Poster #339

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 an incidence of 1 in 2500[1]
- 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[2] and patients with FSH muscular dystrophy[3]

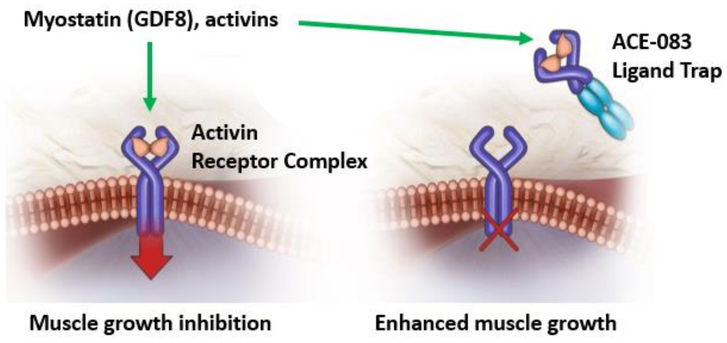


Figure 1: ACE-083 A Locally-Acting Muscle Therapeutic

Phase 2 Study in CMT

- ACE-083 or placebo is injected bilaterally into the tibialis anterior (TA) muscle every 3 weeks
- Preliminary data for Part 1 as of Aug 24, 2018 are presented; Part 2 is ongoing

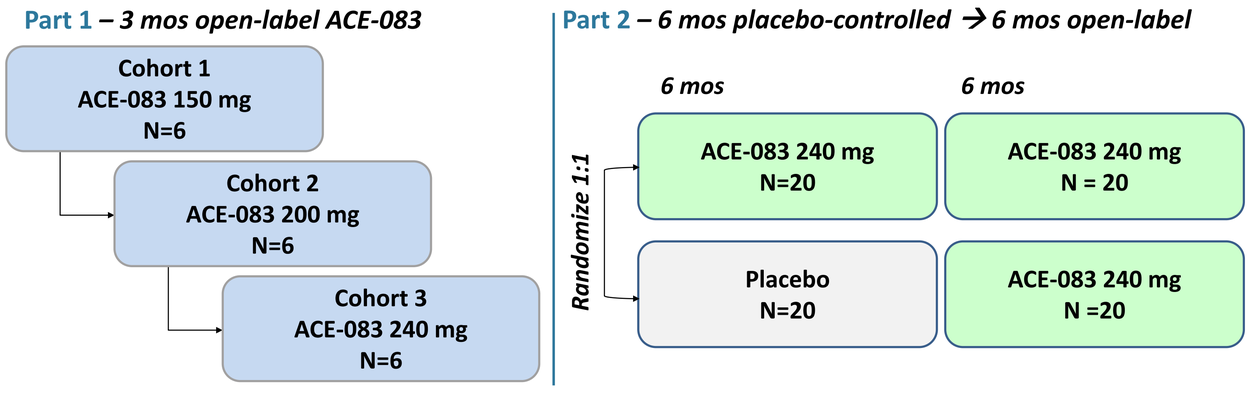


Figure 2: Study Design

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

Assessments and Outcome Measures

- Safety and tolerability
- Total and contractile muscle volume (TMV, CMV), fat fraction (FF) by MRI
- Strength by hand-held dynamometry and manual muscle testing
- 6-minute walk test, 10m walk/run, Berg Balance Scale, gait analysis (Biosensics)
- CMT Examination Score v.2, CMT-Health Index

Phase 2 Study Part 1 Results

Table 1: Demographics and Baseline Disease 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)

6MWD = 6-minute-walk distance
Median (range), unless otherwise indicated

Preliminary data as of 24August2018

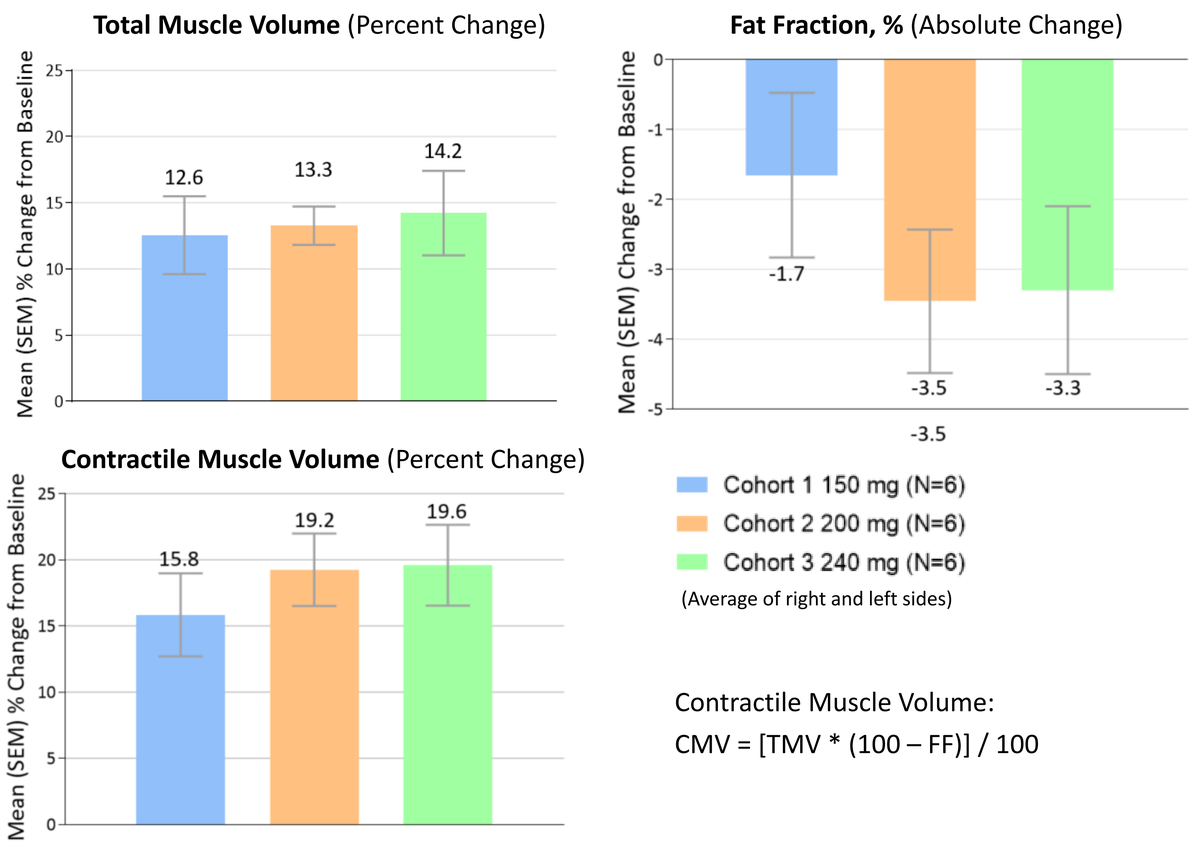
Safety Results

Table 2: 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 common adverse events were injection site reactions, muscle spasms, and myalgia
  - Most adverse events were mild or moderate (grades 1-2)
- No clinically significant laboratory abnormalities on treatment

Imaging Results



Contractile Muscle Volume:
CMV = [TMV * (100 – FF)] / 100

Figure 3: TMV, CMV, and FF by MRI at Day 106 (3 weeks post last dose) vs Baseline

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 outcome measures at 3 weeks post last dose:
  - Mean % 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, including assessments of strength and function, is now enrolling (NCT03124459)
  - Placebo-controlled Part 2 of a separate Phase 2 study in FSHD is now enrolling (NCT02927080) [Poster #365]

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[1]*Saporta MA, et al. Neurol Clin 2013; 31: 597-619*
[2]*Glasser CE, et al. Muscle Nerve 2018; 57: 921-926*
[3]*Statland J, et al. World Muscle Society 2018 Poster 365*

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