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

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Background

- CMT is the most common inherited 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 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 volunteers[1] and patients with FSH muscular dystrophy[2]

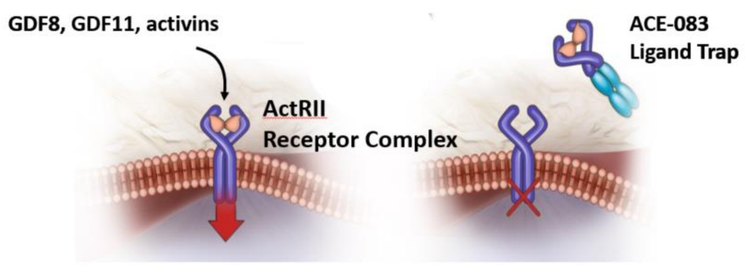


Figure 1: ACE-083 A Locally-Acting Muscle Therapeutic

Phase 2 Study in CMT

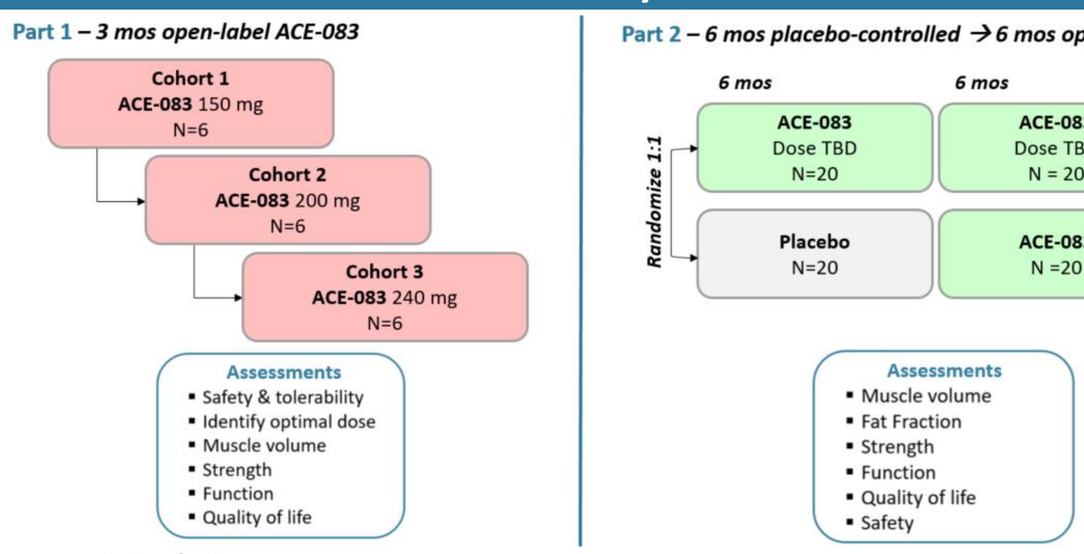


Figure 2: Study Design

Treatment:

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

Key Eligibility Criteria for Part 1:

- Age ≥ 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 ≥ 150 meters
- Left and right ankle dorsiflexion weakness (MRC grade 4- to 4+)
- No severe deformity or (surgical) fixation of ankle

Table 1: Assessments and Outcome Measures

	Assessment	Outcome Measure
Muscle Size/Quality	• Muscle and fat volumes by MRI	• Percent change in total muscle and contractile muscle volume • Absolute change in fat fraction
Muscle Strength	• Hand-held dynamometry	• Percent change in dorsiflexion strength
Muscle Function	• 6-minute walk test • 10m walk/run • Berg Balance Scale • Gait analysis	• Change/percent change in functional parameters
Investigator-/ Patient-Reported Outcomes	• CMT Examination Score (Version 2)[3] • CMT-Health Index (QoL)[4]	• Change in CMTES2 score/sub-scores • Change in CMT-HI score/sub-scores

Phase 2 Study Part 1 Results

Table 2: Baseline Characteristics

	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)

Preliminary data as of 05July2018

Median (range), unless otherwise indicated

Safety Results

Table 3: Possibly or Probably Related Adverse Events in ≥ 10% of Patients Overall

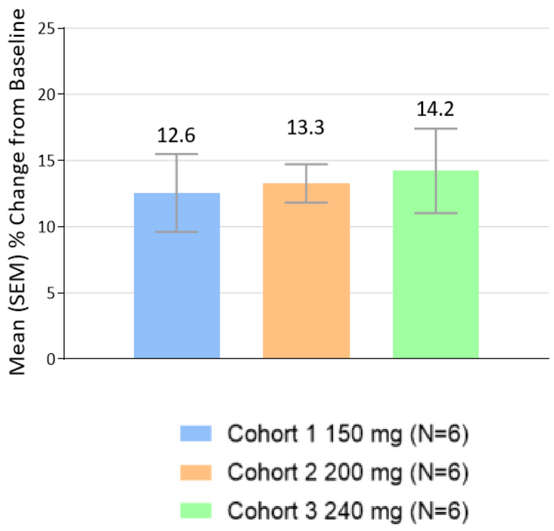
Preferred Term, n(%)	Cohort 1 150 mg N=6	Cohort 2 200 mg N=6	Cohort 3 240 mg N=6	Overall N=18
Injection site discomfort	3 (50%)	2 (33%)	3 (50%)	8 (44%)
Injection site bruising	1 (17%)	2 (33%)	2 (33%)	5 (28%)
Injection site erythema	2 (33%)	1 (17%)	1 (17%)	4 (22%)
Muscle spasms	1 (17%)	2 (33%)	1 (17%)	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%)

- 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

Imaging Results

- MRI assessments at baseline and Day 106 (3 weeks post last dose)

Figure 3: Total Muscle Volume (Percent Change)



(Average of right and left sides)

Figure 4: Fat Fraction, % (Absolute Change)

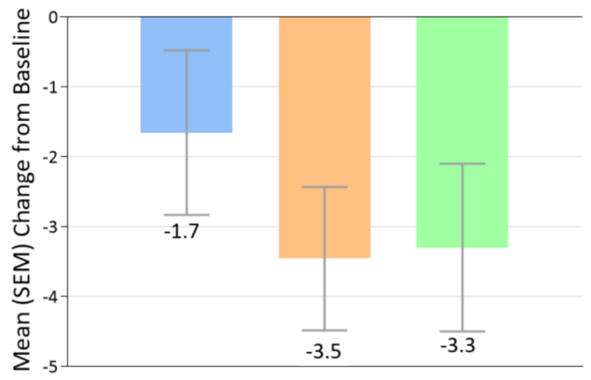
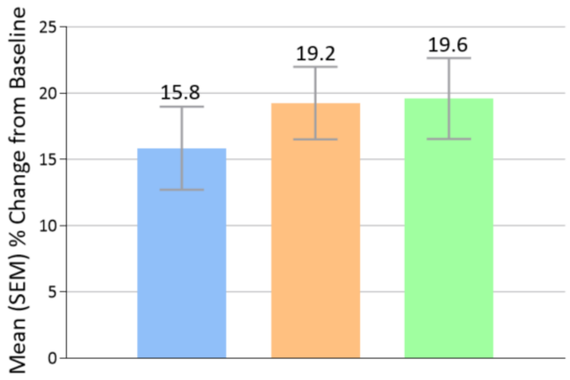


Figure 5: Contractile Muscle Volume (Percent Change)



Contractile Muscle Volume:

CMV = [TMV * (100 – fat fraction)] / 100

Summary/Conclusions

- 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)

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[1] *Glasser CE, et al. Muscle Nerve. 2018; 57:921-926*
[2] *Statland J, et al. American Academy of Neurology, 2018*
[3] *Murphy SM, et al. Journal of the Peripheral Nervous System 2011 16:191–198*
[4] *http://rochester.technologypublisher.com/technology/22384*

For trial updates and list of sites, please go to:
clinicaltrials.gov NCT03124459