

Preliminary Phase 2 Results for ACE-083, Local Muscle Therapeutic, in Patients with CMT1 and CMTX

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Charcot-Marie-Tooth (CMT) Disease – Introduction



- CMT is the most common inherited peripheral neuropathy with roughly 125,000 patients in the US affected
- 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 risk of falls
- CMT has substantial unmet medical need with no drug therapies currently available
 - Orthotics and various forms of bracing can be helpful, but compromise gait mechanics and may lead to muscle atrophy and discomfort

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
- Increased muscle mass demonstrated in healthy volunteers¹ and patients with FSH muscular dystrophy²

GDF8, GDF11, activins



ACE-083
Ligand Trap

Muscle growth inhibition
via Smad2/3 signaling

Enhanced muscle growth via
reduced Smad2/3 signaling

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

² Statland J, et al. *American Academy of Neurology*, 2018

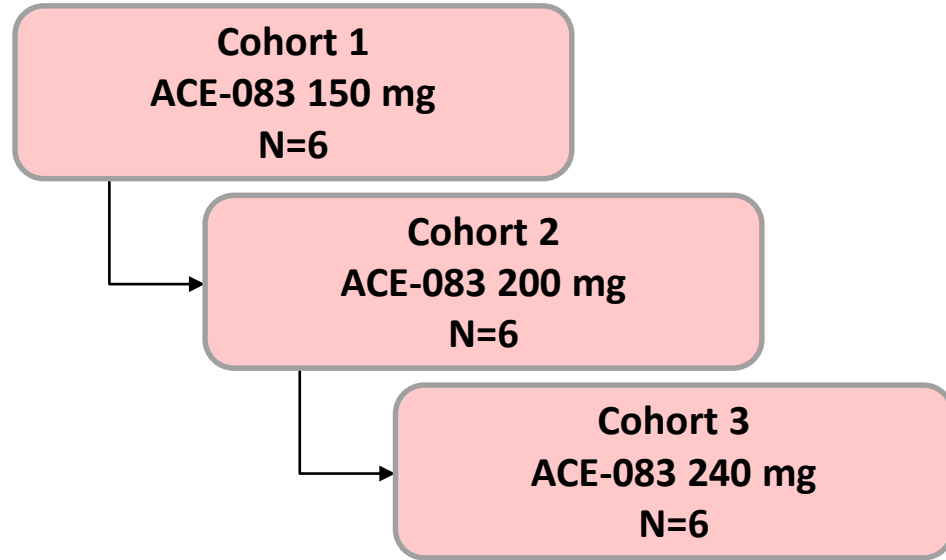
Phase 2 Study of ACE-083 in CMT (Ongoing)



Treatment:

- ACE-083 or placebo injected bilaterally into TA muscle every 3 weeks

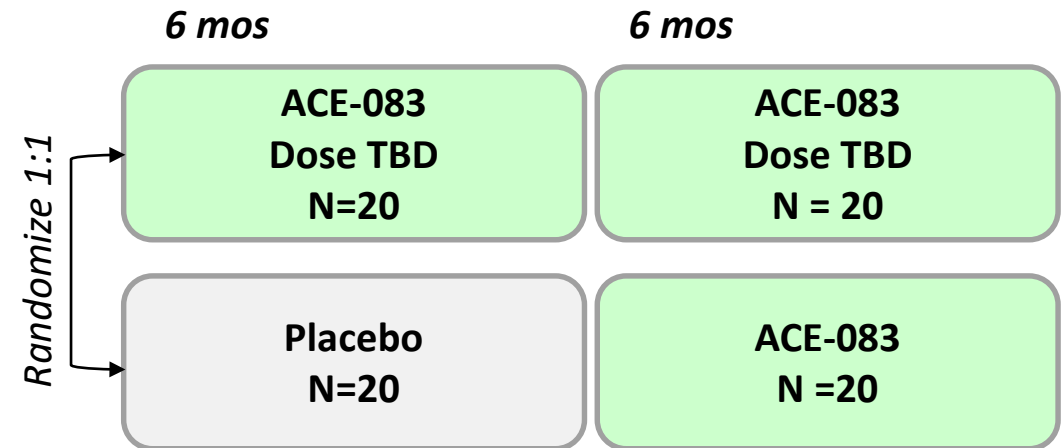
Part 1 – 3 mos open-label ACE-083



Key Assessments

- Safety & tolerability
- Identify optimal dose
- Muscle volume
- Fat fraction

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



Assessments

- Muscle volume
- Fat fraction
- Strength/Function
- Quality of life
- Safety



Key Eligibility Criteria for Part 1:

- Age \geq 18 years
- Genetically-confirmed CMT1 or CMTX, or, genetically-confirmed first-degree relative and clinical signs/symptoms of CMT1 or CMTX
- 6-minute walk distance \geq 150 meters
- Left and right ankle dorsiflexion weakness (MRC grade 4- to 4+)
- No severe deformity or (surgical) fixation of ankle

ACE-083 CMT Study Efficacy/Pharmacodynamic Endpoints



	Assessment	Outcome Measure
Muscle Size/Quality	<ul style="list-style-type: none"> • Muscle and fat volumes by MRI 	<ul style="list-style-type: none"> • Percent change in total muscle and contractile muscle volume • Absolute change in fat fraction
Muscle Strength	<ul style="list-style-type: none"> • Hand-held dynamometry 	<ul style="list-style-type: none"> • Percent change in dorsiflexion strength
Muscle Function	<ul style="list-style-type: none"> • 6-minute walk test • 10m walk/run • Berg Balance Scale • Gait analysis 	<ul style="list-style-type: none"> • Change/percent change in functional parameters
Investigator-/Patient-Reported Outcomes	<ul style="list-style-type: none"> • CMT Examination Score (Version 2)¹ • CMT-Health Index (QoL)² 	<ul style="list-style-type: none"> • Change in CMTES2 score/sub-scores • Change in CMT-HI score/sub-scores

¹ Murphy SM, et al. *Journal of the Peripheral Nervous System* 2011 16:191–198

² <http://rochester.technologypublisher.com/technology/22384>



- Median duration of symptoms was 23 years. Median fat fraction was 30%.

	Cohort 1 150 mg N=6	Cohort 2 200 mg N=6	Cohort 3 240 mg N=6	Overall N=18
Age, yr	35 (23-62)	39 (18-61)	52 (31-58)	48 (18-62)
Gender, n (%)				
Male	3 (50%)	3 (50%)	2 (33%)	8 (44%)
Female	3 (50%)	3 (50%)	4 (67%)	10 (56%)
Duration of symptoms, yr	31 (14-61)	30 (6-51)	12 (2-25)	23 (2-61)
CMT subtype, n (%)				
CMT1	5 (83%)	5 (83%)	5 (83%)	15 (83%)
CMTX	1 (17%)	1 (17%)	1 (17%)	3 (17%)
Total muscle mass, g	66 (38-87)	70 (40-85)	92 (73-141)	78 (38-141)
Fat fraction, %	29 (10-45)	31 (15-37)	27 (9-44)	30 (9-45)
6MWD, m	418 (236-588)	381 (324-501)	459 (265-620)	411 (236-620)

Median (range), unless otherwise indicated

Safety Results



- ACE-083 was generally well tolerated in subjects treated for up to 3 months (5 doses)
 - Most adverse events were mild or moderate (grades 1-2)
 - Most common adverse events were injection site reactions, muscle spasms, and myalgia
- No clinically significant laboratory abnormalities on treatment

Possibly or Probably Related Adverse Events Occurring in ≥10% of Patients Overall

Preferred Term, n(%)	Cohort 1 150 mg N=6	Cohort 2 200 mg N=6	Cohort 3 240 mg N=6	Overall N=18
Injection site discomfort	3 (50%)	2 (33%)	3 (50%)	8 (44%)
Injection site bruising	1 (17%)	2 (33%)	2 (33%)	5 (28%)
Injection site erythema	2 (33%)	1 (17%)	1 (17%)	4 (22%)
Muscle spasms	1 (17%)	2 (33%)	1 (17%)	4 (22%)
Myalgia	2 (33%)	0	2 (33%)	4 (22%)
Injection site pain	1 (17%)	1 (17%)	1 (17%)	3 (17%)
Injection site swelling	1 (17%)	1 (17%)	1 (17%)	3 (17%)
Pain in extremity	1 (17%)	1 (17%)	1 (17%)	3 (17%)
Injection site pruritus	1 (17%)	0	1 (17%)	2 (11%)
Joint stiffness	1 (17%)	0	1 (17%)	2 (11%)
Muscle tightness	1 (17%)	0	1 (17%)	2 (11%)

Imaging Results

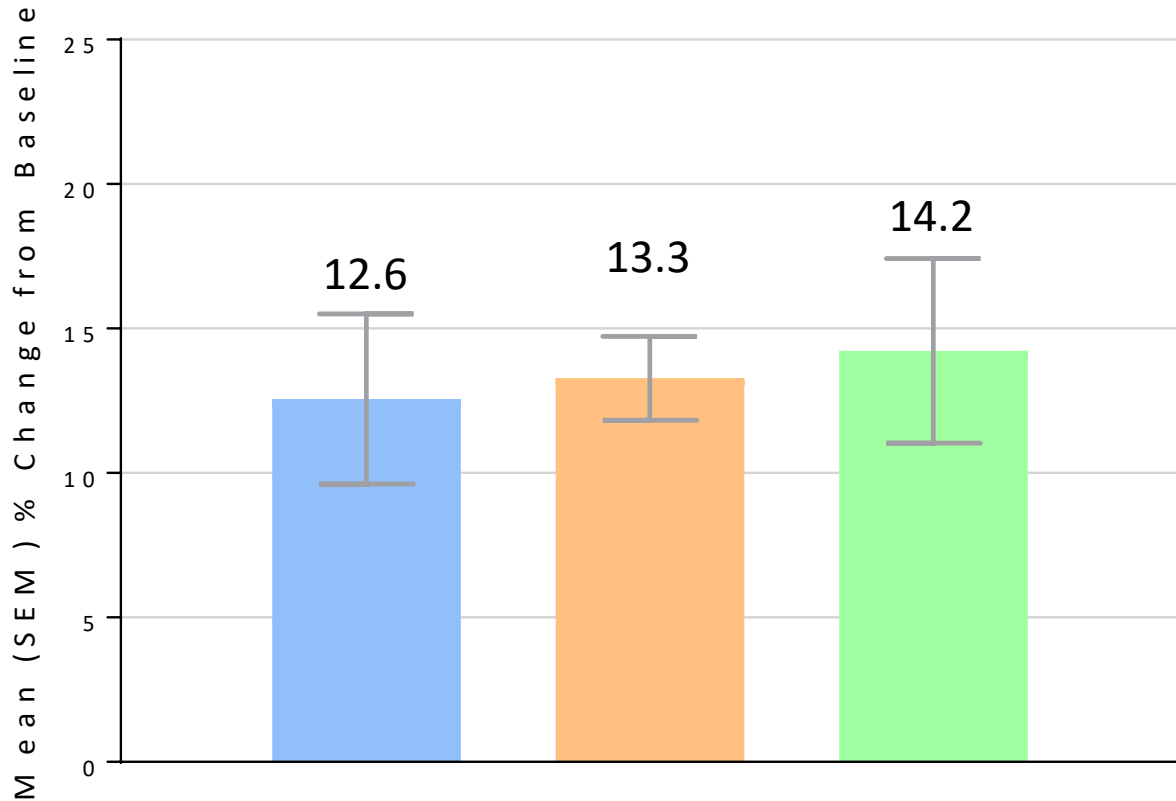
ACE-083 CMT Study – Total Muscle Volume (TMV) and Fat Fraction (FF)

Part 1; Percent Change from Baseline (TMV) / Absolute Change from Baseline (FF)

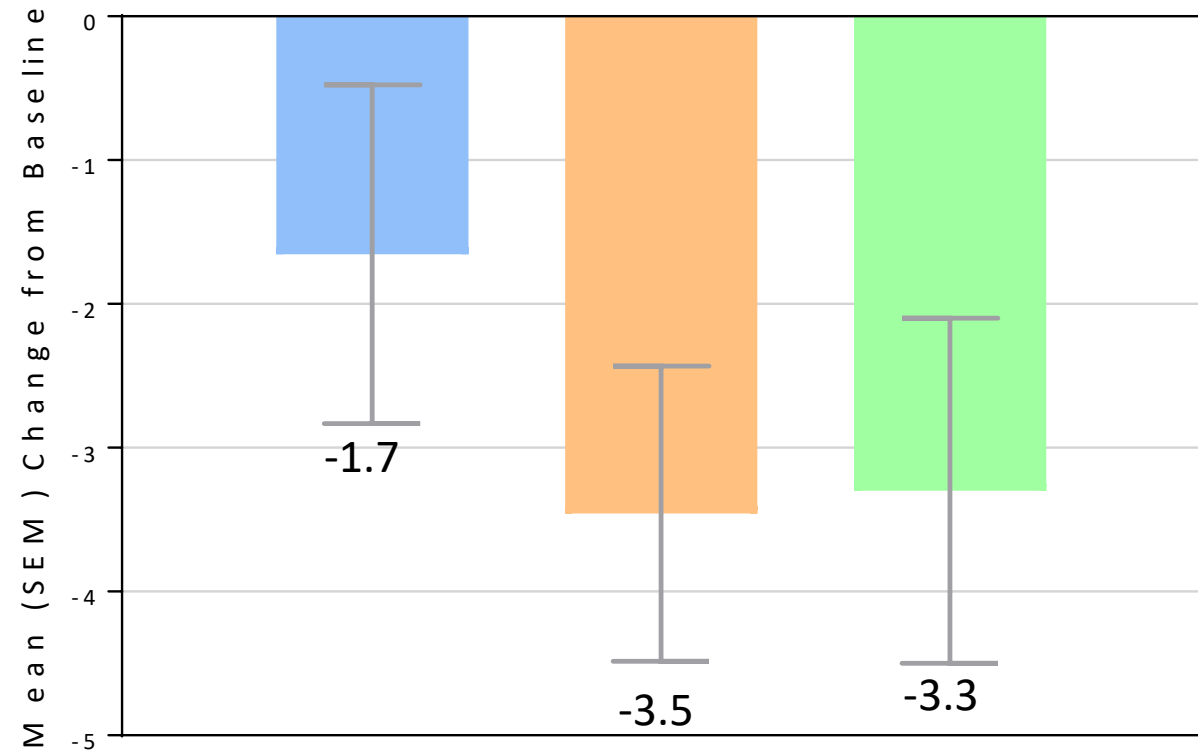


- Increases in TMV observed at Day 106 (3 weeks post last dose) shown below
- Decreases in FF from overall 30% at baseline at Day 106 (3 weeks post last dose) shown below

Total Muscle Volume



Fat Fraction, %



- Cohort 1 150 mg (N=6)
- Cohort 2 200 mg (N=6)
- Cohort 3 240 mg (N=6)

Average of right and left sides

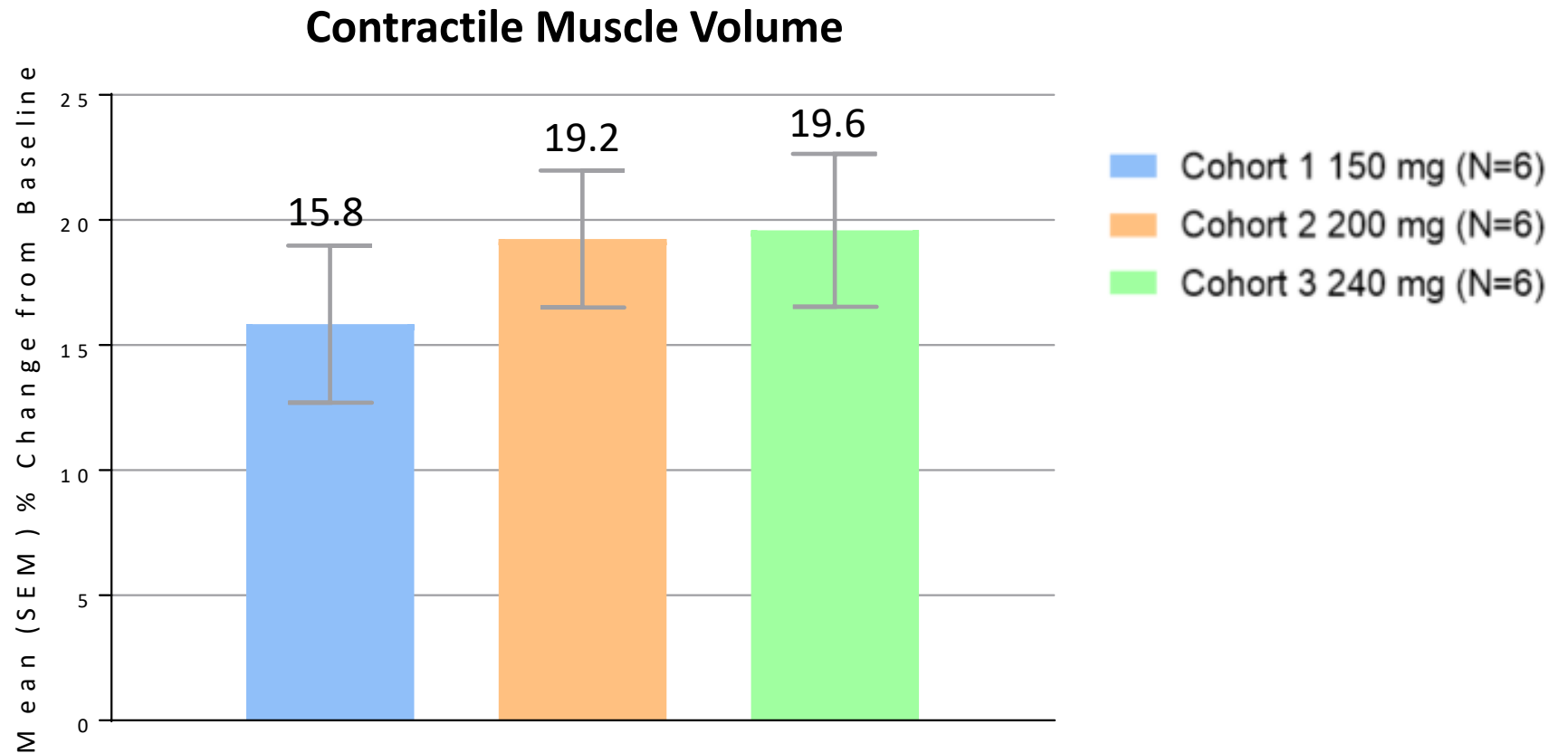
Preliminary data as of 05July2018

ACE-083 CMT Study – Contractile Muscle Volume (CMV)

Part 1; Percent Change from Baseline



- Contractile muscle volume calculated from total muscle volume and fat fraction for entire muscle
 - $CMV = [TMV * (100 - \text{fat fraction})] / 100$
 - Increases in CMV observed at Day 106 (3 weeks post last dose) shown below



Average of right and left sides
Preliminary data as of 05July2018



- ACE-083, a locally-acting muscle therapeutic, acting on myostatin *plus* other inhibitors of muscle growth, had a favorable safety profile and was generally well-tolerated over a 3-month treatment period in patients with CMT injected in the tibialis anterior
- Changes observed in pharmacodynamic / efficacy outcome measures at 3 weeks post last dose:
 - Mean percent increases of >12% total muscle volume and >15% contractile muscle volume
 - Mean absolute decrease in fat fraction of >3% in the 200 mg and 240 mg groups
- These results support continued investigation of ACE-083 in neuromuscular diseases
 - Placebo-controlled Part 2 of this CMT study (NCT03124459) to be initiated in 2018
 - Separate Phase 2 study in FSHD is ongoing (NCT02927080)

ACE-083 CMT Study – Acknowledgments



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