1. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company
Acceleron Pharma Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product
ACE-083</td></tr>
<tr><td>Name of Active Ingredient
ACE-083 is a recombinant fusion protein consisting of a modified form of human follistatin linked to a human immunoglobulin G2 (IgG2) fragment crystallizable (Fc) domain.</td></tr>
<tr><td colspan="3">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</td></tr>
<tr><td colspan="3">Principal Investigator
Jeffrey Statland, MD and Craig Campbell, MD</td></tr>
<tr><td colspan="3">Study center(s)
There were 23 active centers in Canada, Spain, and the United States</td></tr>
<tr><td colspan="3">Publications (reference)
Not applicable</td></tr>
<tr><td colspan="2">Study period (years)
Date first participant enrolled: 25 April 2019
Date last participant completed: 09 April 2020</td><td>Phase of development
Phase 2</td></tr>
<tr><td colspan="3">Objectives
<u>Primary</u>
• To evaluate the long-term safety and pharmacodynamic (PD) effects of ACE-083 in participants with FSHD previously enrolled in Study A083-02 and in participants with CMT disease types 1 and X (CMT1 and CMTX, respectively) previously enrolled in Study A083-03.
<u>Secondary</u>
• To evaluate the safety and PD effects of every 4 week (q4w) dosing in the loading phase, and of q4w and every 8 week (q8w) dosing in the maintenance phase.</td></tr>
</table>

- To evaluate changes in strength, motor function, and quality of life (QOL; patient-reported outcomes) during the loading and maintenance phases of treatment.
- To evaluate the pharmacokinetics (PK) of ACE-083 when administered as a local muscle injection during the loading phase of treatment.

Exploratory

- To evaluate changes in biomarkers.
- To evaluate ACE-083 PK/PD relationships.

Methodology

This was an open-label, multicenter, phase 2 extension study to evaluate the safety, tolerability, PK, PD, and efficacy of ACE-083 in participants with FSHD previously enrolled in Study A083-02 and participants with CMT1 and CMTX previously enrolled in Study A083-03.

This study was conducted in 2 parts: Part 1 consisted of a loading phase of 6 months duration, after which they would continue into Part 2 of the study. Part 2, the maintenance phase, lasted up to 24 months. Enrollment in both parts of the study was concurrent; participants were enrolled into either Part 1 or 2 of this study, depending on when they completed the parent study. The study enrollment for Parts 1 and 2 of this study is presented in Table 1.

Table 1: Enrollment for Parts 1 and 2

Cohort	Disease	Muscle	Dose Interval	Number of Participants
Part 1				
1a	FSHD	Tibialis anterior	q4w	7
1b	FSHD	Biceps brachii	q4w	2
1c	CMT	Tibialis anterior	q4w	13
Part 2				
2a	FSHD	Tibialis anterior	q4w	6
2b	FSHD	Biceps brachii	q4w	7
2c	CMT	Tibialis anterior	q4w	6
3a	FSHD	Tibialis anterior	q8w	6
3b	FSHD	Biceps brachii	q8w	8
3c	CMT	Tibialis anterior	q8w	8

CMT = Charcot-Marie Tooth; FSHD = facioscapulohumeral muscular dystrophy; q4w = every 4 weeks; q8w = every 8 weeks.
Source: Table 14.1.1.1

Part 1 (Loading Phase)

Part 1 was a non-randomized, open-label, loading phase, which included participants previously treated in Part 1 of Studies A083-02 and A083-03 after a washout period of at least 24 weeks. Part 1 of this study consisted of 3 cohorts: Cohorts 1a and 1b included FSHD participants that completed Part 1 of Study A083-02 and Cohort 1c included CMT participants that completed Part 1 of Study A083-03. In this loading phase, participants received bilateral injections of ACE-083 240 mg/muscle q4w for 6 doses (6 months) into either the tibialis anterior (TA) muscle (Cohorts 1a and 1c) or biceps

brachii (BB) muscle (Cohort 1b), depending on the muscle injected in the previous study (TA or BB); participants were not allowed to switch the muscle treated upon enrollment in this study. Upon completion of the 6-month loading phase, these participants continued into Part 2 of this study, which was the maintenance phase.

Part 2 (Maintenance Phase)

Part 2 was an open-label maintenance phase study, which included participants who completed Part 1 of this study (loading phase), Part 2 of Study A083-02, or Part 2 of Study A083-03. Participants entered directly into Part 2 of this study without interruption in ACE-083 treatment; the end-of-treatment visit in the previous study coincided with the Day 1 visit of this study. In order to rollover directly into Part 2 of this study, the participant was to be within 12 weeks of their last dose of study drug in Studies A083-02 or A083-03. If the time since last dose was greater than 12 weeks, the participant could have entered into Part 1 of this study provided that they underwent a washout period (time since last dose of study drug) of at least 24 weeks. Part 2 of this study consisted of 6 cohorts: Cohorts 2a, 2b, 3a, and 3b included FSHD participants and Cohorts 2c and 3c included CMT participants. In this maintenance phase, FSHD and CMT participants were randomized (1:1) and received bilateral injections of 240 mg/muscle ACE-083 either q4w (Cohorts 2a, 2b, and 2c) or q8w (Cohorts 3a, 3b, and 3c) into either the TA muscle (Cohorts 2a, 2c, 3a, and 3c) or BB muscle (Cohorts 2b and 3b), depending on which muscles were previously injected (TA or BB); participants were not allowed to switch the muscle treated upon rollover into the maintenance phase of this study.

Number of participants (planned and analyzed)

Up to 54 participants from Part 1 of Study A083-02 and Part 1 of Study A083-03 were planned to be enrolled into Part 1 of this study. Up to 150 participants were planned to be enrolled in Part 2 of this study, which was to comprise of up to 54 participants from Part 1 of this study, up to 56 participants from Part 2 of Study A083-02, and up to 40 participants from Part 2 of Study A083-03. The total number of participants planned for this study was up to 150.

A total of 63 participants enrolled in this study. This included 36 FSHD participants across Parts 1 and 2: 7 participants in Cohort 1a, 2 participants in Cohort 1b, 6 participants in Cohort 2a, 7 participants in Cohort 2b, 6 participants in Cohort 3a, and 8 participants in Cohort 3b. There were 27 CMT participants enrolled across Parts 1 and 2: 13 participants in Cohort 1c, 6 participants in Cohort 2c, and 8 participants in Cohort 3c.

Diagnosis and main criteria for inclusion

Adult patients diagnosed with FSHD and CMT (types 1 and X) who were previously enrolled in and completed treatment with study drug per protocol and the end of treatment (EOT) visit in Study A083-02 and Study A083-03, respectively.

Test product, dose and mode of administration, batch number

ACE-083 is a recombinant fusion protein consisting of a modified form of human follistatin linked to a human IgG2 Fc domain. ACE-083 drug product was 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 delivered 50 mg ACE-083.

All FSHD and CMT participants were administered ACE-083 240 mg/muscle bilaterally by injection into the target muscles (TA for both FSHD and CMT or BB for FSHD). Using electromyography (EMG) or ultrasound guidance, each dose of ACE-083 was administered into the non-tendinous portion of the TA or BB as a series of 4 injections per side. The use of EMG or ultrasound guidance ensured that viable muscle was present at the injection site. If the degree of atrophy or fibro-fatty infiltration posed administration challenges, injections of ACE-083 were distributed at least approximately 2 cm apart into viable muscle.

For Part 1 of this study, FSHD and CMT participants were administered ACE-083 240 mg/muscle bilaterally by injection into either the TA muscle (Cohorts 1a and 1c) or BB muscle (Cohort 1b) q4w for up to 6 months (6 doses). Depending on the muscle injected (TA or BB) in the previous study, participants were not allowed to switch the muscle treated upon enrollment in this study; therefore, a participant previously treated in the TA muscle was not allowed to switch treatment to the BB muscle and vice versa.

For Part 2 of this study, FSHD and CMT participants were administered ACE-083 240 mg/muscle bilaterally by injection into either the TA muscle (Cohorts 2a and 2c) or BB muscle (Cohort 2b) q4w for up to 24 months (24 doses) or into either the TA muscle (Cohorts 3a and 3c) or BB muscle (Cohort 3b) q8w for up to 24 months (12 doses). Depending on the muscle injected (TA or BB) in the previous study, participants were not allowed to switch the muscle treated upon enrollment in this study; therefore, a participant previously treated in the TA muscle was not allowed to switch treatment to the BB muscle and vice versa.

Each dose of ACE-083 was administered via injections at the clinical site by the study staff and was documented in the study record.

Planned duration of treatment

The planned study duration for a participant initially enrolled in Part 1 of this study and then extended to Part 2 was 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 a participant who enrolled directly into Part 2 of this study from Part 2 of Studies A083-02 and A083-03, the planned duration of the study was approximately 26 months, including a 24-month maintenance phase and a 2-month follow-up period.

If a participant had a positive anti-drug antibody (ADA) result at the last visit, the participant was asked to return for additional ADA testing approximately every 3 months until a negative result was obtained or the titer was no longer increasing.

Reference therapy

No reference treatment was administered in Parts 1 or 2 of this study; all participants received active treatment.

Criteria for evaluation

Efficacy

Efficacy was to be determined by assessing muscle strength (quantitative muscle testing [QMT] via handheld dynamometer and manual muscle testing [MMT]), motor function (via 10-meter walk/run, 6-minute walk test, 4-stair climb, 100-meter timed test, and performance of the upper limb [PUL]), and patient-reported health-related QOL (via FSHD-health index [FSHD-HI] or CMT-health index [CMT-HI]), depending on the disease and muscles treated.

Pharmacokinetics/pharmacodynamics

Blood samples were collected according to the schedule of assessments for PK and PD biomarker evaluation. Changes in the muscle volume and intramuscular fat fraction of TA and BB muscles were assessed by magnetic resonance imaging (MRI).

Safety

Participant safety was assessed by monitoring adverse events (AEs), injection site reactions, concomitant medications, clinical laboratory tests (including hematology, chemistry, and ADA), urinalysis, vital signs, and physical examination findings.

Statistical Methods

The statistical methods outlined below consist of planned analyses described in the protocol. Due to the premature discontinuation of the study, many of the analyses described below could not be done due to the limited data available at the time of overall study discontinuation.

Analysis Populations

The Full Analysis Set (FAS) consisted of all participants enrolled in the study who received at least 1 dose of study drug (Part 1) or all participants randomized in the study (Part 2).

The Safety Population consisted of all participants enrolled/randomized in the study who received at least 1 dose of study drug.

The Per Protocol Set (PPS) consisted of all participants enrolled/randomized in the study, who received at least 1 dose of study drug with no clinical study report-reportable protocol violations and at least 1 post-baseline MRI evaluation.

The PK Population consisted of all participants who received at least 1 dose of study drug and had sufficient PK samples collected and assayed for PK analysis.

Efficacy

The primary analysis population for efficacy data was the PPS. The secondary analysis population was the FAS.

Part 1 (loading phase)

Individual efficacy data was listed for each participant. For muscle strength, both QMT and MMT were measured for the left and right sides and the average of the 2 sides was calculated. QMT was based on maximum voluntary isometric contraction (MVIC) using a hand-held dynamometer, and the MMT was based on Medical Research Council (MRC) grade. The MMT-MRC grades were 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 total score and selected subscale scores, motor function test assessments, raw data, and changes from baseline (percent and absolute change) for the injected muscles were summarized for each scheduled timepoint using descriptive statistics. For each efficacy parameter, a mixed model was fitted and least-square (LS) mean estimates of the effect of ACE-083 and the corresponding 90% confidence intervals (CI) was provided for the percent and/or absolute change from baseline (depending on the parameter).

Part 2 (maintenance phase)

Individual efficacy data was listed for each participant. Descriptive statistics were provided by cohort, treatment regimen, and scheduled timepoint for raw data and changes from baseline. For assessments that were performed on the left and right sides, such as MVIC and decimal MMT-MRC scores, descriptive statistics were 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 was fitted and LS 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% CI were provided for each treatment regimen for MVIC of ankle dorsiflexion (TA participant data, average of left and right sides), MVIC of elbow flexion (BB participant 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 QOL parameter (FSHD-HI total score and selected subscale scores [for FSHD participants] and CMT-HI total score and selected subscale scores [for CMT participants]), a mixed model was fitted and LS estimates of the mean absolute change from baseline for the first 6 months of the maintenance phase along with the corresponding 90% CI were provided for each treatment regimen

for FSHD-HI total score and selected subscale scores (FSHD participant data) as well as for CMT-HI total score and selected subscale scores (CMT participant data).

LS estimates of the mean percent or absolute change from baseline for other scheduled times during the maintenance phase along with the corresponding 90% CI were provided as appropriate.

Pharmacokinetics

Part 1 (loading phase) only

Individual listings of serum ACE-083 concentrations and actual blood sampling times were prepared. PK parameters of ACE-083 were not determined due to limited quantifiable concentration data.

Pharmacodynamics

The primary analysis population for PD data was the PPS. The secondary analysis population was the FAS.

Part 1 (loading phase)

Individual PD data (e.g., total muscle volume, contractile muscle volume, intramuscular fat fraction, and biomarker data) was listed for each participant. For individual PD data that was measured bilaterally (e.g., MRI), the average of the left and right side assessments were also listed and summarized. Descriptive statistics (raw data and change from baseline [percent and absolute change]) were provided by cohort and scheduled timepoint where baseline was 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 was fitted to the data and the LS 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 was determined for each cohort with the corresponding 90% CI, where placebo refers to data from the double-blind component of Part 2 of either Study A083-02 or A083-03. This was 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 every 3 weeks (q3w) regimen versus placebo.

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

Part 2 (maintenance phase)

Individual PD data was listed for each participant. Descriptive statistics were provided by cohort and scheduled timepoint for raw data and changes from the start of the maintenance phase (or equivalently the end of the loading phase).

The primary PD variable was 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 was fitted to the data and a non-inferiority analysis was performed using a non-inferiority margin of -5. The non-inferiority analysis was done for each maintenance dose regimen (q4w and q8w).

Secondary MRI PD variables included 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 included 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 was fitted to the data and LS estimates of the mean difference and corresponding 90% CI was provided for each maintenance dose regimen. For biomarker data, a mixed model was fitted and LS 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% CI was provided for each maintenance dose regimen.

LS estimates of the mean percent or absolute change from baseline for other scheduled times during the maintenance phase along with the corresponding 90% CI was provided as appropriate.

Safety

Part 1 (loading phase) and Part 2 (maintenance phase)

Unless otherwise specified, safety data was summarized, by cohort and overall, using descriptive statistics; individual safety data was listed for each participant. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 15.1) and incidence of treatment-emergent adverse events (TEAEs) were presented by system organ class and preferred term (PT). AE incidence rates were described by cohort with and without regard to causality. The frequency of occurrence of overall toxicity, categorized by toxicity grades (National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.0), was summarized. Change from baseline in clinical laboratory parameters, electrocardiogram, and vital signs were summarized across time. Shift tables were presented for selected laboratory parameters and vital signs. Physical examination results were presented in listings.

Anti-drug Antibody Data

Part 1 (loading phase) and Part 2 (maintenance phase)

Individual ADA data was listed for each participant. The results of ADA testing for ACE-083 versus time as well as results following further characterization of positive ADA samples were presented. Exploratory analyses were performed on the potential effect of ADA on ACE-083 PK exposure if ADA tests were positive.

SUMMARY OF RESULTS

A summary of the results for disposition and demographics, PK, and safety are provided below. Due to premature termination of the study, insufficient efficacy data were obtained to enable meaningful efficacy analyses; therefore, efficacy results are not presented.

DISPOSITION AND DEMOGRAPHICS

Disposition

Overall

Of the 63 participants enrolled into Parts 1 and 2 of this study, 62 participants received at least 1 dose of study drug and were included in the Safety Population. One participant in Cohort 1b did not receive study drug. Reasons for study discontinuation included study terminated by sponsor for FSHD participants (33 [53.3%] participants), study terminated by sponsor for CMT participants (25 [40.3%] participants), lost to follow-up (3 [4.8%] participants), and participant's request (1 [1.6%] participant).

Part 1 (Loading Phase)

Of the 22 participants enrolled into Part 1 of this study, 21 participants received at least 1 dose of study drug and were included in the Safety Population. One participant in Cohort 1b did not receive study drug. Reasons for study discontinuation included study terminated by sponsor for FSHD participants (7 participants; 6 [85.7%] and 1 [100%] participants in Cohorts 1a and 1b, respectively), study terminated by sponsor for CMT participants (11 [84.6%] participants in Cohort 1c), lost to follow-up (2 participants; 1 [14.3%] and 1 [7.7%] participants in Cohorts 1a and 1c, respectively), and participant's request (1 [7.7%] participant in Cohort 1c).

Part 2 (Maintenance Phase)

All 41 participants enrolled into Part 2 of this study received at least 1 dose of study drug and were included in the Safety Population. Reasons for study discontinuation included study terminated by

sponsor for FSHD participants (26 participants; 6 [100%], 7 [100%], 6 [100%], and 7 [87.5%], participants in Cohorts 2a, 2b, 3a, and 3b, respectively), study terminated by sponsor for CMT participants (14 participants; 6 [100%] and 8 [100%] participants in Cohorts 2c and 3c, respectively), and lost to follow-up (1 [12.5%] participant in Cohort 3b).

Demographics

Overall

The Safety Population was evenly split between males and females (30 [48.4%] and 32 [51.6%] participants, respectively). Majority of the participants were White (59 [95.2%] participants), and the mean (standard deviation [SD]) age and body mass index (BMI) was 46.6 (13.3) years and 26.4 (7.0) kg/m^2, respectively.

Part 1 (Loading Phase)

Part 1 of this study was evenly split between males (10 participants; 4 [57.1%] and 6 [46.2%] participants in Cohorts 1a and 1c, respectively) and females (11 participants; 3 [42.9%], 1 [100%], and 7 [53.8%] participants in Cohorts 1a, 1b, and 1c, respectively). All of the participants were White. The mean (SD) age for Cohorts 1a, 1b, and 1c was 47.0 (13.3), 56.0 (0), and 45.2 (15.5) years, respectively. The mean (SD) BMI for Cohorts 1a, 1b, and 1c was 26.7 (7.9), 20.1 (0), and 29.0 (8.4) kg/m^2, respectively.

Part 2 (Maintenance Phase)

Part 2 of this study was evenly split between males (20 participants; 2 [33.3%], 5 [71.4%], 3 [50.0%], 1 [16.7%], 6 [75.0%], and 3 [37.5%] participants in Cohorts 2a, 2b, 2c, 3a, 3b, and 3c, respectively) and females (21 participants; 4 [66.7%], 2 [28.6%], 3 [50.0%], 5 [83.3%], 2 [25.0%], and 5 [62.5%] participants in Cohorts 2a, 2b, 2c, 3a, 3b, and 3c, respectively). Majority of the participants were White (38 participants; 5 [83.3%], 6 [85.7%], 6 [100%], 6 [100%], 7 [87.5%], and 8 [100%] participants in Cohorts 2a, 2b, 2c, 3a, 3b, and 3c, respectively). The mean (SD) age for Cohorts 2a, 2b, 2c, 3a, 3b, and 3c was 51.7 (14.8), 49.7 (14.6), 55.0 (9.3), 40.2 (14.3), 40.4 (11.2), and 45.4 (10.7) years, respectively. The mean (SD) BMI for Cohorts 2a, 2b, 2c, 3a, 3b, and 3c was 25.5 (7.0), 24.0 (4.2), 30.2 (10.0), 22.4 (4.1), 24.6 (5.8), and 28.3 (5.8) kg/m^2, respectively.

PHARMACOKINETICS

Part 1 (Loading Phase)

ACE-083 concentrations ranged from 20.1 to 238.6 µg/L across FSHD and CMT cohorts with the majority of serum concentrations were below the lower limit of quantification (LLOQ) or just above LLOQ.

SAFETY RESULTS

Extent of exposure

Overall

Of the 63 participants enrolled into Parts 1 and 2 of this study, 62 participants received at least 1 dose of study drug and were included in the Safety Population. Overall, the mean (SD) total number of treatments administered during Parts 1 and 2 of this study was 2.9 (1.7) treatments. The total number of participants (by Cohort) who received treatment on Days 1, 29, 57, 85, 113, 141, and 169 is present in Table 2.

Table 2: Total Number of Participants Who Received Treatment Throughout the Study (Parts 1 and 2)

Day	Cohort									Overall (N=62) n (%)
	Part 1			Part 2						
	1a (N=7) n (%)	1b (N=1) n (%)	1c (N=13) n (%)	2a (N=6) n (%)	2b (N=7) n (%)	2c (N=6) n (%)	3a[a] (N=6) n (%)	3b[a] (N=8) n (%)	3c[a] (N=8) n (%)	
1	3 (42.9)	0	1 (7.7)	3 (50.0)	2 (28.6)	1 (16.7)	2 (33.3)	5 (62.5)	3 (37.5)	20 (32.3)
29	2 (28.6)	0	1 (7.7)	1 (16.7)	1 (14.3)	1 (16.7)	0	0	0	6 (9.7)
57	0	0	1 (7.7)	1 (16.7)	2 (28.6)	1 (16.7)	4 (66.7)	2 (25.0)	2 (25.0)	13 (21.0)
85	2 (28.6)	1 (100)	4 (30.8)	1 (16.7)	0	0	0	0	0	8 (12.9)
113	0	0	6 (46.2)	0	2 (28.6)	1 (16.7)	0	1 (12.5)	3 (37.5)	13 (21.0)
141	0	0	0	0	0	1 (16.7)	0	0	0	1 (1.6)
169	0	0	0	0	0	1 (16.7)	0	0	0	1 (1.6)

Source: Table 14.1.7.1

[a] Participants in Cohorts 3a, 3b, and 3c were scheduled to receive treatment on Days 1, 57, 113, and 169.

Part 1 (Loading Phase)

Of the 22 participants enrolled into Part 1 of this study, 21 participants received at least 1 dose of study drug and were included in the Safety Population. For Cohorts 1a, 1b, and 1c, the mean (SD) total number of treatments administered during Part 1 of the study was 2.1 (1.3), 4.0 (0), and 4.0 (1.3) treatments, respectively. The total number of participants (by Cohort) who received treatment on Days 1, 29, 57, 85, 113, 141, and 169 is present in Table 2.

Part 2 (Maintenance Phase)

All 41 participants enrolled into Part 2 of this study received at least 1 dose of study drug and were included in the Safety Population. For Cohorts 2a, 2b, 2c, 3a, 3b, and 3c, the mean (SD) total number of treatments administered during Part 2 of the study was 2.0 (1.3), 2.9 (1.7), 4.0 (2.4), 2.3 (1.0), 2.0 (1.5), and 3.0 (1.9) treatments, respectively. The total number of participants (by Cohort) who received treatment on Days 1, 29, 57, 85, 113, 141, and 169 is present in Table 2.

Adverse events

Overall

All AEs were coded using MedDRA (version 15.1), and the incidence of TEAEs is presented by PT. Of the 62 participants in the Safety Population, 38 (61.3%) participants experienced at least 1 AE during Parts 1 and 2 of this study. Overall, the most commonly reported AEs were injection site discomfort and injection site erythema (8 [12.9%] participants each); injection site bruising and injection site swelling (6 [9.7%] participants each); arthralgia and nasopharyngitis (5 [8.1%] participants each); fall and pain in extremity (4 [6.5%] participants each); and injection site pain, injection site pruritus, myalgia, and sinusitis (3 [4.8%] participants each). The remaining AEs reported occurred in ≤ 2 participants each. Overall, only 1 (1.6%) participant (from Cohort 2c) reported a ≥ Grade 3 AE (joint injury [PT]; left ankle injury [verbatim term]), which resolved and was determined not related to treatment.

Of the 38 (61.3%) participants who experienced at least 1 AE, 17 (27.4%) participants experienced at least 1 AE that was assessed as related to ACE-083. The most commonly reported treatment-related AEs were injection site discomfort (7 [11.3%] participants), injection site erythema (6 [9.7%] participants), injection site swelling (5 [8.1%] participants), and injection site pruritus and

myalgia (3 [4.8%] participants each). The remaining treatment-related AEs reported occurred in ≤ 2 participants each. No ≥ Grade 3 treatment-related AEs were reported.

No SAEs or deaths were reported, and no participants discontinued treatment or the study due to an AE.

Part 1 (Loading Phase)

A summary of the TEAEs reported in ≥ 2 participants enrolled in Part 1 of this study is presented in Table 3. Of the 21 participants enrolled into Part 1 of this study who were included in the Safety Population, 15 participants experienced at least 1 AE (3 [42.9%], 1 [100%], and 11 [84.6%] participants in Cohorts 1a, 1b, and 1c, respectively). The most commonly reported AEs were injection site discomfort (6 participants); injection site erythema and injection site swelling (5 participants each); injection site bruising and injection site pain (3 participants each); nasopharyngitis, pain in extremity, injection site pruritus, myalgia, sinusitis, and vessel puncture site bruise (2 participants each); and arthralgia (1 participant). The remaining AEs reported occurred in 1 participant each. No ≥ Grade 3 AEs were reported.

Table 3: Summary of Treatment-Emergent Adverse Events Reported in ≥ 2 Participants Enrolled in Part 1

	Cohort		
AE Preferred Term	**1a (N=7) n (%)**	**1b (N=1) n (%)**	**1c (N=13) n (%)**
Participants with at least 1 TEAE	3 (42.9)	1 (100)	11 (84.6)
Injection site discomfort	0	0	6 (46.2)
Injection site erythema	0	1 (100)	4 (30.8)
Injection site swelling	1 (14.3)	1 (100)	3 (23.1)
Injection site bruising	0	1 (100)	2 (15.4)
Injection site pain	2 (28.6)	0	1 (7.7)
Nasopharyngitis	0	0	2 (15.4)
Pain in extremity	1 (14.3)	0	1 (7.7)
Injection site pruritus	1 (14.3)	0	1 (7.7)
Myalgia	0	0	2 (15.4)
Sinusitis	0	0	2 (15.4)
Vessel puncture site bruise	1 (14.3)	1 (100)	0

AE = adverse event; TEAE = treatment-emergent adverse event
Source: Table 14.3.1

A summary of the related TEAEs reported in ≥ 2 participants enrolled in Part 1 of this study is presented in Table 4. Of the 15 participants who experienced at least 1 AE, 10 participants experienced at least 1 AE that was assessed as related to ACE-083 (1 [14.3%] and 9 [69.2%] participants in Cohorts 1a and 1c, respectively). The most commonly reported treatment-related AEs were injection site discomfort (6 participants); injection site erythema and injection site swelling (4 participants each); and injection site pruritus, myalgia, and injection site bruising (2 participants each). The remaining treatment-related AEs were reported in 1 participant each. No ≥ Grade 3 treatment-related AEs were reported.

Table 4: Summary of Related Treatment-Emergent Adverse Events Reported in ≥ 2 Participants Enrolled in Part 1

AE Preferred Term	Cohort 1a (N=7) n (%)	Cohort 1b (N=1) n (%)	Cohort 1c (N=13) n (%)
Participants with at least 1 related TEAE	1 (14.3)	0	9 (69.2)
Injection site discomfort	0	0	6 (46.2)
Injection site erythema	0	0	4 (30.8)
Injection site swelling	1 (14.3)	0	3 (23.1)
Injection site pruritus	1 (14.3)	0	1 (7.7)
Myalgia	0	0	2 (15.4)
Injection site bruising	0	0	2 (15.4)

AE = adverse event; TEAE = treatment-emergent adverse event
Source: Table 14.3.4

No SAEs or deaths were reported, and no participants discontinued treatment or the study due to an AE.

Part 2 (Maintenance Phase)

A summary of the TEAEs reported in ≥ 2 participants enrolled in Part 2 of this study is presented in Table 5. Of the 41 participants enrolled into Part 2 of this study who were included in the Safety Population, 23 participants experienced at least 1 AE (3 [50.0%], 4 [57.1%], 5 [83.3%], 3 [50.0%], 4 [50.0%], and 4 [50.0%] participants in Cohorts 2a, 2b, 2c, 3a, 3b, and 3c, respectively). The most commonly reported AEs were arthralgia (4 participants); injection site erythema, injection site bruising, nasopharyngitis, and fall (3 participants each); injection site discomfort, pain in extremity, paresthesia, and sinus congestion (2 participants each); and myalgia and joint swelling (1 participant each). The remaining AEs reported occurred in 1 participant each. Only 1 (1.6%) participant (from Cohort 2c) reported a ≥ Grade 3 AE (joint injury [PT]; left ankle injury [verbatim term]), which resolved and was determined not related to treatment.

Table 5: Summary of Treatment-Emergent Adverse Events Reported in ≥ 2 Participants Enrolled in Part 2

AE Preferred Term	Cohort 2a (N=6) n (%)	2b (N=7) n (%)	2c (N=6) n (%)	3a (N=6) n (%)	3b (N=8) n (%)	3c (N=8) n (%)
Participants with at least 1 TEAE	3 (50.0)	4 (57.1)	5 (83.3)	3 (50.0)	4 (50.0)	4 (50.0)
Arthralgia	0	1 (14.3)	1 (16.7)	1 (16.7)	1 (12.5)	0
Injection site erythema	0	0	0	0	2 (25.0)	1 (12.5)
Injection site bruising	0	3 (42.9)	0	0	0	0
Nasopharyngitis	0	2 (28.6)	0	0	1 (12.5)	0
Fall	1 (16.7)	0	1 (16.7)	0	0	1 (12.5)
Injection site discomfort	0	0	1 (16.7)	0	1 (12.5)	0
Pain in extremity	1 (16.7)	0	1 (16.7)	0	0	0
Paraesthesia	0	0	0	0	1 (12.5)	1 (12.5)
Sinus congestion	0	1 (14.3)	0	1 (16.7)	0	0

AE = adverse event; TEAE = treatment-emergent adverse event
Source: Table 14.3.1

A summary of the related TEAEs reported in ≥ 2 participants enrolled in Part 2 of this study is presented in Table 6. Of the 23 participants who experienced at least 1 AE, 7 participants experienced at least 1 AE that was assessed as related to ACE-083 (2 [33.3%], 3 [50.0%], 1 [12.5%], and 1 [12.5%] participants in Cohorts 2a, 2c, 3b, and 3c, respectively). The most commonly reported treatment-related AEs were injection site erythema and pain in extremity (2 participants each) and injection site swelling and myalgia (1 participant each). The remaining treatment-related AEs were reported in 1 participant each. No ≥ Grade 3 treatment-related AEs were reported.

Table 6: Summary of Related Treatment-Emergent Adverse Events Reported in ≥ 2 Participants Enrolled in Part 2

AE Preferred Term	Cohort 2a (N=6) n (%)	2b (N=7) n (%)	2c (N=6) n (%)	3a (N=6) n (%)	3b (N=8) n (%)	3c (N=8) n (%)
Participants with at least 1 related TEAE	2 (33.3)	0	3 (50.0)	0	1 (12.5)	1 (12.5)
Injection site erythema	0	0	0	0	1 (12.5)	1 (12.5)
Pain in extremity	1 (16.7)	0	1 (16.7)	0	0	0

AE = adverse event; TEAE = treatment-emergent adverse event
Source: Table 14.3.4

No SAEs or deaths were reported, and no participants discontinued treatment or the study due to an AE.

Clinical laboratory evaluation

Overall

Clinical laboratory evaluations are listed but not summarized. Overall, no clinically significant laboratory abnormalities related to treatment were reported.

Part 1 (Loading Phase)

In Part 1 of this study, no clinically significant laboratory abnormalities were reported during treatment. However, 1 (7.7%) participant in Cohort 1c experienced an AE of C-reactive protein increase, which did not resolve and was determined to be not related to treatment.

Part 2 (Maintenance Phase)

In Part 2 of this study, no clinically significant laboratory abnormalities were reported during treatment.

ADA testing

Overall

Of the 62 participants in the Safety Population, 55 participants were tested for ADAs. A total of 4 participants (1 [14.2%], 1 [7.7%], 1 [16.7%], and 1 [16.7%] participants in Cohorts 1a, 1c, 2a, and 3a, respectively) tested positive for anti-ACE-083 antibodies (Table 14.4.1 and Table 14.4.2). Participants were continually monitored until a negative result was obtained or the titer was no longer increasing. Listings of individual ADA data is presented in Listing 16.5.

CONCLUSIONS

In this open-label, multicenter, phase 2 extension study in participants with FSHD and CMT (types 1 and X), treatment with ACE-083 q4w or q8w was generally safe and well tolerated. Overall, the most frequently reported AEs were injection site discomfort, injection site erythema, injection site bruising, and injection site swelling. Non-injection site, treatment AEs included myalgia and pain in extremity. No SAEs or deaths were reported, and no participants discontinued treatment or the study due to an AE.

Participants were discontinued from this study when their respective parent studies were terminated by the sponsor. The decision to discontinue FSHD participants was made in September 2019 and for CMT patients was made in March 2020, at which point Study A083-04 was also terminated. The reason for termination of the studies was that increases in mean total muscle volume did not translate into significant improvements in any of the functional or quality of life secondary endpoints when compared with placebo. Due to premature termination of the study, insufficient efficacy data were obtained to enable meaningful efficacy analyses.

Date of the report

14 October 2020