

Results of a Phase 2 Double-Blind Placebo-Controlled Study of a Local Muscle Therapeutic, ACE-083, in Subjects with Charcot-Marie-Tooth (CMT) Disease

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Disclosures



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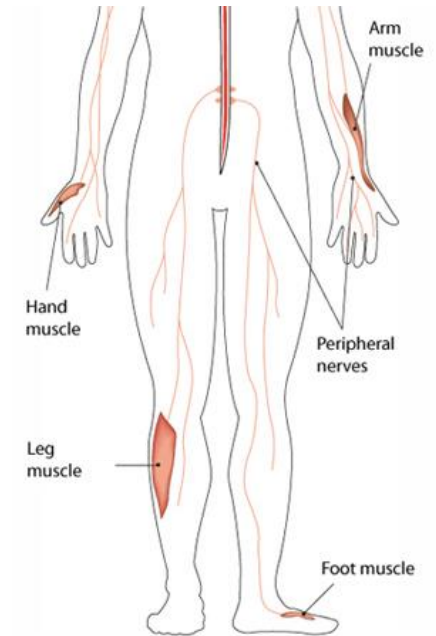
Charcot-Marie-Tooth (CMT) Disease – Introduction



- CMT is the most common inherited peripheral neuropathy, with an incidence of 1 in 2500¹
- CMT is a slowly progressive neuropathy that causes predominantly distal arm and leg weakness, motor and sensory nerve loss, and foot and ankle deformities
 - Tibialis anterior (TA) weakness is a cardinal manifestation of disease, with virtually all patients developing weak ankle dorsiflexion, often early in their disease course
 - Weakness of the TA muscle causes foot drop, impairs ambulation, and increases the risk of falls
- CMT has substantial unmet medical need with no drug therapies currently available
 - Orthotics and bracing can be helpful, but compromise gait mechanics and may lead to muscle atrophy and discomfort

CMT Pathophysiology²

Damage to peripheral nerves results in distal sensory disruption and muscle atrophy



- >80 genes identified
- Several sub-types (CMT 1, 2, 4 and X)
- Initially affects myelin sheath (eg, Type 1) or nerve axon (eg, Type 2)

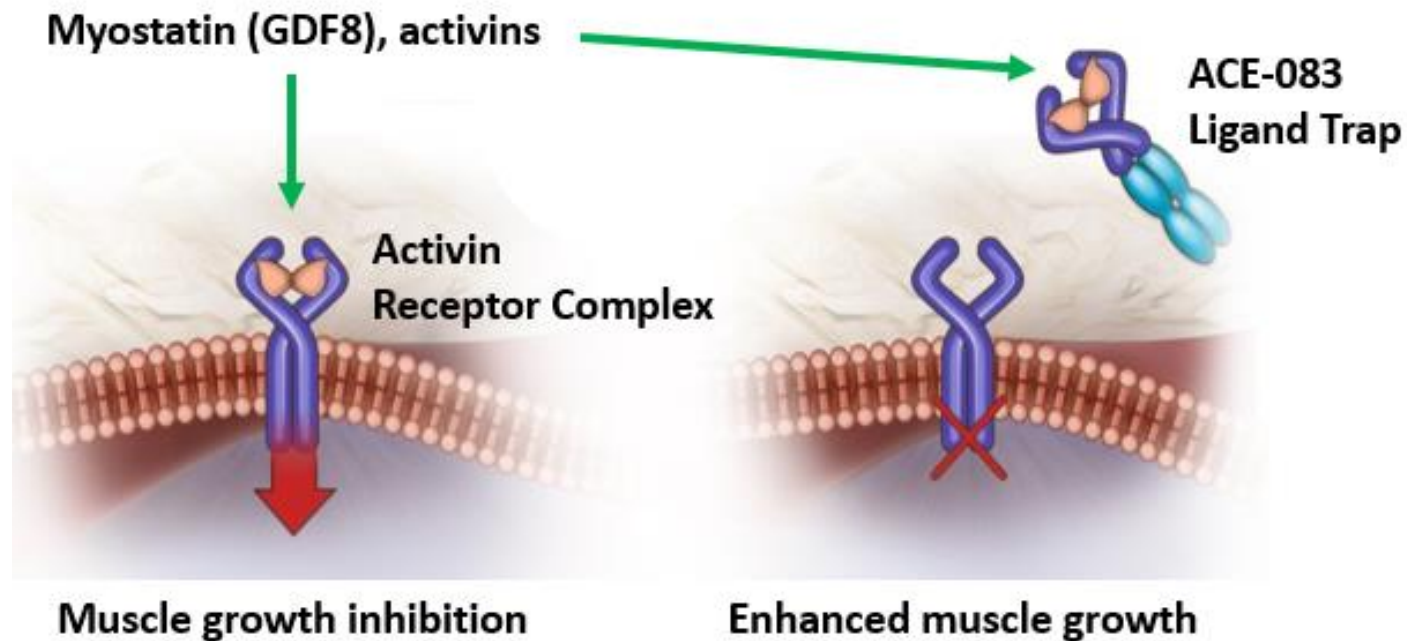
¹Saporta MA, et al. *Neurol Clin* 2013; 31: 597-619

²Charcot-Marie-Tooth Disease (CMT), <https://www.mda.org/disease/charcot-marie-tooth> [Accessed 29 April 2019]

ACE-083 – A Locally-Acting Muscle Therapeutic



- ACE-083 is a locally-acting protein therapeutic in the TGF- β superfamily consisting of a modified form of human follistatin that binds GDF8 (myostatin) *plus* other negative regulators of skeletal muscle
- Designed to be locally injected in affected muscles to increase muscle mass and strength
- Locally increased muscle mass demonstrated in healthy volunteers¹ and patients with FSHD² and CMT³
- Tibialis anterior and biceps were selected as initial muscle targets for a locally acting therapeutic



¹Glasser CE, et al. *Muscle Nerve* 2018; 57:921-926

²Statland J, et al. *World Muscle Society* 2018 Poster 365

³Shy M, et al. *World Muscle Society* 2018 Poster 339

ACE-083 CMT Phase 2 Study Design



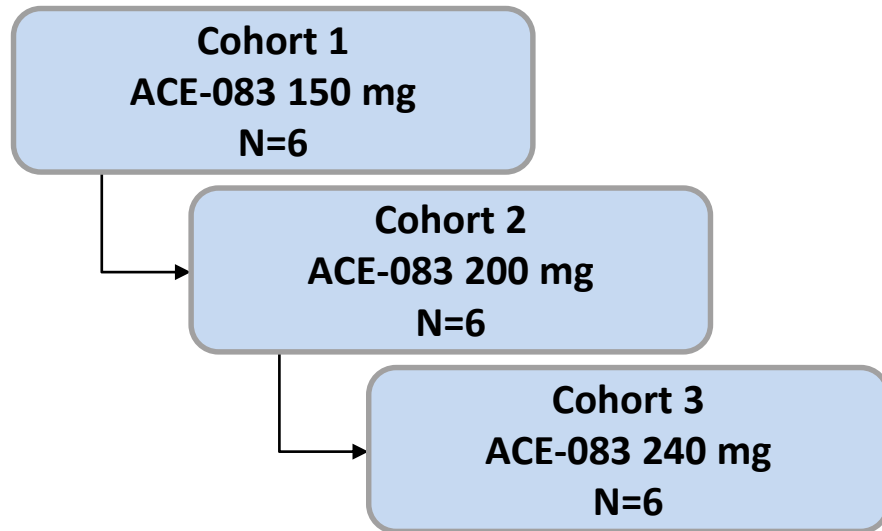
Key Eligibility Criteria:

- Age \geq 18 years
- Genetically-confirmed CMT1 or CMTX, or, genetically-confirmed first-degree relative and clinical signs/symptoms of CMT1 or CMTX
- Left and right ankle dorsiflexion weakness
- 6-minute walk distance \geq 150, \leq 500 meters

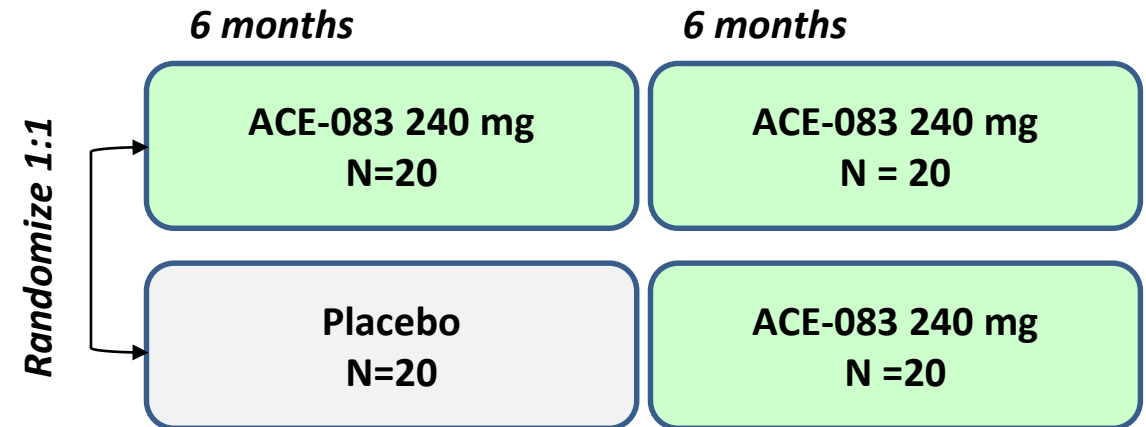
Treatment:

- ACE-083 injection into tibialis anterior (TA) muscle bilaterally every 3 weeks

Part 1 – 3 mos open-label ACE-083



Part 2 – 6 mos placebo-controlled → 6 mos open-label





- Endpoints measured at Study Day 190 compared to baseline vs placebo control group

Primary Endpoint:

- Improvement from baseline to Day 190 (percent change) in total and contractile muscle volume (TMV, CMV, by MRI) with ACE-083 as compared with placebo

Secondary Endpoints:

Improvement from baseline to Day 190 in:

- Functional tests: 6-minute walk test, 10-meter walk/run, Berg balance scale, CMTES2
- Patient-reported outcomes (PRO): CMT-Heath Index (CMT-HI) total and selected subscale scores
- Ankle dorsiflexion strength (MVIC by hand-held dynamometry and MMT-MRC Grade)
- Fat fraction (FF, by MRI)



Statistical Analysis Populations:

- **Per Protocol Set**: All patients randomized who received at least one dose of study drug (includes placebo) with no major protocol violations
- **Safety Set**: All patients randomized who received at least one dose of study drug (includes placebo)

Statistical Methods:

Efficacy (Imaging, Functional [6MWD, 10mW/R], Strength [MVIC, MMT], CMT-HI):

- ANCOVA of Day 190 percent change (raw change for fat fraction, CMT-HI, MMT) from baseline
 - Least squares (LS) mean with p-value and 90% confidence interval (CI) of treatment group effect
 - Treatment group effect (ACE-083 vs. Placebo) tested using a two-sided, 0.10 significance level

Safety: Adverse events, laboratory tests, anti-drug antibody, vital signs, and ECG data were reviewed and summarized; summary of adverse events will be shown

The background of the slide features a close-up of a hand holding a pen, poised to write on a document. The image is overlaid with a semi-transparent blue layer. A dark blue horizontal bar is positioned across the middle of the slide, containing the title text.

Baseline Characteristics, Part 2

ACE-083 CMT Study – Baseline Characteristics, Part 2

Per Protocol Set



	Placebo (N = 20)	ACE-083 (N = 20)
Age (years)	49.0 (20-71)	46.0 (19-67)
Gender, n (%)		
Male	7 (35%)	5 (25%)
Female	13 (65%)	15 (75%)
CMT disease diagnosis, n (%)		
CMT1	17 (85%)	16 (80%)
CMTX	3 (15%)	4 (20%)
Form of CMT		
Demyelinating	14 (70%)	16 (80%)
Axonal	1 (5%)	1 (5%)
Mixed demyelinating and axonal	3 (15%)	2 (10%)
Unknown	2 (10%)	1 (5%)
Duration since onset of symptoms (years)	29.5 (1-64)	24.5 (2-49)
Strength, ankle dorsiflexion MMT, n (%)		
Mild (MRC Grade 4 to 4+)	8 (40%)	10 (50%)
Moderate (MRC Grade 3 to 4-)	12 (60%)	10 (50%)
Fat fraction (%)	29.4 (10.2-53.9)	23.8* (10.2-65.9)
Total muscle mass (g)	56.3 (31.2-148.0)	74.6* (44.3-215.3)

*n=18

Continuous data are presented as median (min - max). Per Protocol Set = all patients randomized who received at least one dose of study drug with no major protocol violations



Imaging Results, Part 2

CMT Study Imaging Results, Part 2 Placebo-Controlled Phase (to Day 190)



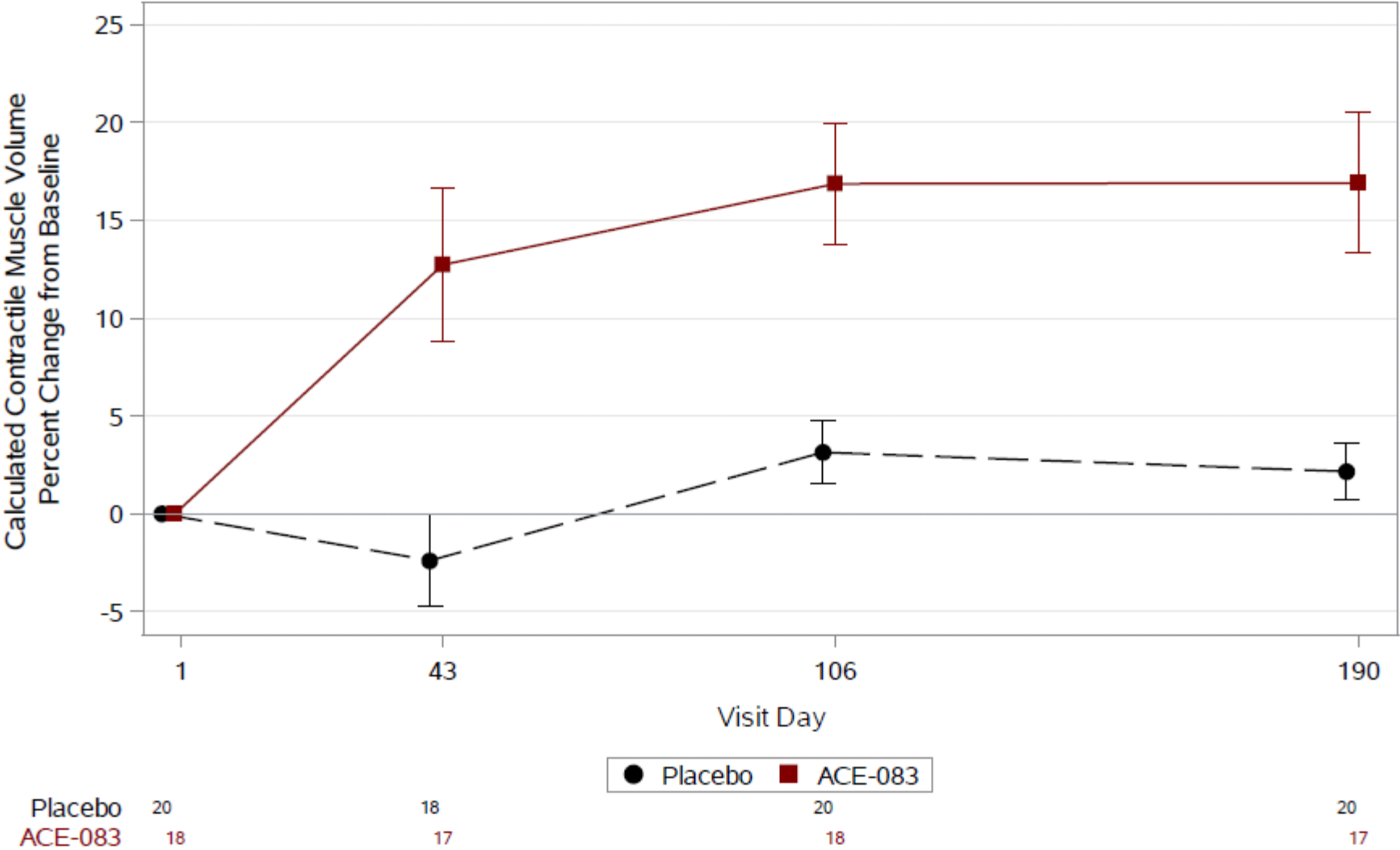
- ACE-083 treatment achieved a 13.5% greater increase in total muscle volume (TMV by MRI) (p=0.01) and a 23.3% greater increase in contractile muscle volume (CMV) vs placebo (p=0.02)
 - $CMV = TMV * [(100 - Fat\ Fraction)] / 100$

Endpoint	LS Mean (SEM)		Difference (ACE-083 – Placebo)		
	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
Raw change in Fat Fraction (%)	1.0 (1.8)	-2.1 (1.9)	-3.1 (2.2)	(-6.8, 0.6)	0.16

CI = confidence interval; LS = least squares; SEM = standard error of the mean

Data as of 14 Feb 2020

Mean (SEM) Percent Change in Contractile Muscle Volume (MRI)





Strength/Function/PRO Results, Part 2

CMT Study Results, Part 2 Placebo-Controlled Phase (to Day 190)



Endpoint	LS Mean (SEM)		Difference (ACE-083 – Placebo)		
	Placebo (N=20)	ACE-083 (N=20)	LS Mean (SEM)	90% CI	p-value
Raw 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
% change in ankle dorsiflexion MVIC	-4.2 (19.8)	30.9 (19.9)	35.1 (23.5)	(-3.6, 73.8)	0.14
Percent change in 6MWD	5.9 (4.0)	9.0 (3.8)	3.1 (4.7)	(-4.7, 10.9)	0.51
Percent change in 10mW/R time	-10.4 (4.7)	-8.7 (4.6)	1.6 (5.4)	(-7.3, 10.6)	0.76
Raw change CMT-HI total score	-0.2 (3.3)	-2.2 (3.1)	-1.9 (3.9)	(-8.4, 4.6)	0.63
Raw change CMT-HI activities subscale score	-4.9 (4.8)	3.5 (4.9)	8.5 (5.7)	(-0.9, 17.8)	0.14
Raw change CMT-HI fatigue subscale score	3.0 (5.1)	-6.7 (5.0)	-9.7 (6.2)	(-20.0, 0.6)	0.12

6MWD = 6-minute walk distance; 10mW/R = 10 meter walk/run; CI = confidence interval; CMT-HI = Charcot-Marie-Tooth Health Index; LS = least squares; SEM = standard error of the mean; MMT = manual muscle test; MVIC = maximum voluntary isometric contraction

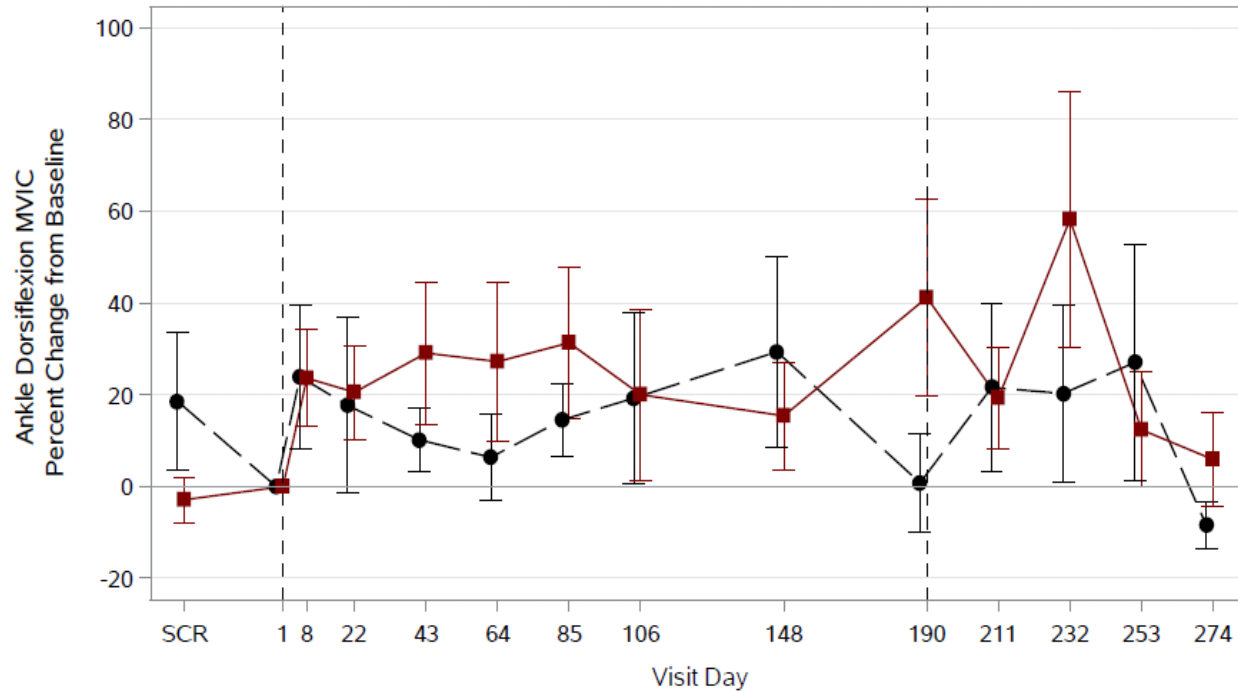
Mean (SEM) Change in Ankle Dorsiflexion Strength



MVIC

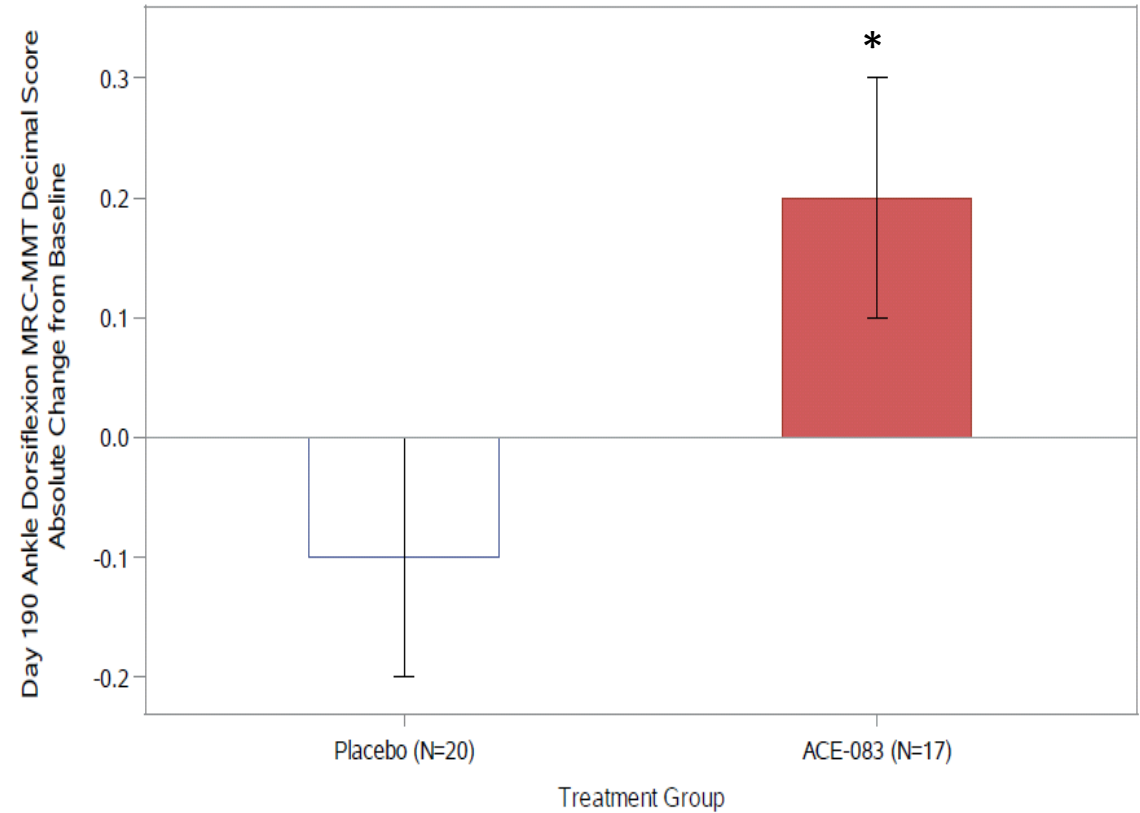
Double-blind

Open-label



Placebo	20	20	20	20	19	20	19	20	19	19	19	19	17	19	19	19	16	16	16	11	12
ACE-083	20	20	20	20	20	20	19	19	19	19	19	19	17	16	16	16	11	11	11	11	10

MMT



*: LS mean difference (ACE-083 vs. Placebo) = 0.30; p = 0.03

SEM = standard error of the mean; MVIC = maximum voluntary isometric contraction; MMT = manual muscle test; LS = Least-squares

Data as of 14 Feb 2020

Mean (SEM) Percent Change in 6MWD, 10mW/R



6MWD

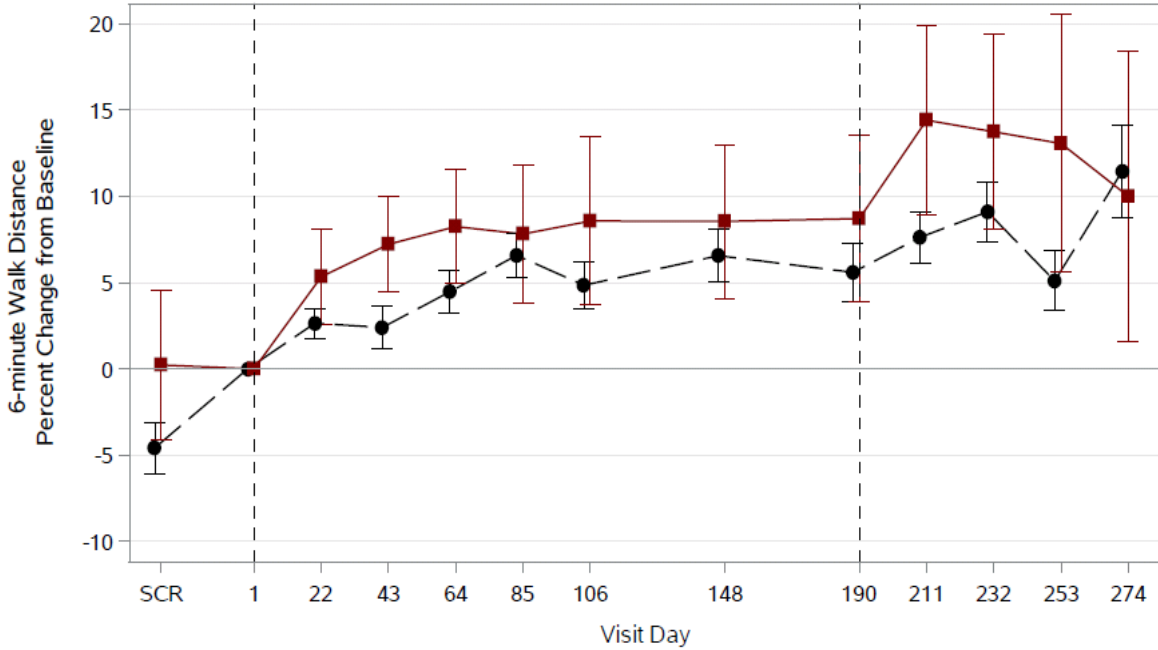
Double-blind

Open-label

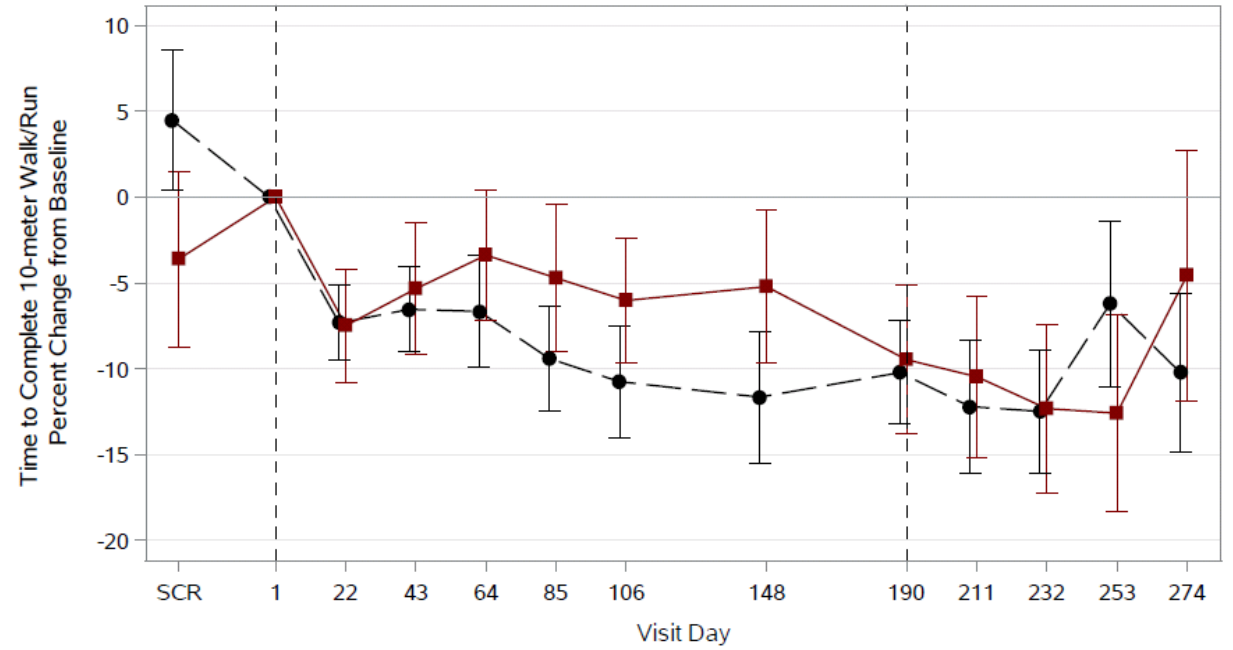
10mW/R

Double-blind

Open-label



	SCR	1	22	43	64	85	106	148	190	211	232	253	274
Placebo	20	20	20	20	19	20	20	19	20	20	18	15	12
ACE-083	20	20	20	19	20	20	19	19	19	17	16	11	10

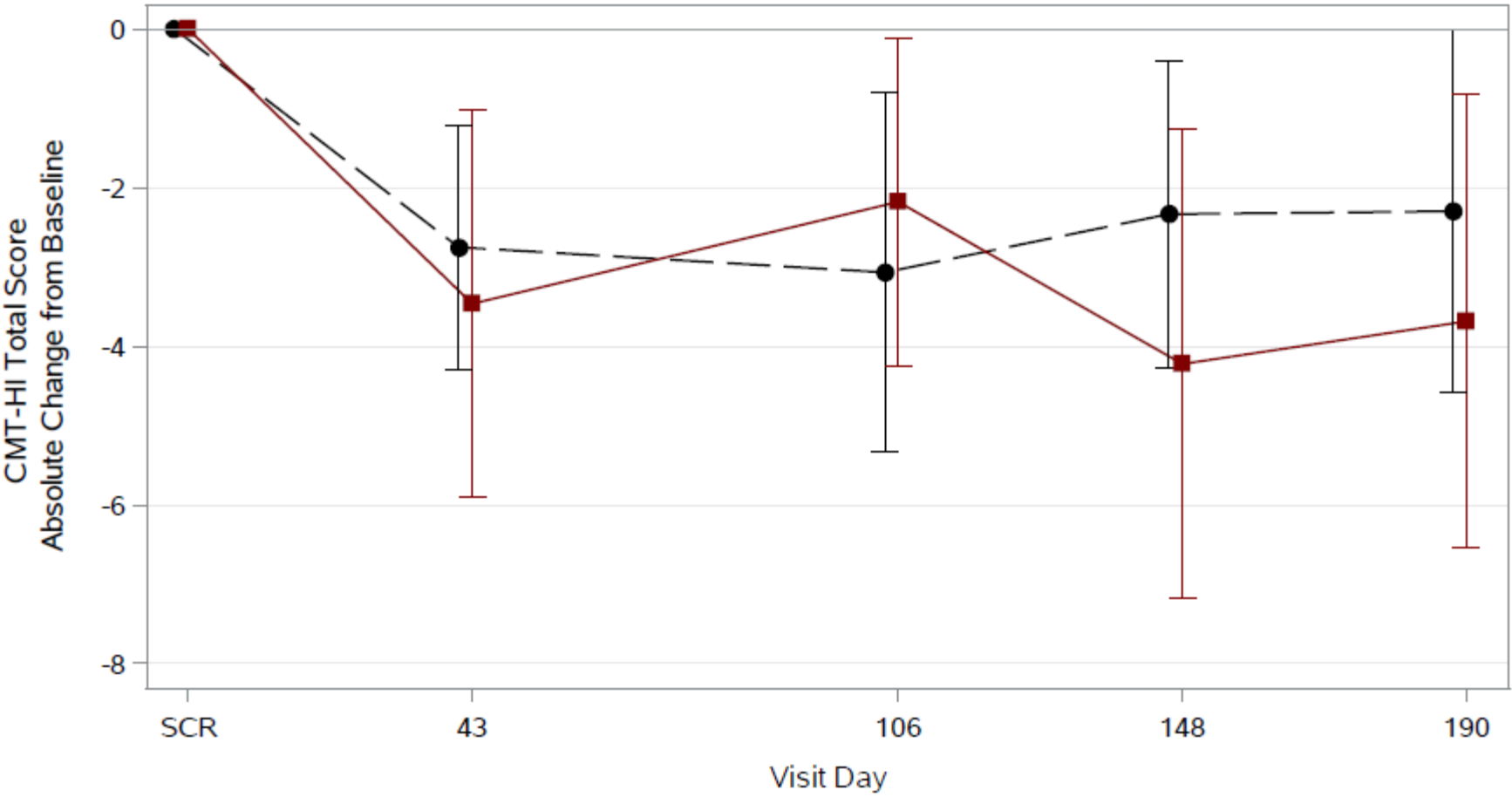


	SCR	1	22	43	64	85	106	148	190	211	232	253	274
Placebo	20	20	20	20	20	20	20	19	20	20	19	15	12
ACE-083	20	20	20	19	20	20	20	19	19	17	16	11	10

SEM = standard error of the mean; 6MWD = 6-minute walk distance; 10mW/R = 10 meter walk/run

Data as of 14 Feb 2020

Mean (SEM) Absolute Change in CMT-HI Total Score



↑ Worsening

↓ Improvement

Placebo	20	19	17	18	19
ACE-083	20	19	18	18	18

A blurred background image showing a person's hands holding a globe. The hands are positioned as if supporting the globe from underneath. The image is out of focus, with a soft, light blue and white color palette.

Safety Results, Part 2

ACE-083 CMT Study –Adverse Events, Part 2



- ACE-083 was generally well tolerated during the double-blind period (to Day 190)
- Majority of AEs were mild/moderate; no drug-related serious adverse events

Possibly or Probably Related AEs Occurring in ≥10% Patients Treated with ACE-083 in the Double-Blind Period

Preferred Term	Double-Blind Period		Open-Label ACE-083
	Placebo N=21 n (%)	ACE-083 N=23 n (%)	N=40 n (%)
At least 1 related TEAE	11 (52.4%)	16 (69.6%)	21 (52.5%)
Injection site erythema	1 (4.8%)	7 (30.4%)	9 (22.5%)
Injection site pain	2 (9.5%)	6 (26.1%)	4 (10.0%)
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%)	5 (12.5%)
Pain in extremity	(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%)	3 (13.0%)	6 (15.0%)
Arthralgia	0	3 (13.0%)	0
Joint swelling	0	3 (13.0%)	1 (2.5%)
Musculoskeletal stiffness	0	3 (13.0%)	0

Note: 4 patients who received at least 1 dose in the double-blind period discontinued prior to the start of the open-label period Data as of 14 Feb 2020



- Consistent with previous clinical studies, ACE-083 treatment resulted in statistically significant muscle volume increases and was generally well tolerated
- The placebo-controlled part of this study met the primary endpoint of statistically significant differences in TMV and CMV percent change between ACE-083 and placebo at study day 190 (6 months)
 - 13.5% greater increase in total muscle volume by MRI (p=0.01)
 - 23.3% greater increase in contractile muscle volume (p=0.02)
- Ankle dorsiflexion strength increased by manual muscle testing by 1 level (p=0.03); no statistically significant improvement by dynamometry
- No statistically significant differences in motor function tests or CMT-HI total score
 - There was a trend for improvement in fat fraction by MRI and CMT-HI fatigue score
- Adverse events (non-ISR) more common in ACE-083 group included myalgia, pain in extremity, arthralgia, joint swelling, and musculoskeletal stiffness
- A learning effect was observed for the motor function tests, supporting consideration of a run-in period and appropriate control arm in future neuromuscular studies

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