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RESEARCH ARTICLE

Randomized Phase 2 Study of ACE-083 in Patients With Charcot-Marie-Tooth Disease

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Abstract

Background and Objectives

The goal of this work was to determine whether locally acting ACE-083 is safe and well tolerated and increases muscle volume, motor function, and quality of life (QoL) in adults with Charcot-Marie-Tooth disease (CMT) type 1.

Methods

This phase 2 study enrolled adults with CMT1 or CMTX (N = 63). Part 1 was open label and evaluated the safety and tolerability of different dose levels of ACE-083 for use in part 2. Part 2 was a randomized, placebo-controlled, 6-month study of 240 mg/muscle ACE-083 injected bilaterally into the tibialis anterior muscle, followed by a 6-month, open-label extension in which all patients received ACE-083. Pharmacodynamic endpoints included total muscle volume (TMV; primary endpoint), contractile muscle volume (CMV), and fat fraction. Additional secondary endpoints included 6-minute walk test, 10-m walk/run, muscle strength, and QoL. Safety was assessed with treatment-emergent adverse events (TEAEs) and clinical laboratory tests.

Results

In part 1 (n = 18), ACE-083 was generally safe and well tolerated at all dose levels, with no serious adverse events, TEAEs of grade 3 or greater, or death reported. In part 2 (n = 45 enrolled, n = 44 treated), there was significantly greater change in TMV with ACE-083 compared with placebo (least-squares mean difference 13.5%; p = 0.0096). There was significant difference between ACE-083 and placebo for CMV and change in ankle dorsiflexion strength. Fat fraction and all other functional outcomes were not significantly improved by ACE-083. Moderate to mild injection-site reactions were the most common TEAEs.

Discussion

Despite significantly increased TMV and CMV, patients with CMT receiving ACE-083 in tibialis anterior muscles did not demonstrate greater functional improvement compared with those receiving placebo.

Trial Registration Information

Clinical Trials Registration: NCT03124459.

Classification of Evidence

This study provides Class II evidence that intramuscular ACE-083 is safe and well tolerated and increases total muscle volume after 6 months of treatment in adults with CMT1 or CMTX.

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CBMRT

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Glossary

AE = adverse event; **CMAP** = compound muscle action potential; **CMT** = Charcot-Marie-Tooth disease; **CMT-HI** = CMT-Health Index; **CMV** = contractile muscle volume; **FSHD** = facioscapulohumeral muscular dystrophy; **GDF** = growth differentiation factor; **ISR** = injection-site reaction; **LS** = least-squares; **MRC** = Medical Research Council; **MMT** = manual muscle testing; **QoL** = quality of life; **SAE** = serious AE; **6MWT** = 6-minute walk test; **SRT** = Safety Review Team; **TA** = tibialis anterior; **TEAE** = treatment-emergent AE; **10 mW/R** = 10-m walk/run; **TMV** = total muscle volume.

Charcot-Marie-Tooth disease (CMT), the most common form of hereditary peripheral neuropathy, affects 2.6 million people worldwide.[1-3] The most common types of CMT result from dominant autosomal (*CMT1*) or X-linked (*CMTX*) sequence variations that cause demyelination of motor and/or sensory nerves, leading to axonal loss and muscle atrophy.[3-6] These variations cause nerve dysfunction of variable severity, with lower leg weakness and sensory loss at the onset and later with involvement of the upper limbs, foot and ankle deformities, imbalance, and pain.[5,6] In the absence of disease-modifying drugs, management strategies include physical therapy, exercise, pain rehabilitation, orthotics, and surgery.[3,7]

ACE-083 is a locally acting investigational drug containing a modified form of human follistatin that binds growth differentiation factor (GDF) 8 (myostatin), activin A, and other negative regulators of skeletal muscle in the transforming growth factor-β superfamily.[8,9] ACE-083 has been engineered and developed as a ligand trap of negative regulators of skeletal muscle growth such as activin and myostatin, in addition to other ligands. Intramuscular administration of ACE-083 causes dose-dependent, localized hypertrophy of the injected skeletal muscle in wild-type mice and mouse models of CMT without systemic muscle effects.[9] In a phase 1 study, ACE-083 increased muscle mass locally in healthy volunteers to a greater extent than systemically acting myostatin inhibitors.[8] Increases in muscle mass were also observed in patients with facioscapulohumeral muscular dystrophy (FSHD), with the most common adverse events (AEs) being injection-site reactions (ISRs) and myalgia.[10]

The objective of this phase 2 study was to evaluate the safety and tolerability of ascending doses of ACE-083 (part 1) and to determine whether treatment with ACE-083 increases muscle volume of the injected muscles compared with placebo after 6 months of randomized treatment followed by 6 months of open-label extension (part 2).

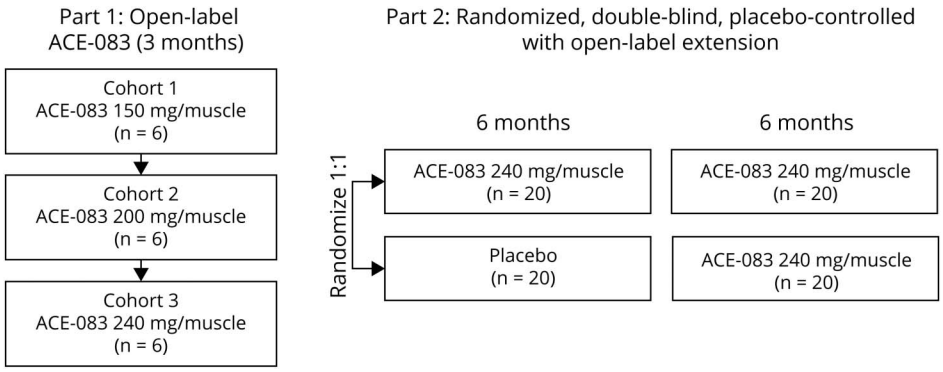
Methods

Study Design

This multicenter phase 2 study (ClinicalTrials.gov identifier NCT03124459) was designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of ACE-083 in persons with CMT and was conducted in 2 parts (Figure 1). Patients were enrolled between July 2017 and July 2019. All study sites were in the United States. Part 1 was an open-label, dose-escalation study in which the primary objective was to evaluate the safety and tolerability of ascending dosages of ACE-083 injected into both tibialis anterior (TA) muscles once every 3 weeks for up to 5 doses. Part 1 consisted of 3 cohorts who received 150, 200, and 240 mg/muscle of ACE-083 with n = 6 in each cohort.

Part 2 consisted of a 6-month randomized, double-blind, placebo-controlled period, followed by a 6-month open-label period (total 12 months). In the double-blind period, patients received injections of 240 mg/muscle of ACE-083 (or placebo) into both TA muscles every 3 weeks for up to 9 doses. In the open-label period of part 2, all patients received injections of ACE-083 into both TA muscles every 3 weeks for

Figure 1 Study Design



Part 1 is a nonrandomized, open-label, dose-escalation study consisting of 3 cohorts of 6 patients each that evaluated ascending doses of ACE-083. In part 2, patients were randomized to receive the recommended dose level chosen in part 1 (240 mg/muscle) or placebo for ≈6 months (9 doses, 1 every 3 weeks). Patients who completed the double-blind treatment period were immediately rolled over to open-label treatment of ACE-083 (8 doses, 1 every 3 weeks).

up to 8 doses. Patients who completed study treatment per protocol were eligible to enroll in a long-term open-label extension study (NCT03943290). Patients who had received placebo in the double-blind period of part 2 received ACE-083 240 mg/muscle in the open-label period, while patients in the ACE-083 group continued to receive the same dose in the open-label period.

Standard Protocol Approvals, Registrations, and Patient Consents

This study received institutional review board approval for all sites for use of human study participants. Patients were required to sign an independent ethics committee/institutional review board–approved informed consent form before any study-related procedures, including screening evaluations. The informed consent form followed principles of informed consent in the Declaration of Helsinki, as well as applicable local and national regulations. This study was registered on ClinicalTrials.gov (NCT03124459).

Participants

To be eligible for enrollment in either part 1 or 2, patients had to be ≥18 years of age; to have a diagnosis of CMT1 or CMTX confirmed clinically and by electrodiagnostic studies, as well as genetic confirmation for the patient or a first-degree relative; and to have left and right ankle dorsiflexion weakness Medical Research Council (MRC) manual muscle testing (MMT) grade 3 to 4+. For part 1 only, inclusion criteria included a 6-minute walk test (6MWT) of ≥150 m without a brace or walker, independent ambulation for at least 10 m without a brace, and left and right ankle plantar flexion MRC MMT grade 4+ to 5, inclusive. In part 2, patients were required to have a 6MWT without a brace or walker of ≥150 and ≤500 m and left and right ankle plantar flexion MRC MMT grade 4– to 5, inclusive. Patients with serious uncontrolled comorbid health conditions were excluded.

Treatment

In both study parts, ACE-083 or placebo was administered with EMG or ultrasound guidance into the nontendinous portion of the TA muscle as a series of up to 4 equal-volume injections per dose. In the double-blind period of part 2, patients were randomly assigned (1:1) to receive either ACE-083 or placebo (normal saline). The randomization was stratified by disease type (CMT1 or CMTX). Only the pharmacist who prepared the study drug, a clinical monitor designated by the sponsor, and the analytical laboratories were unblinded during the double-blind period.

Outcome Measures

The primary endpoints for part 1 were safety and tolerability evaluation of ascending doses of ACE-083 in patients with CMT1 and CMTX. The primary endpoint for part 2 was whether ACE-083 treatment increased total muscle volume (TMV) in the injected muscles from baseline to day 190 compared with placebo. Secondary endpoints included assessments of contractile muscle volume (CMV) and intramuscular fat fraction by MRI, quantitative and manual muscle strength testing, motor function tests, physician- and patient-reported outcomes, safety, and tolerability. Key study measures were either directly measured or derived from data from MRI scans. Bilateral MRI scans of the TA were performed for each patient at protocol-specified time points. The fat fraction was calculated within each voxel (smallest unit of measurement) programmatically using the following equation: (fat/[fat + water]). The functional contractile muscle compartment of TMV was calculated as follows: CMV = TMV × CMF/100, where contractile muscle fraction (CMF) equals (100 – fat fraction). Primary and secondary endpoints in part 2 were measured at day 190 (the final assessment of the double-blind period and the protocol-defined primary analysis time point) for the primary efficacy analyses, with absolute or percent change from baseline compared with the control group. Pharmacodynamic assessments included muscle volume and intramuscular fat fraction of the TA muscle by MRI and compound muscle action potential (CMAP) of the TA; the MRI protocols were standardized, and their execution was monitored throughout the study.

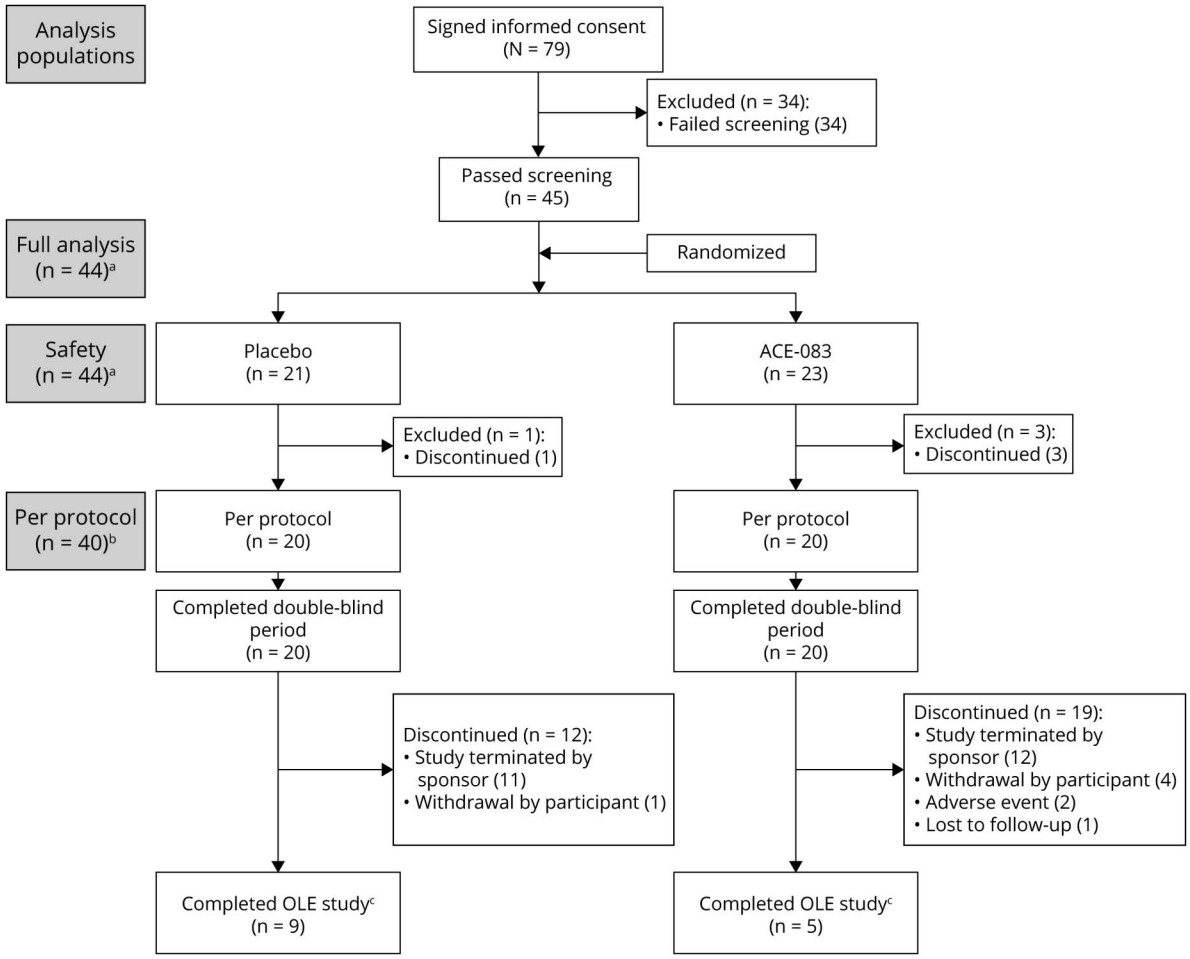
Efficacy was determined by assessing muscle strength, motor function, functional rating, and health-related quality of life (QoL). Ankle dorsiflexion strength was assessed by quantitative muscle testing (maximum voluntary isometric contraction with a handheld dynamometer), and MRC MMT. Motor function was measured with 6MWT, 10-m walk/run (10 mW/R), 100-m timed test (part 2 open label only), gait, activity, and falls using wearable sensors (PAMSys, BioSensics, Cambridge, MA) and the Berg balance scale.[11,12] The physician-reported functional rating scale was the CMT Examination Score version 2, and participant-reported health-related QoL was recorded with CMT-Health Index (CMT-HI).

Safety assessments included AEs, ISRs, concomitant medications, physical examination, vital signs, and clinical laboratory tests (hematology, chemistry, urinalysis, and anti-drug antibodies). In the dose-escalation period of part 1, participant safety was reviewed by a Safety Review Team (SRT) consisting of a principal investigator, a medical monitor, and an independent neuromuscular specialist before the next higher dose cohort was initiated. In part 2, SRT meetings were held every 3 to 6 months.

Statistical Analysis

There was no formal sample size calculation for part 1. Six patients in each cohort were estimated to be sufficient to evaluate tolerability and dosing. The sample size calculation for part 2 was based on the expected percent change from baseline in TMV of the injected TA muscle. Assuming a 2-sided type 1 error rate of 0.10 in a standard t test, a 10% difference in percent change from baseline between ACE-083 and placebo groups in TMV, an SD of 10% for each group (based on MRI data for ACE-083 in the phase 2 FSHD study), and a 1:1 randomization, 90% power was achieved with a total sample size of n = 36 patients (18 active, 18 placebo). To account for a dropout rate of up to 10%, the

Figure 2 Patient Disposition (Part 2)



One patient was randomized but not dosed. [a]The full analysis and safety sets included all randomized patients who had received at least 1 dose of study drug (includes placebo). [b]The per-protocol set consisted of all patients randomized who had received at least 1 dose of study drug (including placebo) with no data or study procedure-related issues that would otherwise affect interpretability of the efficacy and/or pharmacodynamics. [c]Patients who completed the study either were rolled into the extension study or were marked as completing the study as entered on the End of Study page of the case report form. OLE = open-label extension.

study aimed to randomize at least 40 patients 1:1 to ACE-083 or placebo.

Analysis populations in part 2 consisted of the full analysis set, which was defined as all patients randomized who received at least 1 dose of study drug (including placebo); the safety set, which was defined similarly to the full analysis set; and the per-protocol set, which was defined as all randomized patients who received at least 1 dose of study drug (included placebo) with no data or study procedural–related issues that would otherwise affect the interpretability of the efficacy or pharmacodynamics data. Descriptive statistics were calculated for demographic variables by treatment and overall for parts 1 and 2. In part 2, a mixed-model analysis of covariance was used to assess the primary pharmacodynamic and efficacy parameters of ACE-083 vs placebo using a 2-sided 0.10 significance level for the day 190 percent change from baseline; least-squares (LS) mean estimates of the treatment effect and corresponding (SEM) and 90% CI were also provided. Safety data from parts 1 and 2 were reported using descriptive statistics, including the frequency and type of AEs, treatment-emergent AEs (TEAEs), and serious AEs (SAEs).

Data Availability

Scientific and medical researchers interested in access to deidentified patient-level datasets, the protocol, or the statistical analysis plan for this study should contact Barry Miller at Acceleron Pharma for more information (bmiller@xlrn.com). The clinical study protocol and statistical analysis plan are available as supplemental material (eSAP 1–2, links.lww.com/WNL/B923 and links.lww.com/WNL/B925).

Results

Study Part 1

There were a total of 18 patients in part 1, including 11 with CMT1A, 4 with CMT1B, and 3 with CMTX1. The baseline characteristics were similar across cohorts. The median age

Table 1 Demographics and Baseline Clinical Characteristics (Part 2)

Parameter	Placebo (n = 21)	ACE-083 (n = 23)
Full analysis set		
Age, median (minimum–maximum), y	48.0 (18–71)	47.0 (19–67)
Sex, n (%)		
Male	8 (38.1)	6 (26.1)
Female	13 (61.9)	17 (73.9)
Race, n (%)		
White	21 (100)	20 (87.0)
Black	0	0
Asian	0	2 (8.7)
Other	0	1 (4.3)
Ethnicity, n (%)		
Hispanic	2 (9.5)	1 (4.3)
Not Hispanic	19 (90.5)	22 (95.7)
Height, median (minimum–maximum), cm	167.6 (144.0–193.0)	163.0 (152.4–180.0)
Weight, kg	81.5 (49.1–120.5)	87.5 (36.8–112.0)
BMI, median (minimum–maximum), kg/m^2	29.1 (19.9–42.1)	28.5 (15.8–46.6)
Per-protocol set, n	20	20
CMT disease diagnosis, n (%)		
CMT1	17 (85.0)	16 (80.0)
CMTX	3 (15.0)	4 (20.0)
CMT gene variation, n (%)		
CMT1A	13 (76.5)	14 (87.5)
CMT1B	4 (23.5)	2 (12.5)
CMTX1	2 (66.7)	3 (75.0)
CMTX (other)	1 (33.3)	1 (25.0)
Form of CMT, n (%)		
Demyelinating	14 (70.0)	16 (80.0)
Axonal	1 (5.0)	1 (5.0)
Mixed demyelinating and axonal	3 (15.0)	2 (10.0)
Unknown	2 (10.0)	1 (5.0)
Strength, ankle dorsiflexion MVIC, median (minimum–maximum), N	41.5 (15–131.5)	42.5 (15.0–120.0)
Strength, ankle dorsiflexion MMT,[a] n (%)		
Grade 4 to 4+	8 (40.0)	10 (50.0)
Grade 3 to 4−	12 (60.0)	10 (50.0)
Strength, knee extension MMT,[a] n (%)		
Grade 5− to 5	13 (65.0)	12 (60.0)
Grade 3+ to 4+	7 (35.0)	8 (40.0)
Strength, plantar flexion MMT,[a] n (%)		
Grade 4− to 4+	13 (0.65)	13 (0.65)
Grade 5− to 5	7 (0.35)	7 (0.35)
Total muscle mass of TA, median (minimum–maximum), g	56.3 (31.2–148.0)	74.6[b] (44.3–215.3)
Fat fraction of TA, median (minimum–maximum), %	29.4 (10.2–53.9)	23.8[b] (10.2–65.9)
Duration since onset of symptoms, y	29.5 (1–64)	24.5 (2–49)
CMTES2 score	10.0 (4–20)	10.5 (6–21)
CMT-HI total score	27.8 (4.4–66.8)	46.1 (0.2–71.4)
Berg Balance Scale total score	53.0 (49–56)	52.0 (32–56)
Fell to ground in past 6 mo, n (%)		
Yes	9 (45.0)	11 (55.0)
No	11 (55.0)	9 (45.0)
Currently wears lower-limb orthotics, n (%)		
Yes	7 (35.0)	6 (30.0)
No	13 (65.0)	14 (70.0)
History of any fractures, n (%)	10 (50.0)	6 (30.0)
History of any exercise program, n (%)	15 (75.0)	16 (80.0)

Abbreviations: BMI = body mass index; CMT = Charcot-Marie-Tooth; CMT-HI = CMT Health Index; CMTES2 = CMT Examination Score version 2; MMT = manual muscle test (Medical Research Council grade); MVIC = maximum voluntary isometric contraction; TA = tibialis anterior.
Continuous data are presented as median (range).
[a] From weakest side.
[b] n = 18.

was 48 years (range 18–62 years), and 55.6% of patients (n = 10) were female. Symptoms had been present for a median of 23 years (range 2–61 years). Median total muscle mass was higher in patients in cohort 3 (91.7 g, range 73.0–142.4 g) compared with cohort 1 (64.9 g, range 36.6–87.7 g) and cohort 2 (68.9 g, range 38.5–86.6 g). The median fat fraction of the TA muscles was 30.3% (range 9.3%–45.1%).

ACE-083 was generally safe and well tolerated at all dose levels tested in part 1. In assessment of secondary endpoints, there were similar mean percent changes in TMV (12.6% in cohort 1, 13.3% in cohort 2, 14.2% in cohort 3) and CMV (15.8% in cohort 1, 19.2% in cohort 2, 19.4% in cohort 3) on

Table 2 Pharmacodynamic/Efficacy Results Part 2 (Per-Protocol Set): Imaging, Strength, Functional, and QoL (CMT-HI) Data, Day 190 LS Mean Change From Baseline (SEM)

	LS mean (SEM)		Difference (ACE-083 − Placebo)		
Endpoint	**Placebo (n = 20)**	**ACE-083 (n = 20)**	**LS mean (SEM)**	**90% CI**	***p* Value**
Percent change in TMV	2.2 (4.1)	15.8 (4.3)	13.5 (5.2)	4.9, 22.1	0.01
Percent change in CMV	1.7 (7.9)	24.9 (8.6)	23.3 (9.8)	7.2, 39.4	0.02
Absolute change in FF, %	1.0 (1.8)	−2.1 (1.9)	−3.1 (2.2)	−6.8, 0.6	0.16
Absolute change in ankle dorsiflexion MMT decimal score	−0.1 (0.1)	0.2 (0.1)	0.3 (0.1)	0.1, 0.5	0.03
Percent change in ankle dorsiflexion MVIC	−3.4 (19.8)	32.0 (19.8)	35.4 (23.5)	−3.2, 74.0	0.13
Percent change in 6MWT distance	6.0 (4.0)	9.1 (3.8)	3.1 (4.7)	−4.6, 10.9	0.51
Absolute change in 6MWT distance, m	24.8 (13.9)	30.0 (13.4)	5.3 (16.4)	−21.6, 32.2	0.75
Percent change in 10 mW/R time	−10.1 (4.7)	−8.2 (4.7)	1.9 (5.5)	−7.1, 10.9	0.73
Absolute change in 10 mW/R time, s	−0.9 (0.4)	−1.0 (0.3)	−0.1 (0.4)	−0.7, 0.6	0.90
Absolute change CMT-HI total score[a]	−0.2 (3.3)	−2.2 (3.1)	−1.9 (3.9)	−8.4, 4.6	0.63
Absolute change CMT-HI fatigue subscale score[a]	3.0 (5.1)	−6.7 (5.0)	−9.7 (6.2)	−20.0, 0.6	0.12
Absolute change CMT-HI activities subscale score[a]	−4.9 (4.8)	3.5 (4.9)	8.5 (5.7)	−0.9, 17.8	0.14
Absolute change CMT-HI foot/ankle strength subscale score[a]	−5.4 (5.8)	−8.8 (6.1)	−3.4 (7.3)	−15.3, 8.6	0.64
Absolute change CMT-HI mobility subscale score[a]	−5.9 (4.9)	−4.9 (4.7)	1.1 (5.8)	−8.4, 10.5	0.85
Absolute change CMT-HI balance subscale score[a]	0.3 (4.9)	0.9 (4.8)	0.6 (5.7)	−8.8, 10.0	0.92
Absolute change gait midswing foot angle, °	−1.4 (2.2)	1.9 (2.2)	3.3 (2.5)	−1.0, 7.6	0.20

Abbreviations: CMT-HI = Charcot-Marie-Tooth Health Index; CMV = contractile muscle volume; FF = fat fraction; LS = least-squares; MMT = manual muscle testing; MVIC = maximum voluntary isometric contraction; QoL = quality of life; 6MWT = 6-minute walk test; 10 mW/R = 10-m walk/run; TMV = total muscle volume.
The 90% CI and 2-sided *p* values are based on an analysis of covariance model with multiple imputation for missing data; lower score on CMT-HI indicates improvement.
[a] Lower score indicates improvement.

day 106. The absolute changes in fat fraction were somewhat greater in cohorts 2 (−3.5%) and 3 (−3.2%) compared with cohort 1 (−1.7%).

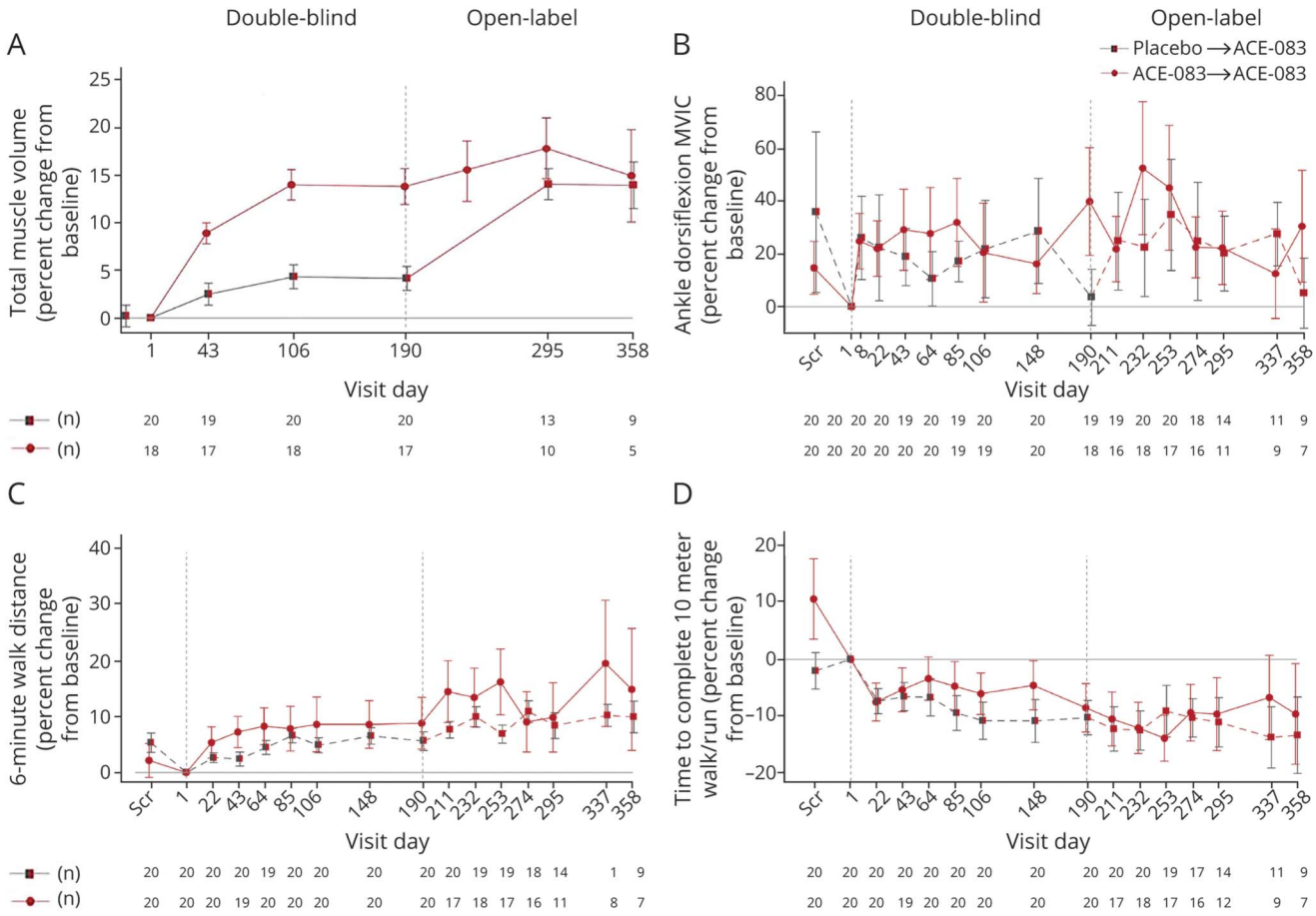
On completion of part 1, the SRT reviewed safety and imaging data for all 3 cohorts to recommend a dose for further study in part 2. The sponsor decided, on the basis of SRT recommendations, to proceed to part 2 with the highest tested dose of ACE-083 (i.e., 240 mg/muscle) for the greatest likelihood of safely increasing TMV and improving function.

Patient Disposition, Demographics, and Baseline Characteristics (Study Part 2)

Of 79 patients with CMT1 or CMTX, 34 failed screening; 44 were randomized to the double-blind treatment period, with 21 patients receiving placebo and 23 receiving ACE-083 (full analysis and safety sets). Among patients with *CMTX1* variation (n = 5), 4 were female. Of 44 patients receiving study drug, 40 had no major protocol violations and were included for statistical analyses in the per-protocol set. Among the 4 patients excluded due to protocol violations, 3 discontinued before the day 43 visit (dose 3). For 1 patient, MRI at day 190 was done ≈36 days after initiating the open-label dosing and after having received 2 open-label doses of ACE-083. These violations were considered issues that could affect the interpretability of the efficacy or pharmacodynamic data and were thus excluded from the per-protocol set before unblinding. A total of 14 patients completed the study, whereas 31 patients discontinued early; the most common reason for discontinuation was the termination of the study by the sponsor (23 patients [51.1%]). Other reasons for discontinuation were withdrawal by patient (5 patients [11.1%]), AEs (2 patients [4.4%]), and loss to follow-up (1 patient [2.2%]) (Figure 2). Overall, the demographic characteristics were similar in the ACE-083 and placebo groups for the full analysis set (n = 44; also the safety set) (Table 1). A higher proportion of women were enrolled in part 2 than in part 1, and nearly all patients were White and non-Hispanic. In the per-protocol set (n = 40), 82.5% of patients had CMT1, and 87.5% had a demyelinating or mixed demyelinating/axonal form of CMT. Among these, 75.0% had demyelinating form, 5.0% had axonal from, 12.5% had mixed demyelinating and axonal form, and 7.5% had an unknown form of CMT.

There were similar proportions of patients receiving placebo and ACE-083 with grade 3 to 4− ankle dorsiflexion strength,

Figure 3 Change in TMV and Other Functional Endpoints Over Time



Mean (SEM) percent change from baseline to day 358 in (A) total muscle volume (TMV)[a]; (B) ankle dorsiflexion strength, maximum voluntary isometric contraction (MVIC); (C) 6-minute walk test distance; and (D) time to complete 10-m walk/run (part 2; per-protocol set). [a]Two patients in the ACE-083 treatment group had missing baseline MRI data. Scr = screening.

grade 4 to 4+ knee extension strength, and grade 4– to 4+/grade 5– to 5 plantar flexion strength. Fifty percent of patients in part 2 had fallen to the ground in the prior 6 months, and 32.5% wore lower-limb orthotics (Table 1).

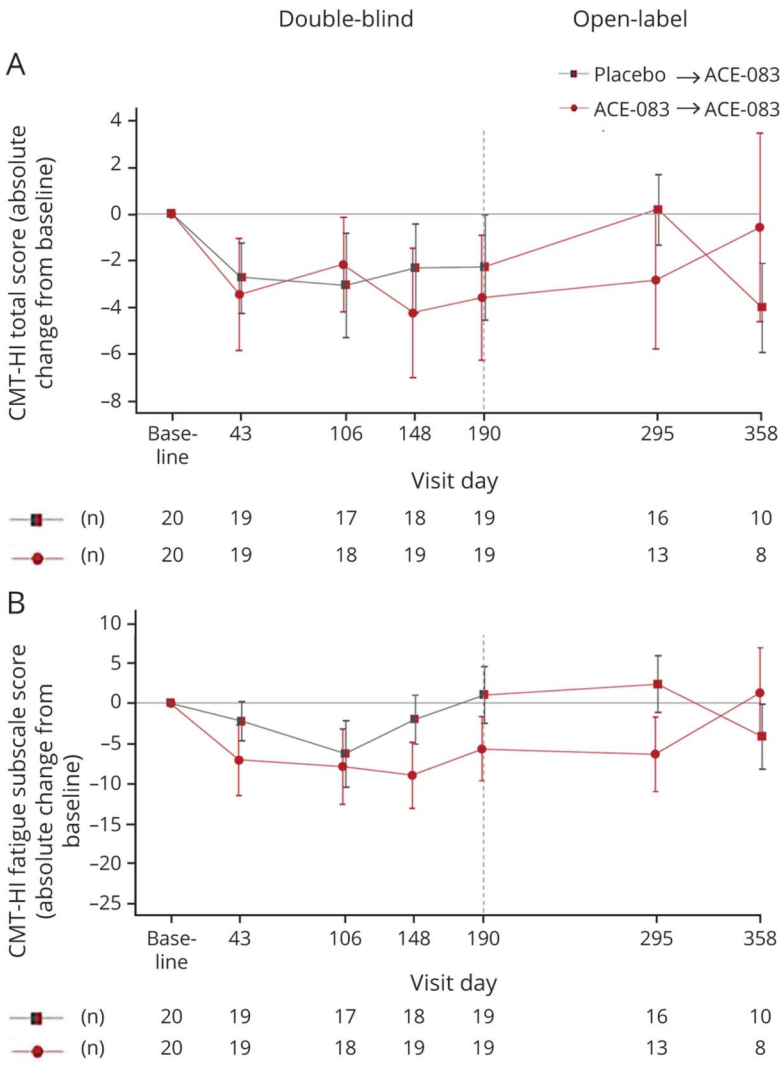
Pharmacodynamics/Efficacy (Study Part 2)

Table 2 displays the pharmacodynamics and efficacy results for the per-protocol population, including imaging, functional, and QoL endpoints. Data are presented as the change or percent change from baseline to day 190 LS mean (from analysis of covariance with SEM), along with LS mean difference between treatment groups, 90% CI, and p value for the difference.

The percent change in TMV (LS mean [SEM] 13.5% [5.2]; 90% CI 4.9–22.1; p = 0.01) and CMV (LS mean [SEM] 23.3% [9.8]; 90% CI 7.2–39.4; p = 0.02) showed statistically significant differences from placebo during the double-blind period, but there was no statistically significant difference between groups in absolute change in fat fraction (LS mean [SEM] –3.1% [2.2]; 90% CI –6.8 to 0.6; p = 0.16) (Table 2). Similar percent increases in TMV and CMV were observed in the original placebo group during treatment with ACE-083 during the open-label period of part 2 (Figure 3A).

The absolute change in ankle dorsiflexion MMT decimal score was significantly greater for patients treated with ACE-083 compared with patients receiving placebo (LS mean [SEM] 0.3 [0.1]; 90% CI 0.1–0.5; p = 0.03) (Table 2). The increase from baseline in LS mean ankle dorsiflexion strength by handheld dynamometer (maximum voluntary isometric contraction) in the ACE-083 group vs placebo at day 190 was not statistically significant (LS mean [SEM] 35.4 [23.5]; 90% CI –3.2 to 74.0; p = 0.13) (Table 2) or apparent at other time points (Figure 3B). None of the other assessed endpoints differed significantly between the ACE-083 and placebo groups (Table 2, Figure 3, C and D, and Figure 4, A and B). Percent changes in 6MWT and 10 mW/R time were not substantially different between treatment groups during the double-blind period, and no improvement was observed in the placebo group on switching to ACE-083 in the open-label phase. Notably, 6MWT distance and time to complete 10 mW/R improved similarly in both the ACE-083 and placebo groups, particularly over the first few measurements and at the

Figure 4 Change in CMT-HI Over Time



Mean (SEM) absolute change from baseline (day 1–190) in the patient-reported Charcot-Marie-Tooth Health Index (CMT-HI) (A) total score and (B) fatigue subscale score (part 2, per-protocol set). Lower score indicates improvement.

start of the open-label phase, suggesting a placebo or learning effect. For patient-reported outcomes, there was no significant difference in the mean absolute changes from baseline in CMT-HI total score ($p = 0.63$) or any of the subscale scores between the ACE-083 and placebo groups. The changes suggesting improvement in the fatigue subscale score were not statistically significant. For physician-reported outcomes at day 190, median percentage changes from baseline were small in CMT Examination Score version 2 score for the placebo (−1.0) and ACE-083 (0.5) treatment groups. For exploratory endpoints, at day 190, the median CMAP percentage change from baseline was small for the placebo (5.1) and ACE-083 (3.8) treatment groups. There were no notable ACE-083–mediated effects on either hemoglobin or C-terminal collagen crosslinks biomarkers. Treatment with ACE-083 showed no statistically significant decrease in the risk of first fall (hazard ratio, ACE-083/placebo 1.04; 90% CI 0.50–2.18; $p = 0.93$) or risk of recurrent fall (hazard ratio, ACE-083/placebo 1.41; 90% CI 0.72–2.74; $p = 0.40$).

Safety and Tolerability (Study Parts 1 and 2)

Treatment with ACE-083 was generally well tolerated during parts 1 and 2, with a similar profile of reported TEAEs. In part 1, all 18 participants experienced at least 1 TEAE, all of which were considered related to the study drug. None of the participants experienced an SAE or a TEAE of grade 3 or higher that was considered related to the study drug, and no deaths were reported. One participant (in the ACE-083 240 mg/muscle treatment group) experienced a TEAE leading to dose interruption, and none of the participants experienced a TEAE leading to dose reduction or treatment withdrawal (eTable 1, links.lww.com/WNL/B922). In part 2, the majority of AEs were mild to moderate in severity. Most patients experienced ≥1 TEAEs that were possibly or probably related to study drug. The most common treatment-related TEAEs were ISRs (including erythema, pain, swelling, bruising, pruritus, and discomfort), myalgia, and pain in extremity (Table 3). No clinically significant laboratory abnormalities were reported during the studies. Two patients receiving

Table 3 Summary of Possibly or Probably Related AEs Occurring in ≥10% of Patients Treated With ACE-083 in the Double-Blind Period (Part 2, Safety Set)

Preferred term	Double-blind, n (%)		Open-label ACE-083 (n = 40), n (%)
	Placebo (n = 21)	ACE-083 (n = 23)	
At least 1 related TEAE	11 (52.4)	16 (69.6)	22 (55.0)
Injection-site erythema	1 (4.8)	7 (30.4)	10 (25.%)
Injection-site pain	2 (9.5)	6 (26.1)	5 (12.5)
Injection-site swelling	2 (9.5)	6 (26.1)	8 (20.0)
Myalgia	2 (9.5)	6 (26.1)	4 (10.0)
Injection-site bruising	1 (4.8)	6 (26.1)	6 (15.0)
Pain in extremity	1 (4.8)	6 (26.1)	5 (12.5)
Injection-site pruritus	0	5 (21.7)	6 (15.0)
Injection-site discomfort	4 (19.0)	4 (17.4)	4 (10.0)
Injection-site warmth	2 (9.5)	4 (17.4)	7 (17.5)
Arthralgia	0	3 (13.0)	0
Joint swelling	0	3 (13.0)	1 (2.5)
Musculoskeletal stiffness	0	3 (13.0)	0

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.
Four patients who received at least 1 dose in the double-blind period discontinued prior to the start of the open-label period.

ACE-083 discontinued treatment because of TEAEs deemed possibly related to the study drug. One participant discontinued during the double-blind period after developing moderate erythema and moderate peripheral swelling, and 1 participant discontinued during the open-label period for moderately severe newly diagnosed systemic lupus erythematosus. Anti–ACE-083 anti-drug antibodies were detected in 47.8% of the ACE-083 group compared with 0% in the placebo group at any time point during the double-blind phase.

There were no drug-related SAEs. In part 1, grade 3 TEAE hypokalemia was detected for 2 days in 1 participant in the ACE-083 240 mg/muscle group and was reported as an SAE deemed unrelated to ACE-083. In part 2, 1 participant receiving placebo reported an SAE of suicide attempt, which resolved after 14 days and was deemed unrelated to study drug. In the open-label phase of part 2, 1 participant in the ACE-083 treatment group experienced an SAE of grade 2 cellulitis deemed unlikely to be related to study drug.

Classification of Evidence

This study provides Class II evidence that intramuscular ACE-083 is safe and well tolerated and increases TMV after 6 months of treatment in adults with CMT1 or CMTX.

Discussion

ACE-083 treatment of patients with CMT1 or CMTX resulted in statistically significant muscle volume increases compared with placebo (part 2, double-blind period) and was generally well tolerated. The primary endpoint of the placebo-controlled period was met, with an LS mean difference in percent change in TMV of 13.5% with ACE-083 compared with placebo at day 190, consistent with a similar study in FSHD.[10] The increase in muscle volume was driven largely by increases in the contractile muscle fraction, but this outcome did not result in statistically significant improvements in motor function tests or disease-related QoL measures.

Patients receiving ACE-083 had significantly increased ankle dorsiflexion strength when measured by MMT, although increases in quantitative muscle testing by handheld dynamometry were not statistically significant, possibly due in part to the high variability associated with this technique. Apparent improvements in 6MWT, 10 mW/R, and CMT-HI scores were seen in both the placebo and study drug arms at day 190, suggesting a placebo or learning effect. Further improvement in the open-label period could have been due either to these same effects or to a treatment effect. Despite good tolerability with few drug-related non-ISR TEAEs and increased muscle volume, the failure to provide clinically relevant improvements in muscle function compared with placebo led the sponsor to suspend further development of ACE-083 for CMT.

Many of the features of CMT reflect neuropathy of the longest nerve fibers in the body such as in the lower leg. During the design of this study, we proposed that locally acting depletion of GDF/activin signaling would permit substantial muscle growth and improved strength in atrophied TA

muscles in patients with CMT, leading to improved function and mobility. In this phase 2 study, we assessed whether treatment can improve muscle function as assessed by widely used clinical measures for CMT progression.[13-15]

However, the expectation that large increases in muscle volume would lead to functional improvement was not fulfilled over the duration of this study. The investigators and sponsor calculated sample size to power the study for effects on muscle volume and 6MWT, but not for other measures such as those for muscle strength. Improvement in functional mobility relies on the coordinated activity and strength of several muscles, and in the absence of prescribed exercise, the increased mass and strength of the TA muscles alone may be insufficient to improve motor scores. Moreover, there was some evidence for a learning or placebo effect in motor function tests, which could lead to false conclusions without the proper comparator group. The presence of a learning/placebo effect in functional tests highlights the importance of including a placebo control group when possible, as opposed to historic controls, for sufficiently long duration to allow assessment of the functional effects of studied treatments. Studies with larger sample size, longer duration, run-in periods, and outcomes less susceptible to the effect of entering a trial may be needed to minimize the learning/placebo effects.

There have been few randomized clinical studies of pharmacotherapy for CMT. An exploratory study of a combination of baclofen, naltrexone, and sorbitol reported modest improvement in the high-dose group for composite neurologic scores over a 1-year period, but the study did not assess changes in muscle volume.[16] Like the study reported here, a training effect in the placebo group, and nonsignificant improvements in 6MWT between the treatment and placebo groups were reported in another pharmacotherapeutic trial for CMT.[16] Similarly, study patients receiving the combination treatment did not have higher scores for patient-reported outcome assessments (i.e., visual analog scale, clinical global impression), but the authors proposed that their 12-month trial was of insufficient duration to capture an improvement in self-assessment for patients with CMT.[16] High-dose ascorbic acid as a treatment for CMT had no clinically meaningful effect in a controlled clinical trial of 110 patients.[17] The recurrence of placebo and training effects in studies of candidate therapies for CMT suggests that larger sample sizes may be needed and confirms the conclusion that placebo groups should be included in studies with motor function and QoL endpoints.

Myostatin inhibition has previously been explored as a potential treatment modality in muscle diseases, including muscular dystrophy, peripheral neuropathies, sarcopenia, cachexia, and other muscle-wasting disorders.[15,18-24] However, the results of these agents in clinical trials have been mixed. For several agents, there has been discordance between increases in muscle or bone volume and functional improvements or no significant benefit over placebo, and research into the majority of myostatin inhibitors has been discontinued.[25] Most myostatin inhibitors tested have been systemic preparations, which are generally associated with smaller increases in muscle volume (typically ≈5%), albeit in multiple muscles, but still are insufficient to demonstrate functional benefit.[25] Agents with activity against multiple ligands (e.g., GDF8, activin A), demonstrate larger pharmacodynamic effects, although sometimes associated with unacceptable safety profiles.[25] ACE-083 treatment resulted in substantially greater increases in muscle volume in single muscles but failed to produce a functional benefit within 6 months with the outcome measures available.

Despite increased muscle volume and MMT assessment of ankle dorsiflexion strength, ACE-083 administration every 3 weeks into TA muscles was not sufficient to improve functional outcomes in patients with CMT1 or CMTX. The conclusions from this study are limited by the challenges in study design and certain aspects of this complicated disease. There was no placebo arm in part 1, which did not allow unequivocal interpretation of encouraging results. The efficacy data in part 2 indicated the occurrence of placebo or learning effects in the functional tests to explain these positive trends. The gradual changes in these measures point to the possible importance of longer duration of therapy for these functional outcomes. The clinical diversity of the CMT patient population may have obscured functional improvements. The absence of an exercise regimen may have prevented adequate strength development of the increased muscle mass.

ACE-083 was associated with significantly greater increases in muscle volume and muscle strength parameters than placebo but was not associated with clinically relevant functional improvements after 6 months of treatment. On the basis of these results, the ACE-083 development program for the treatment of CMT was discontinued.

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Thomas H. Brannagan III, MD	Columbia University Medical Center, New York, NY	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
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Urvi Desai, MD	Carolinas MDA Care Center, Atrium Health, Charlotte, NC	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
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Katy J. Eichinger, PhD	University of Rochester Medical Center, NY	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
Nicholas E. Johnson, MD, MS-CI	Virginia Commonwealth University, Richmond	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
Chafic Karam, MD	Oregon Health & Science University, Portland	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content

Appendix *(continued)*

Name	Location	Contribution
Alan Pestronk, MD	Washington University School of Medicine, St. Louis, MO	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
Colin Quinn, MD	University of Pennsylvania, Philadelphia	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
Michael E. Shy, MD	University of Iowa, Iowa City	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
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Sub H. Subramony, MD	University of Florida, Gainesville	Study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
David Walk, MD	University of Minnesota, Minneapolis	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
Katherine Stevens-Favorite, PhD	Cadent Medical Communications, LLC, a Syneos Health group company, New York, NY	Drafting/revisions of the manuscript for content, including medical writing for content
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Ashley Leneus, MPH	Acceleron Pharma, Cambridge, MA	Analysis and interpretation, critical revision of the manuscript for important intellectual content
Marcie Fowler, PhD	Acceleron Pharma, Cambridge, MA	Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
Marc van de Rijn, MD	Acceleron Pharma, Cambridge, MA	Study concept and design, supervision, analysis and interpretation, critical revision of the manuscript for important intellectual content
Kenneth M. Attie, MD	Acceleron Pharma, Cambridge, MA	Medical monitor, study concept and design, supervision, analysis and interpretation, critical revision of the manuscript for important intellectual content

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