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Journal

Muscle and Nerve, 66(1)

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Publication Date

2022-07-01

DOI

10.1002/mus.27558

Peer reviewed

Received: 23 September 2021 | Revised: 7 April 2022 | Accepted: 9 April 2022

DOI: 10.1002/mus.27558

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

Randomized phase 2 study of ACE-083, a muscle-promoting agent, in facioscapulohumeral muscular dystrophy

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Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; 10 mW/R, 10-meter walk/run; ADA, antidrug antibody; ANCOVA, analysis of covariance; BB, biceps brachii; CMF, contractile muscle fraction; CMV, contractile muscle volume; EMG, electromyography; FF, fat fraction; FSHD, facioscapulohumeral muscular dystrophy; FSHD-HI, FSHD-Health Index; IRT, interactive response technology; ISR, injection-site reaction; LS, least squares; MRC-MMT, Medical Research Council manual muscle testing; MRI, magnetic resonance imaging; MVIC, maximum voluntary isometric contraction; OLE, open-label extension; PRO, patient-reported outcome; PUL, performance of upper limb; TA, tibialis anterior; TEAE, treatment-emergent adverse event; TGF-β, transforming growth factor-beta; TMV, total muscle volume.

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Abstract

Introduction/Aims: Facioscapulohumeral muscular dystrophy (FSHD) is a slowly progressive muscular dystrophy without approved therapies. In this study we evaluated whether locally acting ACE-083 could safely increase muscle volume and improve functional outcomes in adults with FSHD.

Methods: Participants were at least 18 years old and had FSHD1/FSHD2. Part 1 was open label, ascending dose, assessing safety and tolerability (primary objective). Part 2 was randomized, double-blind for 6 months, evaluating ACE-083240 mg/muscle vs placebo injected bilaterally every 3 weeks in the biceps brachii (BB) or tibialis anterior (TA) muscles, followed by 6 months of open label. Magnetic resonance imaging measures included total muscle volume (TMV; primary objective), fat fraction (FF), and contractile muscle volume (CMV). Functional measures included 6-minute walk test, 10-meter walk/run, and 4-stair climb (TA group), and performance of upper limb midlevel/elbow score (BB group). Strength, patient-reported outcomes (PROs), and safety were also evaluated.

Results: Parts 1 and 2 enrolled 37 and 58 participants, respectively. Among 55 participants evaluable in Part 2, the least-squares mean (90% confidence interval, analysis of covariance) treatment difference for TMV was 16.4% (9.8%-23.0%) in the BB group ($P < .0001$) and 9.5% (3.2%-15.9%) in the TA group ($P = .01$). CMV increased significantly in the BB and TA groups and FF decreased in the TA group. There were no consistent improvements in functional or PRO measures in either group. The most common adverse events were mild or moderate injection-site reactions.

Discussion: Significant increases in TMV with ACE-083 vs placebo did not result in consistent functional or PRO improvements with up to 12 months of treatment.

KEYWORDS
facioscapulohumeral muscular dystrophy, FSHD, randomized, controlled trial

1 | INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is a common form of muscular dystrophy, characterized by slowly progressive and asymmetric weakness in muscles of the face, shoulder, upper arm, lower leg, and trunk.[1,2] In FSHD, epigenetic derepression of the transcription factor DUX4 causes a toxic gain of function, occurring in two genetically distinct but clinically similar forms: FSHD1 and FSHD2.[1,2] There is currently no approved therapy for FSHD,[3-5] but potential treatments include modalities to increase muscle volume and strength, such as myostatin inhibition.[1,6]

ACE-083 is a recombinant fusion protein composed of modified human follistatin linked to the human immunoglobulin G2 Fc domain that functions as a ligand trap for the transforming growth factor (TGF)-β superfamily, particularly activins and myostatin, which inhibit skeletal muscle growth and regeneration.[7] In animal models, ACE-083 caused

localized muscle hypertrophy and improved function.[8] In a phase 1 study, locally injected ACE-083 increased muscle volume in healthy volunteers, was generally well tolerated, and was largely undetectable in serum.[7]

The aim of this study was to evaluate safety, tolerability, and efficacy of ACE-083 in participants with FSHD.

2 | 2 METHODS

2.1 | Study design

In this study we evaluated participants from November 22, 2016, to October 9, 2019, at 26 sites in the United States, Canada, and Spain (Figure 1).

Part 1 was an open-label, uncontrolled, dose-escalation study (3 months) evaluating multiple ascending doses of ACE-083 injected into the biceps brachii (BB) or tibialis anterior (TA) muscle, unilaterally or bilaterally. Part 2 was a randomized, double-blind, placebo-controlled study (6 months) followed by a 6-month open-label period to evaluate ACE-083 vs placebo injected bilaterally into either the BB or TA muscle. Participants who completed this study were eligible to enroll into a long-term open-label extension (OLE) study of ACE-083 (ClinicalTrials.gov identifier NCT03943290). Part 2 and the OLE study were terminated early because treatment with ACE-083 did not achieve secondary endpoints measuring function and patient-reported outcomes (PROs) at the time of the planned analysis of primary and secondary endpoints at the end of the 6-month placebo-controlled period.

2.2 | Standard protocol approvals, registrations, and patient consent

This study received institutional review board approval for all sites. Each participant provided informed consent. This study was registered on ClinicalTrials.gov (NCT02927080).

2.2.1 | Participants

Study participants were at least 18 years of age with genetically confirmed FSHD1 or FSHD2 (or had a first-degree relative with genetically confirmed FSHD1 or FSHD2). Participants in Part 1 were not eligible for inclusion in Part 2.

In Part 1, participants in the BB cohorts had left and/or right elbow flexion strength of Medical Research Council manual muscle testing (MRC-MMT) grade 3 to 4^+, inclusive; the contralateral, untreated side could be any MRC-MMT grade. Participants in the TA cohorts were required to have 6-minute walk distances (6MWDs) of at least 150 meters (without braces) and left and/or right ankle dorsiflexion strength of MRC-MMT grade 3 to 4^+, inclusive. In TA cohorts treated unilaterally, the contralateral side could have been MRC-MMT grades 3 to 5. In Part 2, both left and right elbow flexion strength (for the BB group) and both left and right ankle dorsiflexion strength (for the TA group) MRC-MMT grades must have been 3 to 4^+, inclusive. In Part 2, each participant in the TA group had to have a 6MWD of at least 150 meters and less than 500 meters.

Exclusion criteria included serious comorbid health conditions, pregnancy, increased risk of bleeding, recent major surgery, or taking chronic systemic corticosteroids, androgens, or growth hormone. Participants were asked to maintain their current level of physical activity during the study and not add additional exercise.

2.3 | Treatment

Using electromyography (EMG) or ultrasound guidance, each dose of the study drug was administered into the nontendinous portion of the BB or TA as up to five equal-volume injections in the same location at each dosing visit.

In Part 1, ACE-083 was administered in the BB cohorts unilaterally at 150, 200, or 240 mg per muscle. In the TA cohorts, ACE-083 was administered unilaterally at 150 or 200 mg per muscle or bilaterally at 200 mg per muscle. ACE-083 was administered every 3 weeks for up to 5 doses (≈3 months).

In the double-blind period of Part 2, participants were assigned to the BB or TA groups based on inclusion criteria and the investigator's discretion. Participants were randomized 1:1 to ACE-083 or placebo with interactive response technology (IRT) and stratified by muscle (BB or TA) and MRC-MMT grade category (mild, 3 to 4^-; moderate, 4^- to 4^+ on the weaker side). Participants with MRC-MMT grade 4^- were randomly assigned to either the mild or moderate MRC-MMT strength category via IRT. ACE-083 240 mg per muscle or placebo was administered bilaterally in the BB or TA every 3 weeks for

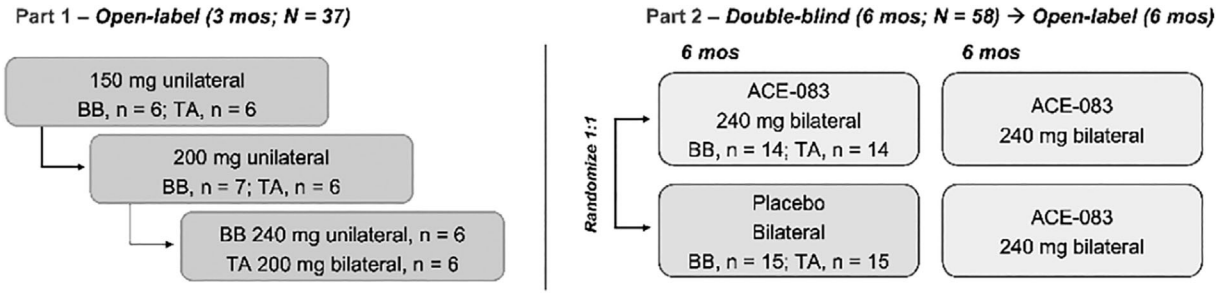

FIGURE 1 Study design (Parts 1 and 2). Abbreviations: BB, biceps brachii; TA, tibialis anterior.

27 weeks (nine doses). Only the pharmacist who prepared the study drug, a clinical monitor designated by the sponsor, and the analytical laboratory were unblinded to treatment assignments. All participants who continued to the open-label period received ACE-083 240 mg per muscle bilaterally every 3 weeks for 24 weeks (eight doses).

2.4 | Outcome measures

The primary objective of Part 1 was to evaluate safety and tolerability, and, for Part 2, to assess the increase from baseline in total muscle volume (TMV) by magnetic resonance imaging (MRI). Secondary endpoints for strength, motor function, and PROs are summarized in what follows.

2.4.1 | MRI measures

Bilateral MRI scans of the injected muscles (BB or TA) were obtained (including contralateral muscle in participants treated unilaterally in Part 1), and muscle volumes and fat fraction (FF) were determined for the entire muscle. TMV was measured as the sum of voxels identified as either muscle or intramuscular fat. FF was measured as the amount of fat in each voxel using the two-point Dixon scan, averaged across the entire muscle. Contractile muscle volume (CMV) was calculated as: TMV $\times$ (contractile muscle fraction [CMF] / 100), where CMF $=$ 100 $-$ FF.

2.4.2 | Motor function, PRO, and strength

The motor function test for the BB group was the performance of upper limb (PUL) midlevel/elbow dimension score, which includes nine assessments of upper limb motor function.[9] Motor function tests for the TA group included the 6-minute walk test (6MWT),[10] 10-meter walk/run (10 mW/R), and 4-stair climb.[11]

The FSHD-Health Index (FSHD-HI)[12,13] assessed disease impact in the BB and TA groups across 14 separate subdomains with a score ranging from 0 to 100, with higher values indicating increased disease impact.

Strength assessments included elbow flexion (BB group) and ankle dorsiflexion (TA group) measured by handheld dynamometry (microFET; Hoggan Scientific, LLC, Salt Lake City, UT) as maximum voluntary isometric contraction (MVIC) and by MRC-MMT grade in Part 2.[14] In both groups, MVIC was the maximum force from three measurements.

2.4.3 | Safety

Safety assessments included treatment-emergent adverse events (TEAEs), injection-site reactions (ISRs), concomitant medications, physical examinations, vital signs, and clinical laboratory tests (hematology, chemistry, urinalysis, antidrug antibodies [ADAs], confirmed as anti–ACE-083 or anti-follistatin [FST315]). Related TEAEs were assessed by the investigator for relationship to study drug; events with missing assessments were assumed to be probably related.

In the dose-escalation period of Part 1, participant safety was reviewed by a safety review team, comprising a principal investigator, medical monitor, and independent neuromuscular specialist, before initiating the next-higher-dose cohort. In Part 2, safety review team meetings were held every 3 to 6 months.

2.5 | Statistical analysis

Analysis was performed using SAS version 9.4 or higher (SAS Institute, Inc, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria). There was no formal sample size calculation for Part 1. A 10% difference between the ACE-083 and placebo groups in percent change in TMV was used to power Part 2 based on clinical experience in Part 1 and expert opinion regarding a potentially meaningful magnitude of change. Assuming a two-sided type I error rate of 0.10 (one-sided, 0.05), a 10% difference in percent change from baseline in TMV between treatment groups, a standard deviation of 9% for each group (estimated from Part 1), and 1:1 randomization, 83% power was achieved with a total sample size of 24 for each muscle (12 active, 12 placebo) based on a standard *t* test. To account for dropouts (up to 15%), 28 participants were planned to be randomized to study treatment for each muscle (14 active, 14 placebo) to ensure at least 12 participants per treatment group would complete the double-blind period.

Efficacy outcomes were analyzed in all participants receiving at least one dose of study drug without major protocol violations (per protocol set). The analysis set for safety data included all recipients of at least one dose of study drug.

Descriptive statistics were calculated for continuous variables; frequency counts were tabulated for categorical variables. Study drug exposure was reported based on the number of treatment cycles and participants with dose delay or reduction. Safety and tolerability were assessed by the frequency and nature of adverse events.

In Part 2, mean (standard error of the mean [SEM]) changes in efficacy measures from baseline were plotted by scheduled day. For MRI and MVIC data, changes from baseline were determined for the left and right sides and averaged for a single value for each time-point. For selected efficacy variables, analysis of covariance (ANCOVA) models were fitted to changes from baseline at day 190 (double-blind period), from which least-squares (LS) mean differences and SEM for treatment effects were determined.

For MRI data, covariates in the ANCOVA model included muscle (BB or TA), treatment (ACE-083 or placebo), baseline value, MRC-MMT grade category (mild or moderate), muscle-by-treatment interaction, and baseline-by-muscle interaction. For MVIC data, covariates included treatment, baseline value, and MRC-MMT grade category.

For the BB functional endpoint, covariates in the ANCOVA model included treatment, baseline value, and MRC-MMT grade category. For the TA functional endpoints, covariates included treatment,

baseline value, MRC-MMT grade category, and height (only for 6MWD and 10 mW/R). For FSHD-HI data, covariates included muscle, baseline value, treatment, MRC-MMT grade category, and muscle-by-treatment interaction.

Hypothesis testing for treatment effect was performed at the two-sided 0.10 significance level, and the corresponding 90% confidence interval for treatment effect was provided. Standard multiple imputations were performed for missing data, and there were no planned adjustments for multiplicity.

3 | RESULTS

3.1 | Participant disposition and results (Part 1)

In Part 1, 19 participants were treated with ACE-083 in the BB cohorts and 18 were treated in the TA cohorts (Figure 1). Eighteen participants (94.7%) in the BB cohorts and 17 (94.4%) in the TA cohorts completed the planned treatment per protocol. One participant in the BB cohorts and one participant in the TA cohort discontinued treatment (both ACE-083200 mg unilateral) prematurely. The reasons for discontinuation were patient request and an adverse event of muscle swelling, respectively.

Baseline characteristics for participants treated in Part 1 are presented in Table 1. In the BB cohorts, participants in the cohort given 240 mg per muscle had lower median age, body mass index, and BB muscle volume than the other BB cohorts.

Increases in TMV were seen in all groups, with changes of greater than 15% observed at ACE-083 doses of 200 to 240 mg per muscle. FF decreased from baseline with ACE-083 in each of the TA groups, but changed minimally in the BB groups.

In the BB groups, the PUL midlevel elbow dimension score did not demonstrate consistent mean changes; decreases (improvements) in FSHD-HI mean scores were more apparent in the two higher dose groups. In the TA group, 6MWD and 10 mW/R increased from baseline with treatment, but without evidence of a dose response.

Based on safety and tolerability of ACE-083 at all tested doses and MRI findings, investigators believed longer treatment with the highest tested dose (240 mg per muscle bilaterally) provided the best likelihood of improving strength and function in Part 2.

3.2 | Participant disposition and baseline characteristics (Part 2)

Participant disposition for Part 2 is presented in Figure 2. Baseline characteristics for Part 2 were similar between muscle and treatment groups (Table 2). There was a predominance of males in the BB group, but not in the TA group. Most participants had FSHD1 and a D4Z4 fragment size of at least 19 kb, and approximately half of the participants had symptoms for at least 20 years. Differences were observed for median muscle mass (smaller) and FF (greater) in the BB ACE-083 group compared with the BB placebo group.

During the double-blind period, all participants received nine treatment administrations, except for five who discontinued early: two participants in each placebo group, four in the BB ACE-083 group, and eight in the TA ACE-083 group had dose delay or reduction. During the open-label period, participants received a median of eight administrations in both the BB (range of three to eight) and TA (range of one to eight) groups. Eight and 13 participants had a dose delay or reduction during the open-label period in the BB and TA groups, respectively.

3.3 | Imaging primary and secondary endpoints (Part 2)

For the primary endpoint of TMV measured by MRI, LS mean percentage change from baseline to day 190 in the BB group was 16.4% greater with ACE-083 vs placebo ($P < .0001$; Table 3). In the TA group, this difference was 9.5% ($P = .01$; Table 2). Changes in TMV with ACE-083 treatment in the BB group remained relatively stable through day 295 (Figure 3A). In the TA group, increases in TMV from baseline observed with ACE-083 during the double-blind period appeared to wane with extended treatment (Figure 3B).

The treatment difference in LS mean CMV from baseline to day 190 with ACE-083 vs placebo was statistically significant in both the TA and BB groups; however, reductions in FF favoring ACE-083 were only statistically significant in the TA group (Table 3), similar to observations in Part 1.

3.4 | Function, PRO, and strength secondary endpoints (Part 2)

In the BB group, the change in PUL midlevel domain score from baseline to day 190 was greater with ACE-083 vs placebo (Table 3), but was not uniformly so throughout the double-blind or open-label treatment periods (Figure 3C). In the TA group, there were no statistically significant differences (Table 3) in functional tests (6MWT, 10 mW/R, and 4-stair climb) between patients treated with ACE-083 or placebo in the double-blind period, nor were there consistent trends suggesting improvement with up to 12 months of treatment (Figure 3D,E, and data not shown).

For the PRO measure, FSHD-HI, there were no statistically significant differences between treatment groups in LS mean change from baseline to day 190 in total score (Appendix Table S1). In the BB group, improvement (decreased score) was observed with ACE-083 in change from baseline in FSHD-HI arm/shoulder subscale score over 12 months but not in total score (Figure 4). Post hoc subgroup analyses suggested a more significant decrease in the FSHD-HI arm/shoulder subscale score in the more mildly affected BB subgroups (ie, baseline elbow

TABLE 1 Demographics and baseline clinical characteristics (Part 1)

Part 1 (full analysis set)[a]	Biceps brachii ACE-083			Tibialis anterior ACE-083		
Characteristic	**150 mg Uni (n = 6)**	**200 mg Uni (n = 7)**	**240 mg Uni (n = 6)**	**150 mg Uni (n = 6)**	**200 mg Uni (n = 6)**	**200 mg Bi (n = 6)**
Age, years	52.5 (36-66)	54.0 (20-69)	38.5 (23-61)	46.5 (42-52)	43.5 (19-63)	49.5 (42-60)
Sex, n (%)						
Male	4 (66.7)	4 (57.1)	4 (66.7)	3 (50.0)	3 (50.0)	2 (33.3)
Female	2 (33.3)	3 (42.9)	2 (33.3)	3 (50.0)	3 (50.0)	4 (66.7)
Race, n (%)						
White	6 (100)	6 (85.7)	6 (100)	6 (100)	5 (83.3)	6 (100)
Black or African American, or other	0	1 (14.3)	0	0	1 (16.7)	0
Body mass index, kg/m^2	26.1 (23.1-36.2)	25.6 (23.0-36.3)	22.7 (20.4-29.3)	22.6 (18.7-36.4)	23.3 (18.8-33.1)	25.6 (20.0-38.2)
Total muscle volume, mm^3[b]	76,674 (40,444-127,897)	89,001 (44,323-212,207)[c]	53,912 (31,057-116,337)	67,443 (35,468-151,858)	84,221 (36,870-118,297)	72,859 (52,127-115,777)
Contractile muscle volume, mm^3[b]	68,182 (11,150-103,444)	81,208 (9303-184,683)[c]	41,274 (6575-99,107)	35,360 (19,650-131,160)	37,903 (14,364-143,774)	38,546 (16,022-64,506)
Fat fraction, %[b]	16.8 (5.7-72.4)	11.4 (6.9-79.0)[c]	15.8 (10.2-78.8)	36.5 (13.6-68.7)	36.2 (12.0-82.1)	51.0 (35.0-78.1)

Note: Continuous data are presented as median (minimum-maximum).

Abbreviations: BB, biceps brachii; Bi, bilateral; TA, tibialis anterior; Uni, unilateral.

[a]All participants enrolled in the study and who have received at least one dose of study drug.

[b]Data are presented for the treated muscle for unilateral (Uni) treatment groups (BB and TA) and the average of left and right sides for the bilateral (Bi) TA group.

[c]n = 6.

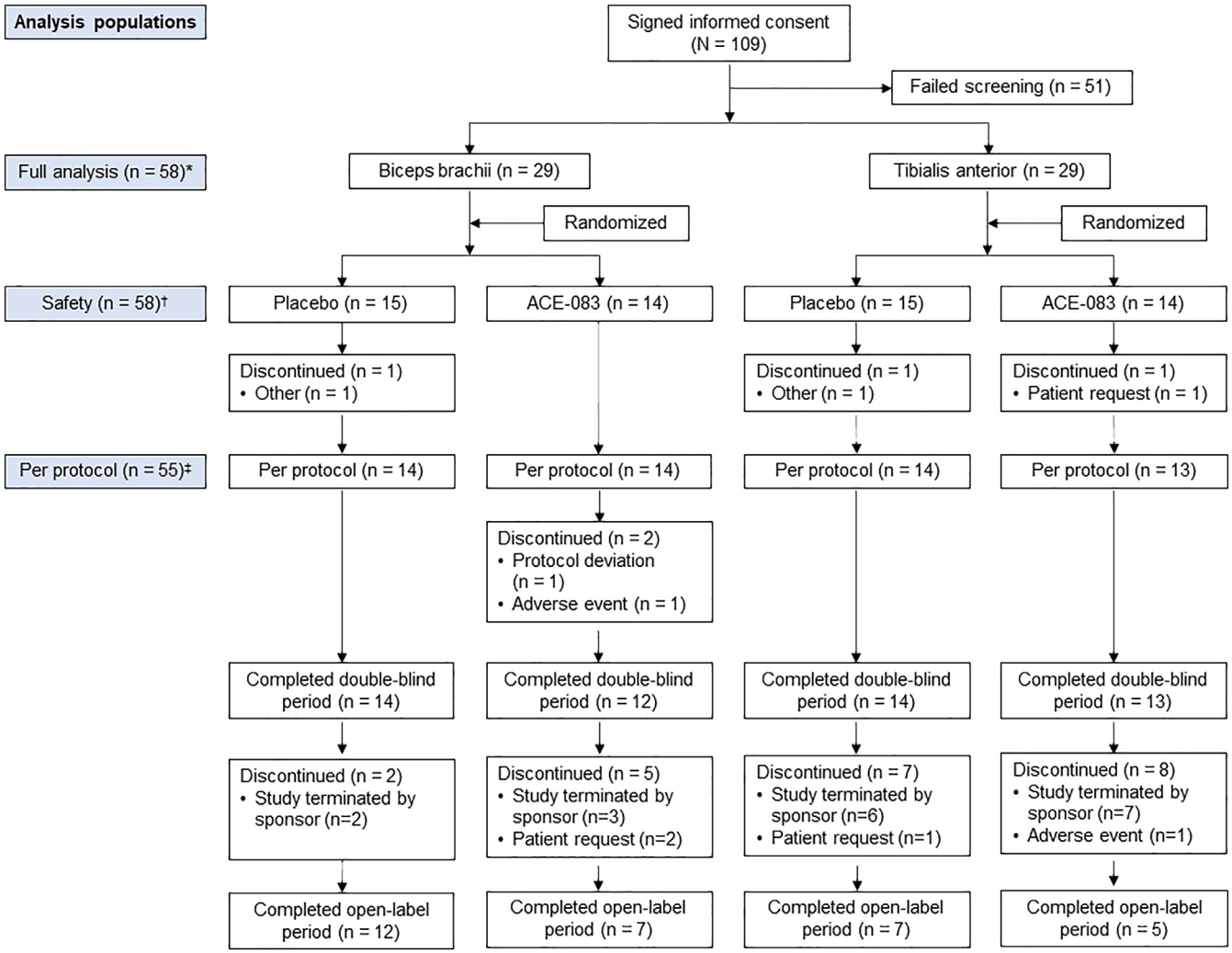

FIGURE 2 CONSORT flow diagram (Part 2). *All randomized participants. †All randomized participants who received at least one dose of study drug (includes placebo). ‡All participants randomized who received at least one dose of the study drug (including placebo) with no major protocol violations.

flexion MRC-MMT grade 4 to 4^+ or baseline FF less than the median; data not shown).

For quantitative muscle strength testing in the BB group, the difference in percent change from baseline to day 190 in elbow flexion MVIC for participants treated with ACE-083 vs placebo was statistically significant (Table 3); however, this improvement was not observed at other time-points during 12 months of treatment. No improvement in strength measurements was observed with ACE-083 in the TA group (Table 3). There was no improvement in strength measurements after switching from placebo to active drug in either muscle group.

3.5 | Safety and tolerability (Parts 1 and 2)

Across Parts 1 and 2, the most common TEAEs possibly or probably related to study drug were ISRs and myalgia (Appendix Table S2). These side effects were generally mild to moderate and of short duration. Among ISRs during the double-blind period, erythema (in the TA group), discomfort, swelling, pruritus, and warmth were more common with ACE-083 than with placebo. Myalgia and peripheral or joint swelling were also more common with ACE-083.

In Part 1, most participants had at least 1 TEAE possibly or probably related to study drug, with none being serious (Appendix Table S3). One participant receiving ACE-083200 mg in the TA had myalgia and muscle swelling leading to dose reduction and drug withdrawal. Both events were probably related to the study drug and later resolved.

In Part 2 (double-blind and open-label periods), all related TEAEs were grade ≤2, with none being serious (Appendix Table S3). One participant who received ACE-083 in the TA group during the double-blind period had left foot paresthesia, left partial peroneal nerve axonal injury, and hypoesthesia of the dorsum of the left foot (all grade 2, probably drug-related) that led to dose reduction. The events resolved with sequelae (progressively improving weakness). One participant receiving ACE-083 in the BB had a tingling sensation starting from the feet (grade 2 paresthesia, probably related) that led to drug

TABLE 2 Demographics and baseline clinical characteristics (Part 2)

Part 2 (per protocol set)[a]	Biceps brachii		Tibialis anterior	
Characteristic	**Placebo (n = 14)**	**ACE-083 (n = 14)**	**Placebo (n = 14)**	**ACE-083 (n = 13)**
Age, years	42.5 (21-65)	47.5 (28-68)	43.5 (18-62)	54.0 (31-70)
Sex, n (%)				
Male	11 (78.6)	10 (71.4)	7 (50.0)	6 (46.2)
Female	3 (21.4)	4 (28.6)	7 (50.0)	7 (53.8)
Race, n (%)				
White	12 (85.7)	12 (85.7)	13 (92.9)	11 (84.6)
Black or African American	1 (7.1)	0	0	1 (7.7)
Asian	0	2 (14.3)	0	1 (7.7)
Other	1 (7.1)	0	1 (7.1)	0
Hispanic ethnicity, n (%)	0	0	1 (7.1)	0
Body mass index, kg/m^2	23.5 (12.0-27.9)	23.96 (19.1-35.0)	25.73 (15.6-51.2)	23.80 (19.7-28.9)
FSHD disease type, n (%)				
FSHD1	13 (92.9)	14 (100)	12 (85.7)	11 (84.6)
FSHD2	1 (7.1)	0	2 (14.3)	2 (15.4)
D4Z4 fragment size, kb				
Available for analysis, n	13	14	12	11
≤18 (1-3 repeats), n (%)	3 (23.1)	4 (28.6)	3 (25.0)	1 (9.1)
19-28 (46 repeats), n (%)	7 (53.8)	8 (57.1)	6 (50.0)	7 (63.6)
>28 (>6 repeats), n (%)	3 (23.1)	2 (14.3)	3 (25.0)	3 (27.3)
Duration since onset of symptoms, years	20.5 (5-50)	21.5 (4-42)	19.5 (2-44)	24.0 (4-62)
Strength, MMT, n (%)				
Mild	5 (35.7)	5 (35.7)	7 (50.0)	5 (38.5)
Moderate	9 (64.3)	9 (64.3)	7 (50.0)	8 (61.5)
Total muscle volume, mm^3	97,630 (17,058-227,630)[b]	83,722 (31,393-211,187)	75,747 (21,620-202,728)	83,718 (50,123-125,442)
Contractile muscle volume, mm^3	76,199 (5494-200,809)[b]	48,475 (14,108-207,653)	57,080 (9803-189,487)	69,152 (20,654-91,717)
Fat fraction, %	13.7 (5.2-87.5)[b]	28.2 (1.7-73.9)	21.7 (2.9-69.3)	26.2 (8.3-74.6)

Note: Continuous data are presented as median (minimum-maximum).
Abbreviations: D4Z4, region with repeated segments on chromosome 4 that regulates expression of *DUX4* gene; FSHD, facioscapulohumeral muscular dystrophy; MMT, manual muscle testing.
[a]All participants randomized who received at least one dose of the study drug (including placebo) with no major protocol violations.
[b]n = 13.

withdrawal and later resolved. During the open-label period, 2 participants had unrelated TEAEs (knee swelling, breast carcinoma) that led to drug interruption and withdrawal of treatment, respectively.

No clinically relevant changes in laboratory measures were observed during the study, including biomarkers of systemic exposure to ACE-083 (eg, hemoglobin and serum C-terminal collagen crosslinks). No new safety signals were observed in the terminated OLE study.

In Part 1, eight participants (21.6%; four in each muscle group) tested positive for anti–ACE-083 antibodies. During the double-blind period of Part 2, 11 participants receiving ACE-083 (39.3%; 4 in the BB, 7 in the TA) and 1 participant receiving placebo (3.3%) had anti–ACE-083 antibodies. During the open-label period, 17 participants (32.1%) tested positive for anti–ACE-083 antibodies (7 BB and 10 TA participants).

4 | DISCUSSION

ACE-083 was safe and well tolerated in participants treated in either the TA or BB muscles, increased TMV, but had inconsistent effects on strength, motor function, and PRO in participants with FSHD. Several reasons may help explain this apparent mismatch between TMV and other secondary outcomes: (1) this class of drugs increases muscle volume but may not directly improve strength or function in patients with muscular dystrophy; (2) the sparsity of available BB and TA outcome measures could have limited detection of localized functional effects; (3) the study may have been underpowered for some endpoints to detect drug effect; (4) functional and PRO benefits may take substantially longer to manifest than changes in muscle composition; (5) treatment of multiple muscles may be necessary to improve

TABLE 3 LS mean (SEM) change in key outcome parameters to day 190 (Part 2, per protocol set, double-blind period)

	LS mean (SEM)		Difference (ACE-083 − placebo)		
Biceps brachii	**Placebo (n = 14)**	**ACE-083 (n = 14)**	**LS mean (SEM)**	**90% CI**	***P* value**
Percent change in TMV	2.7 (2.81)	19.1 (2.82)	16.4 (4.03)	9.8 to 23.0	<.0001
Percent change in CMV	2.6 (5.16)	25.8 (5.45)	23.3 (7.59)	10.8 to 35.8	.002
Absolute change in FF, %	1.0 (0.96)	−0.22 (0.98)	−1.3 (1.36)	−3.5 to 1.0	.36
Percent change in PUL midlevel domain score	−1.2 (1.2)	1.7 (1.2)	2.9 (1.7)	0.1 to 5.7	.09
Percent change in elbow flexion MVIC	−3.54 (10.00)	32.58 (10.44)[a]	36.12 (14.18)	11.78 to 60.46	.02
Percent change in elbow flexion MRC-MMT decimal score	0.20 (1.62)	−2.48 (1.75)	−2.68 (2.39)	−6.77 to 1.41	.27
Tibialis anterior	**Placebo (n = 14)**	**ACE-083 (n = 13)**	**LS mean (SEM)**	**90% CI**	***P* value**
Percent change in TMV	4.3 (2.72)	13.8 (2.85)	9.5 (3.88)	3.2 to 15.9	.01
Percent change in CMV	5.6 (4.89)	24.0 (5.24)	18.4 (7.01)	6.9 to 30.0	.009
Absolute change in FF, %	−0.32 (0.89)	−3.1 (0.95)	−2.7 (1.30)	−4.9 to −0.6	.04
Percent change in 6MWD	8.6 (2.76)	3.3 (2.94)	−5.3 (4.07)	−12.0 to 1.4	.20
Percent change in 10 mW/R time	−8.6 (3.35)	−3.9 (3.59)	4.7 (4.97)	−3.5 to 12.9	.35
Percent change in 4-stair ascend time	−5.2 (4.07)	−4.8 (4.32)	0.45 (6.03)	−9.5 to 10.4	.94
Percent change in ankle dorsiflexion MVIC	8.72 (7.76)	−5.82 (8.37)[a]	−14.54 (11.50)	−34.29 to 5.20	.22
Percent change in ankle dorsiflexion MRC-MMT decimal score	1.97 (2.15)	2.84 (2.32)	0.88 (3.17)	−4.56 to 6.31	.78

Abbreviations: 6MWD, 6-minute walk distance; 10 mW/R, 10-meter walk/run; CI, confidence interval; CMV, contractile muscle volume; FF, fat fraction; FSHD, facioscapulohumeral muscular dystrophy; LS, least squares; MRC-MMT, Medical Research Council manual muscle testing; MVIC, maximum voluntary isometric contraction; PUL, performance of the upper limb test; SEM, standard error of the mean; TMV, total muscle volume.
[a]n = 12.

complex motor function; and/or (6) functional and strength improvements may require another intervention (notably, exercise) in addition to the pharmacological treatment.

ACE-083, a molecule based on the naturally occurring ligand trap follistatin, was evaluated because it binds both growth differentiation factors and activins.[7] Furthermore, ACE-083 was designed to be delivered and to act locally due to suspected higher concentration of ligands in tissue compared with the circulation.[15] Indeed, ACE-083 treatment achieved relatively large mean changes (≈10% to 15%) in TMV (in the targeted muscle) compared with smaller changes (≈5%) observed more widely in studies of systemic myostatin inhibitors.[16,17] It was also found to lack some of the adverse effects observed in clinical trials of systemic myostatin inhibitors.[18]

Quantitative MRI has been used to assess changes in muscle volume and composition in FSHD.[19-22] In a previous natural history study of 45 individuals with FSHD that described progression of MRI parameters over 1 year, changes by MRI correlated with certain functional outcome measures.[19] Most other studies have suggested that early changes in FF may predict later changes in functional measures, but the size of the change and timing are not known.[19-22]

The BB and TA muscles were chosen for treatment and analysis because impairments in shoulders and upper arms, as well as difficulties with mobility and walking due in part to foot drop, have the greatest impact on the lives of patients with FSHD.[12] The outcome measure that may be anticipated to change first would be isolated motor strength. At the prespecified 6-month time-point, MVIC strength in the BB, but not TA, appeared to improve. However, the strength data were highly variable. Furthermore, the improvement did not appear to be maintained throughout the 12 months of ACE-083 treatment and was not observed in the placebo group when it was switched to ACE-083 in the open-label period.

When considering function, it was unknown at the time of study design whether targeting a single muscle (eg, the TA) would affect outcomes such as 6MWT, 10 mW/R, or 4-stair climb, which may depend on the interplay of multiple muscle groups that are affected in FSHD.[23,24] In addition, a learning effect for several motor function tests, particularly the 6MWD in the TA group, is suspected because increases in mean 6MWD were observed regardless of treatment assignment. Modeling of these data suggests that in this patient set, "improvements" independent of intervention are observed primarily during the first three or four test performances, which may support a longer run-in period and an appropriate control arm for future studies.

The FSHD-HI, on the other hand, did not show a learning effect. The FSHD-HI is a disease-specific PRO instrument designed to match patient-reported disease areas of high prevalence and health impact[3,13]; however, the total score and subscores are not tailored to detect effects of TA or BB function. Nonetheless, the trend for improvement in the BB group in FSHD-HI arm/shoulder subscale score with extended treatment raises the possibility that prolonged therapy of the biceps muscle may have led to more demonstrable changes in PRO if supported by continued trends in strength and function.

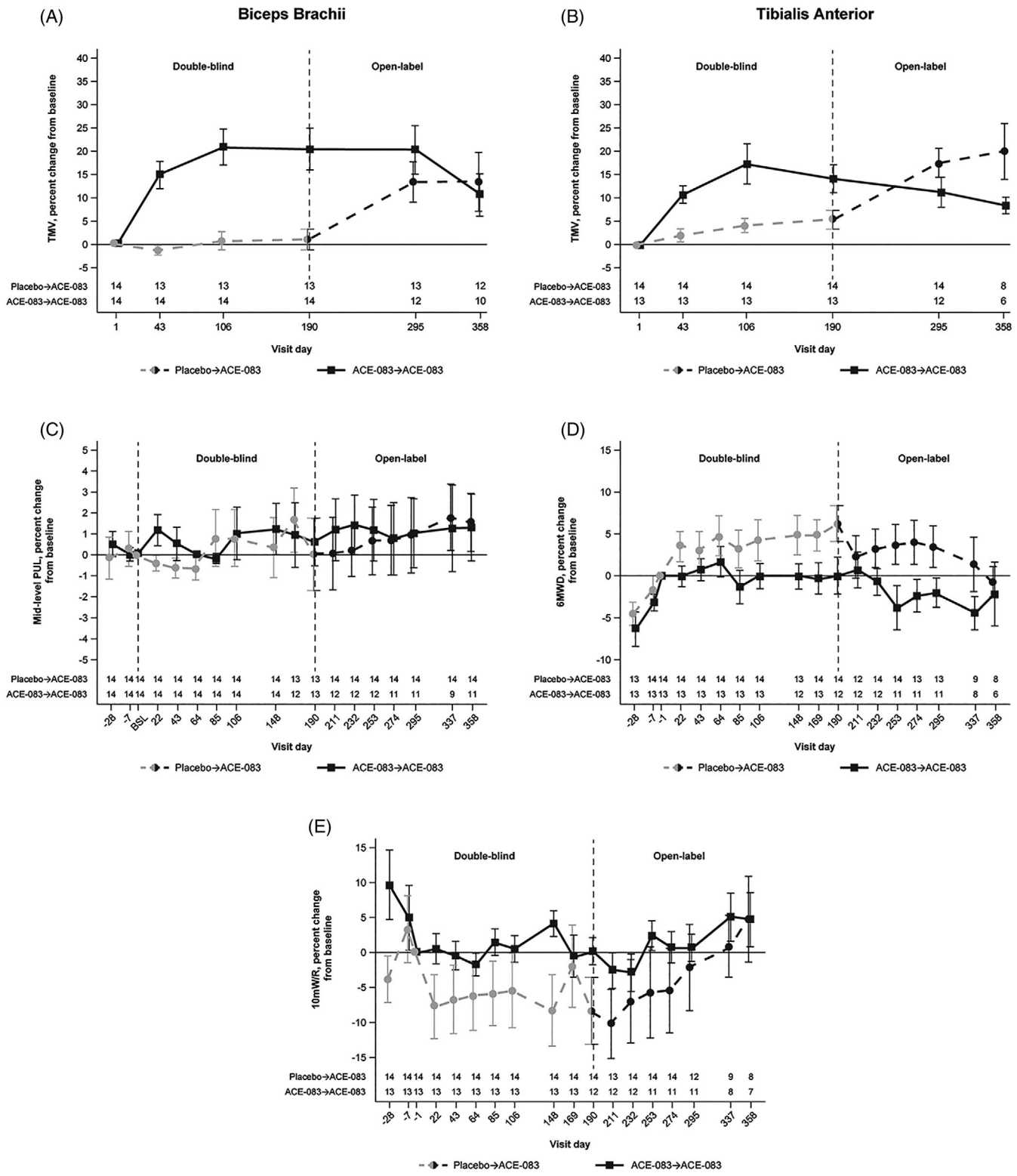

FIGURE 3 Mean ± SEM change from baseline in TMV and functional endpoints. A, TMV in the biceps brachii group. B, TMV in the tibialis anterior group. C, PUL midlevel domain score in the biceps brachii group. D, 6MWD in the tibialis anterior group. E, 10 mW/R in the tibialis anterior group (Part 2, per protocol set). Abbreviations: 6MWD, 6-minute walk distance; 10 mW/R, 10-meter walk/run; BSL, baseline; PUL, performance of the upper limb; SEM, standard error of the mean; TMV, total muscle volume.

This study has limitations. In Part 1, even the lowest dose levels increased muscle volume compared with the untreated side; the lack of dose response for secondary endpoints could not be easily interpreted at the time because of the muscle volume response at all dose levels.

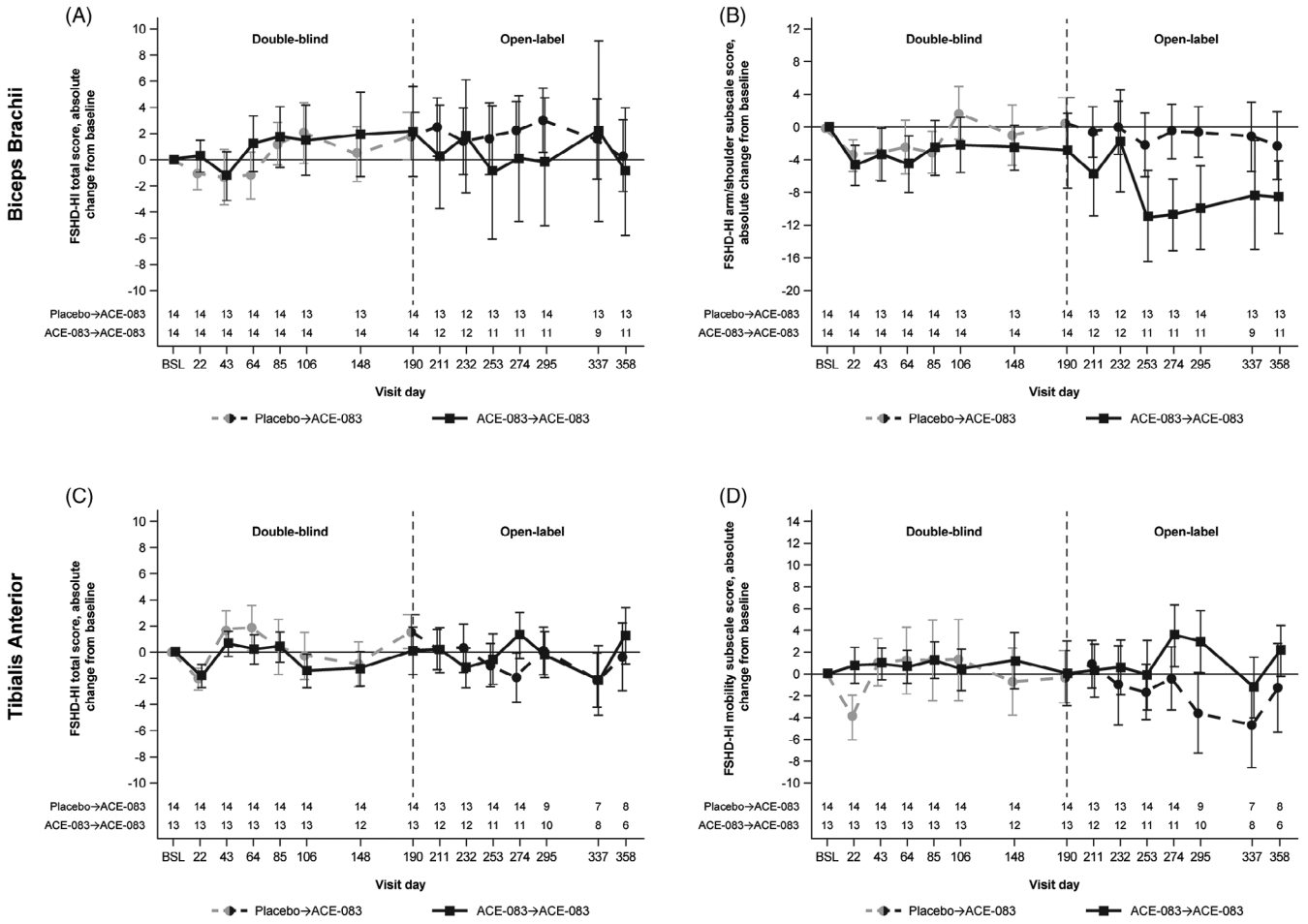

FIGURE 4 Mean ± SEM change from baseline in the patient-reported FSHD Health Index. A, Total score in the biceps brachii group. B, Arm/shoulder subscale score in the biceps brachii group. C, Total score in the tibialis anterior group. D, Mobility/ambulation subscale score in the tibialis anterior group (Part 2, per protocol set). Abbreviations: BSL, baseline; FSHD, facioscapulohumeral muscular dystrophy; FSHD-HI, FSHD Health Index; SEM, standard error of the mean.

Although investigators chose to power Part 2 for a 10% difference between groups in TMV, which was believed to be outside a change due to chance and consistent with Part 1 findings, it was underpowered to detect changes in strength measurements and may have been underpowered to detect early changes in other functional and PRO parameters. In addition, Part 2 was designed to detect improvements in muscle strength and function with ACE-083 treatment rather than changes to the rate or course of FSHD progression. A study with extended duration and potentially greater numbers of participants likely would be needed to detect such changes to the natural history of this slowly and asymmetrically progressing muscular dystrophy.

Data from this study may inform the design of future clinical trials in muscle diseases. Myostatin inhibition has been explored as a potential treatment in neuromuscular diseases, including other types of muscular dystrophy, peripheral neuropathies, sarcopenia, cachexia, and other muscle-wasting disorders.[6,18,25-32] In the future, a role may exist for local targeting of muscles within the context of systemic therapy, with more sensitive outcome measures, with additional interventions (eg, exercise), and/or with longer treatment duration.

This study demonstrated statistically significant increases in TMV with local injection of ACE-083 vs placebo; however, increased TMV and CMV and decreased FF did not translate to consistent improvement in function, strength, or PRO. Based on results of this Phase 2 study, the ACE-083 development program for treatment of FSHD was discontinued.

ACKNOWLEDGMENTS

Preliminary results from this study were presented at the 70th Annual American Academy of Neurology Meeting, April 2018, Los Angeles, California; the 23rd International Annual Congress of the World Muscle Society, February 2018, Mendoza, Argentina; and the Muscular Dystrophy Association Clinical & Scientific Congress, April 2019, Orlando, Florida. The authors thank the participants and their families for their participation and contributions, as well as the following team members: **subinvestigators:** Jorge Alonso-Pérez, MD, Richard Barohn, MD, Elena Bravver, MD, Benjamin Brooks, MD, Nizar Chahin, MD, Adam Comer, MD, Mazen Dimachkie, MD, Stacy Dixon, MD, PhD, Christopher Doughty, MD, Miriam Freimer, MD, Melanie Glenn, MD, Stanley Iyadurai, MD, Omar Jawdat, MD, Vern Juel, MD, Doris Leung,

MD, PhD, Eric Logigian, MD, Samantha LoRusso, MD, Craig McDonald, MD, Nuria Muelas, MD, PhD, Erin O'Ferrall, MD, Mamatha Pasnoor, MD, Colin Quinn, MD, Rodney Li Pi Shan, MD, Amro Shino, MD, Francy Shu, MD, Joana Turon, MD, Lisa Hobson-Webb, MD, Eugenio Zapata, MD; **evaluators:** Anabel Alba, Melissa Currence, Lujan Diago, Xi Dong, Lauren Draper, Katy Eichinger, Keegan Fitzgerald, Julaine Florence, Patricia Flynn, Carme García-Fernández, Molly Grames, Laura Herbelin, Scott Holsten, Andrea Jaworek, Brandi Johnson, Laura Juel, Renee King, Wendy Koesters, Jose Martinez, Melissa McIntyre, Angela Micheels, Elena Montiel-Morillo, Alina Nicorici, Crystal O'Conner, Stephanie Poelker, Mohammed Sanjak, Cheryl Scholtes, Catherine Siener, Christy Skura, Nikia Stinson, Amelia Wilson; **clinical site coordinators:** Colleen Anthonisen, Genila Bibat, Natalya Burlakova, Megan Christ, Bryant Gordon, Sandy Guingrich, Shivali Gupta, Bridget Hoskins, Kianoush Kamali, Cynthia Lary, Leann Lewis, Jennifer Mabry, Pilar Marti, Ayla McCalley, Sterling Meisner, Kelsey Moulton, Alison Newell-Sturdivant, Jennifer Petzke, Lisa Ranzinger, Kristen Roe, Linda Schimoeller, Nikita Shah, Katherine Summerton, Alexa Vareldzis, Nuria Vidal-Fernández, Mary Yep. **Medpace:** Emily Birkmeyer, Shanshan Cui, Megan Kolthoff, Chad Leslie, Taylor Meece, Stephanie Porter, Georgiana Salyers, Richard Scheyer, MD, Wendy van den Branden, Alexa Vareldzis, Nuria Vidal; **Acceleron:** Bronwyn Owens, Barbara Leibo, Balasubrahmanyam Budda, SaraBeth Hahn, Jade Sun, Saba Qamar, Amelia Pearsall, Carrie Barron, Joseph Reynolds, Shuree Harrison, Josh Black, Matthew Sherman, Chad Glasser, VirtualScopics, VirtuSense, ATOM, University of Rochester (Chad Heatwole), ERT; **editorial assistance** (including incorporation of authors' edits and preparation of tables and figures based on the clinical study report): Joshua Ziel, PhD, Lisa Baker, PhD (Cadent Medical Communications, LLC, a Syneos Health group company), in accordance with Good Publication Practice principles and was supported by Acceleron Pharma.

CONFLICT OF INTEREST

J.M. Statland received grant support from the NIH, MDA, FSHD Society, and the Friends of FSH Research; he is a consultant or has served on advisory boards for Dyne, Fulcrum, Acceleron, Avidity, Strongbridge, Sarepta, and Genzyme. U. Desai has served on advisory boards for Alexion, CSL Behring, Argenx, Akcea, and Stealth Biotherapeutics and has served on the speaker's bureau for Alexion. C. Karam has undertaken consulting or educational activities for Akcea, Alexion, Alnylam, Argenx, Biogen, CSL Behring, Medscape, and Sanofi Genzyme and has received research grants from Sanofi Genzyme and Akcea. J. Díaz-Manera has served as a consultant or on advisory boards for Sanofi-Genzyme, Amicus, Audentes, Sarepta, and Spark. He has also received industry grant support from Sanofi Genzyme and Boehringer Ingelheim. J.T. Guptill has served as a consultant or on advisory boards for Immunovant, Alexion, Momenta, Ra Pharma, Grifols, Argenx, Jacobus, Becton Dickinson, Cabaletta, Regeneron, and Piedmont Pharmaceuticals and receives industry grant support from UCB for a fellowship training grant. A. Genge serves as a consultant for Mitsubishi Tanabe Pharma America, Sanofi Genzyme, AL-S Pharma, AB Sciences, Biogen, Novartis, CSL Behring, Anavex, AveXis, Alexion, Wave Life Sciences, Revalesio, Roche, Cytokinetics, Orion, Akcea, Clene, Bayshore, and QurAlis. She participates as CRU Medical Director, PI, or sub-PI on trials sponsored by AB Sciences, AL-S Pharma, Acceleron, Amicus, Alnylam, Bioblast, Biogen, BMS, Boston Biomedical Cytokinetics, Sanofi Genzyme, Grifols, Ionis, Eli Lilly, Mallinckrodt, MedImmune, Novartis, Orion, Orphazyme, Pfizer, Ra Pharmaceuticals, Roche, Teva, and UCB. R.N. Tawil serves as an advisory board member or consultant for Acceleron Pharma, Fulcrum Therapeutics, MT Pharma, and Arrowhead Pharma. L. Elman has served on advisory boards for Roche/Genentech and Biogen and received royalties from *UpToDate* (Wolters Kluwer). K.R. Wagner has served on advisory boards or consulted for AskBio, Dyne, Arrowhead Pharma, Catabasis, Santhera, and Vita. G. Manousakis has served on advisory boards for Stealth Biotherapeutics and Argenx. A.A. Amato is an associate editor for *Neurology* and has served as a medical consultant or on advisory boards for Sarepta, Alexion, and Serono; he received royalties from *UpToDate* (Wolters Kluwer) and *Harrison's Principles of Internal Medicine, Neuromuscular Disorders, 2nd ed.* R.J. Butterfield is receiving funding via contracts for clinical trials from AveXis, PTC Therapeutics, Sarepta Therapeutics, Pfizer, Biogen, Capricorn, and Catabasis; he serves on scientific advisory boards for Sarepta Therapeutics, Biogen, AveXis, and Pfizer. M. Wicklund has received research funding from the NIH, MDA, Acceleron, Alexion, Baxalta, ML Bio, Orphazyme, and Sarepta Therapeutics and has served on advisory boards or in consultation for Affinia, Amicus, ML Bio, Sanofi, and Sarepta. J. Gamez has received grant funding from Fondo de Investigación Sanitaria (FIS-FEDER) (grants PI16/01673 and PI19/00593). N.E. Johnson has received grant funding from the NINDS (4K23NS091511; R01NS104010), CDC (DD19-002), and the FDA (7R01FD006071-02); he receives royalties from the Congenital and Childhood Onset Myotonic Dystrophy Health Index and the Charcot-Marie-Tooth Health Index; receives research funds from Dyne, AveXis, CSL Behring, Vertex Pharmaceuticals, Fulcrum Therapeutics, ML Bio, Sarepta, and Acceleron Pharma; and has provided consultation for AveXis, AMO Pharma, Strongbridge BioPharma, Acceleron Pharma, Fulcrum Therapeutics, Dyne, Avidity, and Vertex Pharmaceuticals. B. Miller, A. Leneus, M. Fowler, M. van de Rijn, and K. Attie were employed by Acceleron Pharma during the study and had stock ownership and/or options. The remaining authors declare no conflicts of interest.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are openly available at ClinicalTrials.gov at https://clinicaltrials.gov/ct2/show/results/NCT02927080.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Statland JM, Campbell C, Desai U, et al. Randomized phase 2 study of ACE-083, a muscle-promoting agent, in facioscapulohumeral muscular dystrophy. *Muscle & Nerve*. 2022;66(1):50-62. doi:10.1002/mus.27558