = 2.0, 2- = 1.67, 1+ = 1.33, 1=1.0.

For the MVIC values and the decimal MMT-MRC scores for each side treated as well as the average from the left and right sides, CMT-HI total score and selected subscale scores, FSHD-HI subscale scores, FSHD-HI total score, and motor function test assessments, raw data and changes from baseline (percent and absolute change) for the injected muscles will be summarized for each scheduled time using descriptive statistics. For each efficacy parameter, a mixed 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 and/or absolute change from baseline (depending on the parameter).

Pharmacokinetics: Individual listings of serum ACE-083 concentrations, actual blood sampling times, and PK parameters, including graphs of concentration versus time, will be prepared. 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.

Part 2

Pharmacodynamics: Individual PD data will be listed. Descriptive statistics will be provided by cohort and scheduled time for raw data and changes from the start of the maintenance phase (or equivalently the end of the loading phase).

The primary PD variable will be the difference in mean percent change in total muscle volume (average of left and right side) at the first 6 months of the maintenance phase (Day 169, q4w or q8w) from the total muscle volume (average of left and right sides) at the start of the maintenance phase (or equivalently the end of the loading phase). A mixed model will be fitted to the data and a non-inferiority analysis will be performed using a non-inferiority margin of -5.

Secondary MRI PD variables include the difference in mean percent change for contractile muscle volume (average of left and right side) as well as intramuscular fat fraction (average of left and

right side) at the end of the first 6 months of the maintenance phase (Day 169, q4w or q8w) from the start of the maintenance phase (or equivalently the end of the loading phase). Secondary PD variables also include the difference in mean percent and/or absolute (raw) change from the start of the maintenance phase for biomarker variables such as CTX at the end of the first 6 months of the maintenance phase (Day 169, q4w or q8w).

For each secondary MRI PD variable, a mixed model will be fitted to the data and least square estimates of the mean difference and corresponding 90% confidence interval will be provided for each maintenance dose regimen. For biomarker data, a mixed model will be fitted and least square estimates of the mean percent and/or absolute change from baseline for the first 6 months of the maintenance phase along with the corresponding 90% confidence interval will be provided for each maintenance dose regimen.

Least square estimates of the mean percent or absolute change from baseline for other scheduled times during the maintenance phase along with the corresponding 90% confidence interval may be provided as appropriate.

Safety: Same as in Part 1

Efficacy: Individual efficacy data will be listed. Descriptive statistics will be provided by cohort, treatment regimen and scheduled time for raw data and changes from baseline. For assessments that are performed on the left and right sides, such as MVIC and decimal MMT-MRC scores, descriptive statistics will be provided for each side as well as the average of the left and right sides.

For each muscle strength and motor function efficacy parameter, a mixed model will be fitted and least-square estimates of the mean percent change from maintenance phase baseline (Day 1) for the first 6 months of the maintenance phase along with the corresponding 90% confidence interval will be provided for each treatment regimen for MVIC of ankle dorsiflexion, plantar flexion, and knee extension (TA patient data, average of left and right sides), MVIC of elbow flexion (BB patient data, average of left and right sides) decimal MMT-MRC scores (average of left and right sides), and each motor function test. For each patient reported health-related quality of life parameter (FSHD-HI total score and selected subscale scores [for FSHD subjects] and CMT-HI total score and selected subscale scores [for CMT subjects]), a mixed model will be fitted and least square estimates of the mean absolute change from baseline for the first 6 months of the maintenance phase along with the corresponding 90% confidence interval will be provided for each treatment regimen for FSHD-HI total score and selected subscale scores [FSHD subject data] as well as for CMT-HI total score and selected subscale scores [CMT subject data].

Least square estimates of the mean percent or absolute change from baseline for other scheduled times during the maintenance phase along with the corresponding 90% confidence interval may be provided as appropriate.

Pharmacokinetics: Same as in Part 1

Anti-drug antibody data (Parts 1 and 2): Individual ADA data will be listed. 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 positive.

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.[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, which 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 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. When administered by injection into muscle, ACE-083 remains primarily within the injected muscle, resulting in an increase in mass and strength of the targeted muscle while minimizing systemic distribution and off-target effects.

As described in the ACE-083 Investigator's Brochure (IB), a number of nonclinical pharmacology studies have defined the ligand-binding properties of ACE-083 and assessed 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 is a result of increased fiber hypertrophy and not hyperplasia. This ACE-083-induced muscle hypertrophy translates 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, 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 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.[6] Forty-two subjects have received ACE-083 at doses of 50 to 200 mg administered as single or multiple injections into either the right rectus femoris or right TA 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 was noted in the subjects treated with ACE-083.[6]

5.2. Study Rationale

ACE-083 is intended for the treatment of focal myopathies that affect specific skeletal muscles and/or muscle groups (e.g., facioscapulohumeral muscular dystrophy [FSHD], Charcot Marie Tooth [CMT] disease, and sporadic inclusion body myositis [sIBM]). The initial clinical indications being pursued are FSHD and CMT disease, as specific features of these diseases lend themselves favorably to treatment with ACE-083. The ongoing Phase 2 studies (Study A083-02 and Study A083-03) in subjects with FSHD and CMT, respectively, have been designed to assess safety and tolerability of ACE-083, as well as to determine if local injection of ACE-083 results in clinically meaningful effects on specific skeletal muscles that could result in improved clinical function. This study is an extension of A083-02 and A083-03 with the primary goal of establishing long-term safety and tolerability of ACE-083.

This extension study will also assess the efficacy of ACE-083 in the treatment of FSHD and CMT by examining muscle volume, muscle strength, and motor function parameters, as well as patient- and physician-reported disease burden and quality of life measures. Part 2 of this study will evaluate the long-term safety, tolerability, and efficacy of ACE-083, as well as assess different dosing regimens in the maintenance phase to determine if dosing less frequently (q8w versus q4w) is sufficient to maintain increases in total muscle volume that are produced with an initial 6-month loading phase of q3w and/or q4w. Less frequent dosing may improve patient convenience and compliance.

FSHD is one of the most common muscular dystrophies and has an autosomal dominant inheritance pattern in most patients.[7,8] FSHD is characterized by complex genetic mechanisms relating to the double homeobox protein 4 gene (DUX4). DUX4 is normally repressed in somatic cells through epigenetic mechanisms but is derepressed in FSHD, leading to toxic damage to skeletal muscle cells. The DUX4 gene is located in the D4Z4 microsatellite array in the 4q35 region. In FSHD1, one D4Z4 allele is contracted (1 to 10 repeat units) and has been associated with DNA hypomethylation and chromatin structural changes. FSHD2 is also characterized by hypomethylation of both normal D4Z4 alleles. Mutations in the SMCHD1 gene resulting in changes in the D4Z4 chromatin structure have been linked to FSHD2. The types are phenotypically indistinguishable.[9] Laboratory and muscle biopsy findings are often non-specific and therefore are not required for diagnosis; diagnosis of the most common variants of FSHD, as well as other rare atypical variants of the disease, is by genetic testing.

Patients with FSHD typically present in their second decade of life and live a normal lifespan. The disease is clinically characterized by slowly progressive focal and asymmetric areas of muscle weakness, typically involving facial, scapular, upper arm, lower leg, and abdominal muscles. Weakness of the tibialis anterior (TA), a commonly affected lower extremity muscle in FSHD patients, often results in impaired dorsiflexion and foot drop, which can lead to gait instability and falls requiring the use of assistive devices. The biceps brachii (BB) muscle, located in the upper arm, is another muscle that is often affected in FSHD and whose loss of function is detrimental to patient movement and quality of life.

Another indication being pursued for ACE-083 is the treatment of hereditary motor sensory neuropathy (HMSN), more commonly known as Charcot-Marie-Tooth (CMT) disease. CMT is the most common form of hereditary peripheral neuropathy, with a worldwide prevalence of 1 in 2500 individuals; it affects approximately 125,000 people in the US.[10] A specific mutation in

one of several myelin genes results in defects in myelin formation, structure, and maintenance in patient with CMT type 1. 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 (CMTX) account for approximately 10 to 15 percent of cases[11].

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

There is a high unmet medical need for drug therapy options in both CMT and FSHD. Although some clinical and pharmacological trials have been performed in both patient populations, the results have not been encouraging, and there is currently no approved therapy available for either condition.[9,12] To date, treatment for both FSHD and CMT has been restricted to symptomatic interventions. 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 can successfully treat some, but not all, foot deformities (in CMT) and foot drop (in CMT and FSHD), but surgical intervention is not appropriate for every case. Exercise is recommended for some patients; however, the safety of exercise, as well as the appropriate regimen of exercise, must be established for each individual patient.[13]

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. In Phase 2 Studies A083-02 and A083-03, subjects received 150 to 240 mg/muscle, unilaterally or bilaterally q3w for 3 months (5 doses, Part 1) or 240 mg/muscle bilaterally for 12 months (17 doses, Part 2). Preliminary data for Part 1 of the study indicated that the study drug was well tolerated and produced significant muscle volume increases that were maintained for up to 8 weeks following the last dose.

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 muscles that are contributing to functional limitations. In CMT and FSHD patients with lower limb weakness and atrophy of the TA, or in FSHD patients with affected BB muscles, an ACE-083-mediated increase in muscle volume has the potential to increase strength and function associated with ankle dorsiflexion or elbow flexion, respectively. This could improve a patient's mobility, activities of daily living, and ultimately their quality of life. This study will evaluate the longer-term safety, tolerability, efficacy, and pharmacokinetics of ACE-083 for up to 30 months.

6. OBJECTIVES AND ENDPOINTS

Table 5: Objectives and Endpoints

Objectives	Endpoints
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.	• Presence and nature of adverse events (AE) including injection site reactions and changes in clinical laboratory parameters • Percent change from baseline in muscle volume of injected muscle by magnetic resonance imaging (MRI)
Secondary	
• To evaluate 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 PK of ACE-083 when administered as a local muscle injection during the maintenance and loading phases of treatment. • To evaluate safety and PD effects of every 4 week (q4w) dosing in the loading phase, and of q4w and q8w dosing in the maintenance phase.	• 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 for ACE-083 serum concentrations over time
Exploratory	
• To evaluate changes in biomarkers • To evaluate ACE-083 PK/PD relationships.	• Percent and absolute change from baseline in biomarkers • Percent and absolute change in PD parameters as a function of ACE-083 exposure.

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.

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)

8. Severe deformity or ankle fixation that would sufficiently limit passive range of motion to affect functional assessments (TA patients only)
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 other investigational agent (not including ACE-083) 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. 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
15. Any condition that would prevent MRI scanning or compromise the ability to obtain a clear and interpretable scan of the treated muscles (e.g., knee/hip replacement metallic implants)
16. Known active substance abuse, including alcohol
17. History of sensitivity to protein pharmaceuticals
18. Female that is pregnant or 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 re-screenings 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. 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 (EOT) visit should complete the tests and evaluations (excluding the MRI if it has been done within 4 weeks of study withdrawal) scheduled for the EOT visit (Day 673) 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 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 subject 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 SUBJECTS

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 target muscle (TA or BB) as a series of up to 4 equal-volume injections. The use of EMG or ultrasound guidance will help to 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 IP Handling Guide.

For Part 1 of this study, the dose and schedule will be 240 mg/muscle administered bilaterally by injection into the TA or BB muscles every 4 weeks for up to 6 doses.

For Part 2, ACE-083 will be administered q4w for up to 24 months (24 doses) or q8w for up to 24 months (12 doses). Subjects who complete the Phase 1 loading phase treatment period will immediately be randomized into the 24-month maintenance phase. The planned dose schemes for Parts 1 and 2 are shown in Table 6 and Table 7.

Table 6: 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

Table 7: Part 2: Maintenance Phase; N=Up to 150; ACE-083 240 mg/muscle bilaterally

Cohort	Disease	Muscle	Dose Interval	N
2a	FSHD	TA	q4w	Up to 23
2b	FSHD	BB	q4w	Up to 23
2c	CMT	TA	q4w	Up to 29
3a	FSHD	TA	q8w	Up to 23
3b	FSHD	BB	q8w	Up to 23
3c	CMT	TA	q8w	Up to 29

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 dose may be reduced. Dose delay and/or modification may be considered and implemented unilaterally or bilaterally. Up to two dose reductions are permitted: from 240 mg/muscle to 200 mg/muscle and from 200 mg/muscle to 150 mg/muscle. Dose will not be reduced below 150 mg/muscle. A maximum of 3 dose delays are allowed for subjects receiving q4w injections of ACE-083; only one dose delay is permitted for subjects in the q8w arm of Part 2 of the study.

10.2. Safety Review Team

An SRT, comprised at minimum of a principal investigator, medical monitor, and an independent neuromuscular specialist, will meet periodically (approximately every 3 months for the first six months, every six months thereafter) to review safety for each cohort. The reviews will include all collected safety data and will begin when at least 10 subjects have received at least 3 doses of ACE-083. The SRT will review safety data, including AEs, laboratory results, and vital signs, to assess overall safety. The SRT may request review of additional data including PD and efficacy measurements.

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

- Continue ACE-083 administration at the current dose
- Reduce the dose for all subjects within a cohort, or for the study as a whole
- Discontinue one or more cohorts, or the study as a whole

Any changes in the dose level or schedule (e.g., continued treatment with q4w or q8w) in this study will be determined following review of study data and recommendations from the SRT. Further details on the role of the SRT are included in the SRT Guidelines.

10.3. Concomitant Medications

During screening and throughout the study, subjects 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 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.

Subjects are not permitted to take the following: anticoagulation/platelet modifying therapies, systemic corticosteroids, systemic androgens, growth hormone, insulin, or estrogen ± progesterone 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 or FSHD. 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 extension study enrolling subjects from Study A083-02 part 1 and Study A083-03 part 1 and does not require randomization.

Part 2: Subjects who have signed the informed consent and meet all eligibility criteria will be grouped by disease (FSHD or CMT) and target muscle (for FSHD; BB or TA) and then randomized to receive 240 mg/muscle bilateral ACE-083 either q4w or q8w. The randomization scheme will be computer-generated and will be prepared by a statistical group designated by the sponsor.

Because this study is an open-label extension of Studies A083-02 and A083-03, no blinding is necessary. Subjects will retain the unique identifying number assigned to them in the previous study.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

Study drug is ACE-083. ACE-083 is a recombinant fusion protein consisting of a modified form of human follistatin linked to a human IgG2 Fc domain.

11.2. Study Drug Packaging and Labeling

ACE-083 drug product is provided as a lyophilized powder contained in stoppered and sealed glass vials (64 mg/vial; nominal strength of each vial is 50 mg of ACE-083). After reconstitution with 1.2 mL of sterile water for injection, 1.0 mL will deliver 50 mg ACE-083.

11.3. Study Drug Storage

ACE-083 should be stored as a lyophilized powder at 2−8°C until use.

11.4. Study Drug Preparation

Please refer to the IP Handling Guideline, provided separately, for detailed study drug handling, administration, and storage instructions.

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 (subject-by-subject 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 management 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

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

12.2. Study Assessments

For each subject, 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.

If a subject has a positive ADA result at the last visit, the subject will be asked to return for additional ADA testing approximately every three months, until a negative result is obtained or the titer is no longer increasing.

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) measured by quantitative muscle testing (by handheld dynamometer) and manual muscle testing (MRC grade). For subjects who receive BB treatment, elbow flexion will be assessed. In TA-treated subjects, ankle dorsiflexion, plantar flexion, and knee extension will be assessed.

Motor function tests: 10-meter walk/run, 6-minute walk test, 4-stair climb (subjects from A083-02 only), 100-meter timed test, and PUL

Patient-reported health-related quality of life (QoL): FSHD-HI (FSHD patients) or CMT-HI (for CMT patients) total score and subscale scores

12.5. Pharmacokinetic and Pharmacodynamic Assessments

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

Pharmacodynamic assessments

Muscle assessments: Muscle volume and the intramuscular fat fraction of TA or BB muscles by MRI

Biomarkers: including but not limited to: 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 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.

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:

- **Muscle strength**: Quantitative muscle testing (maximum voluntary isometric contraction [MVIC] by hand-held dynamometer) and manual muscle testing (MRC grade) of elbow flexion, ankle dorsiflexion, plantar flexion, and/or knee extension
- **Motor function tests**: TA muscle function by 10-meter walk/run, 6-minute walk test, 4-stair climb (subjects from A083-02 only), 100-meter timed test; BB muscle function by PUL test
- **Patient-reported health-related quality of life (QoL)**: FSHD-HI (for FSHD patients) or CMT-HI (for CMT patients) total score and subscale scores

Part 1

Individual efficacy data will be listed. For muscle strength (as assessed by hand-held dynamometer [MVIC] and MMT assessment), the MVIC value as well as the decimal MMT-MRC score will be derived for each side and the average of the two sides will be determined for each individual and scheduled time. Decimal MMT-MRC scores will be derived from MMT-MRC grades in the following way: 5 = 5.0, 5- = 4.67, 4+ = 4.33, 4 = 4.0, 4- = 3.67, 3+ = 3.33, 3 = 3.0, 3- = 2.67, 2+ = 2.33, 2 = 2.0, 2- = 1.67, 1+ = 1.33, 1=1.0.

For the MVIC value for each side treated as well as the average of the left and right sides, decimal MMT-MRC score for each side treated as well as the average of the left and right sides, CMT-HI total score and selected subscale scores (CMT patients), FSHD-HI total score and subscale scores (FSHD patients) and motor function test assessments, raw data and changes from baseline (percent and absolute change) will be summarized for each scheduled time using descriptive statistics. For each muscle strength, motor function test, and selected patient-reported health-related quality of life parameters, a mixed model will be fitted and least squares estimates of the effect of ACE-083 and the corresponding 90% confidence interval will be provided for the percent and/or absolute change from baseline (depending on the parameter). Baseline is defined as the last non-missing value prior to first dose of study medication. Theoretically, this should be the Day 1 pre-dose value. Additional analyses may be performed as appropriate.

Part 2

Individual efficacy data will be listed. Descriptive statistics will be provided by cohort and scheduled time for raw data and changes from baseline. Unless otherwise specified, baseline is defined to be the last non-missing value prior to first dose of the maintenance phase. For assessments that are performed on the left and right sides, such as MVIC and decimal MMT-MRC scores (as described for Part 1 above), descriptive statistics will be provided for each side as well as the average of the left and right sides.

For each muscle strength and motor function test parameters, a mixed model will be fitted and least squares estimates of the mean percent change from baseline to the first 6 months of the maintenance phase (Day 169) along with the corresponding 90% confidence interval will be provided for each treatment regimen for MVIC of ankle dorsiflexion (TA subject data – average of left and right sides), MVIC of elbow flexion (BB subject data – average of left and right sides), decimal MMT-MRC scores (including plantar flexion and knee extension, as appropriate; average of left and right sides), and each motor function test. For each patient reported health-related quality of life parameter (FSHD-HI total score and selected subscale scores [for FSHD subjects] and CMT-HI total score and selected subscale scores [for CMT subjects], a mixed

model will be fitted and least squares estimates of the mean absolute change from baseline to the first 6 months of the maintenance phase along with the corresponding 90% confidence interval will be provided for each treatment regimen for FSHD-HI total score and selected subscale scores [FSHD subject data] as well as for CMT-HI total score and selected subscale scores [CMT subject data].

Least squares estimates of the mean percent or absolute change from baseline for each treatment regimen at other scheduled times during the maintenance phase along with the corresponding 90% confidence interval may be provided as appropriate.

Additional analyses may be performed as appropriate.

14.2.4. Pharmacodynamic Data

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

Pharmacodynamic parameters consist of the following:

- **Muscle assessments**: Muscle volume and intramuscular fat fraction of TA or BB by MRI
- **Biomarkers**: including, but not limited to, serum C-terminal collagen crosslinks (CTX)

Part 1

Individual pharmacodynamic data (e.g., total muscle volume, contractile muscle volume, intramuscular fat fraction, and biomarker data) will be listed. For individual pharmacodynamic data that are measured on the left and right side, the average of the left and right side assessments will also be listed and summarized. Descriptive statistics (raw data and change from baseline [percent and absolute change]) will be provided by cohort and scheduled time where baseline is defined to be the last non-missing assessment done prior to first dose.

For the percent change in total muscle volume at 6-months from baseline, a mixed model will be fitted using the data from Part 1 as well as the data from the double-blind component of Part 2 of studies A083-02 and A083-03 and the loading dose treatment effect will be assessed. Baseline is defined to be the last non-missing value prior to first dose of study medication. The least squares mean difference for each loading dose regimen (q4w and q3w) vs. placebo and corresponding 90% confidence interval will be provided where placebo subjects come from the double-blind component of Part 2 of A083-02 and A083-03. This will also be provided by cohort. If data from the 6-month (Day 169) visit are missing, the missing data mechanism will be investigated and an appropriate method for handling the missing data will be applied. Sensitivity analyses will also be performed.

For contractile muscle volume and intramuscular fat fraction, similar analyses as described above for total muscle volume 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 cohort and scheduled time.

Additional analyses may be performed as appropriate.

Individual pharmacodynamic parameter data will be listed. Descriptive statistics will be provided by cohort, treatment regimen and scheduled time for raw data and changes from baseline.

The primary pharmacodynamic variable will be the difference in mean percent change in total muscle volume (average of left and right side) for the first 6 months of the maintenance phase (Day 169) from the total muscle volume (average of left and right sides) at the start of the maintenance phase (or equivalently the end of the loading phase). An mixed model will be fitted to the data and a non-inferiority analysis will be performed using a non-inferiority margin of -5. The non-inferiority analysis will be done for each maintenance dose regimen (q4w and q8w). The lower bound of the one-sided 95% confidence interval will be used to assess non-inferiority. If data from the 6-month (Day 169) visit are missing, the missing data mechanism will be investigated and an appropriate method for handling the missing data will be applied. Sensitivity analyses will also be performed. In addition, using the same mixed model, the percent change in total muscle volume for the first 6 months of the maintenance phase (Day 169) from the start of the maintenance phase (or equivalently the end of the loading phase) will be compared between the two dosing regimens (q8w vs q4w).

Secondary MRI pharmacodynamic variables include the difference in mean percent change for contractile muscle volume (average of left and right sides) as well intramuscular fat fraction (average of left and right sides) at the end of the first 6 months of the maintenance phase (Day 169, q4w or q8w) from the start of the maintenance phase (or equivalently the end of the loading phase). Secondary pharmacodynamic variables also include the percent and/or absolute (raw) change in biomarker variables such as CTX at the end of the first 6 months of the maintenance phase (Day 169). For each secondary MRI pharmacodynamic variable, an mixed model will be fitted to the data and least square estimates of the mean difference and corresponding 90% confidence interval will be provided for each maintenance dose regimen. If data from the 6-month (Day 169) visit are missing, the missing data mechanism will be investigated and an appropriate method for handling the missing data will be applied. Sensitivity analyses will also be performed.

For biomarker data, a mixed model will be fitted and least-square estimates of the mean percent and/or absolute change from baseline for the first 6 months of the maintenance phase along with the corresponding 90% confidence interval will be provided for each maintenance dose regimen. If data from the 6-month (Day 169) visit are missing, the missing data mechanism will be investigated and an appropriate method for handling the missing data will be applied. Sensitivity analyses will also be performed.

Least square estimates of the mean percent or absolute change from the start of the maintenance phase (or equivalently the end of the loading phase) for other scheduled times during the maintenance phase along with the corresponding 90% confidence interval may be provided as appropriate.

Additional analyses may be performed as appropriate.

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 current version of the Medical Dictionary for Regulatory Activities, and 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 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

Individual ADA data will be listed. The results of ADA testing for ACE-083 over 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 was no formal sample size calculation for Part 1 or Part 2 of this study.

The sample size for Part 1 is determined by how many subjects from Part 1 of Studies A083-02 and A083-03 decide to participate in this study. Similarly, the sample size for Part 2 is based upon how many subjects from Part 2 of Studies A083-02 and A083-03 and Part 1 of this study participate in Part 2 of this study.

Non-inferiority of the q8w or q4w maintenance dose regimen during the first 6 months of the maintenance phase for the percent change in total muscle volume relative to the start of the maintenance phase (or equivalently the end of the loading phase – either from Part 2 of phase 2 studies A083-02 and A083-03 or from Part 1 of this study) will be analyzed.

Based on data from Parts 1 of Studies A083-02 and A083-03, it is assumed that the standard deviation is approximately 9. A non-inferiority margin of -5 and a 0.05 significance level is used. If 75 subjects per maintenance regimen participate and the observed mean percent change in total muscle volume at the first 6 months of the maintenance regimen from the start of the maintenance regimen is -2, the probability to conclude that the effect of any single maintenance regimen (q8w or q4w) is non-inferior is approximately 89%. If 65 subjects per maintenance regimen participate and the observed mean percent change is -2, the probability to conclude that the effect of any single maintenance regimen (q8w or q4w) is non-inferior is approximately 85%. If 57 subjects per maintenance regimen participate, the probability is approximately 80%.

14.4. Interim Analysis

Periodic reviews of the available safety and tolerability will be planned and reported to the SRT in accordance with the SRT charter. During the course of Part 2, an interim analysis may be performed when some or all subjects have completed 6 months post start of the maintenance phase in order to assess adequacy of dosing regimens in this study and to plan for future studies with ACE-083. Details will be described in the Statistical Analysis Plan.

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. Subject Information and Consent

Informed written consent is required from each subject 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 subjects. It is the responsibility of the investigator to obtain consent and to provide the subject with a copy of the signed and dated ICF. Confirmation of a subject's informed consent must also be documented in the subject'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. Subject Data Protection

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

The subject 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/IRB, 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 subject 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 subject's confidentiality will be maintained and will not be made publicly available. The subject'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/IRB 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/IRB, as appropriate.

21. DATA HANDLING AND RECORDKEEPING

21.1. Case Report Form Completion

CRFs will be completed for each enrolled subject. It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject'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 subjects 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 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.

APPENDIX 4. PERFORMANCE OF THE UPPER LIMB