Poster #365

Results for a Dose-Escalation Phase 2 Study to Evaluate ACE-083, a Local Muscle Therapeutic, in Patients with Facioscapulohumeral Muscular Dystrophy

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Background

- Characteristic presentation of facioscapulohumeral muscular dystrophy (FSHD) with variable involvement of muscles of face, shoulders, upper arm, and distal lower extremity; asymmetry in some patients

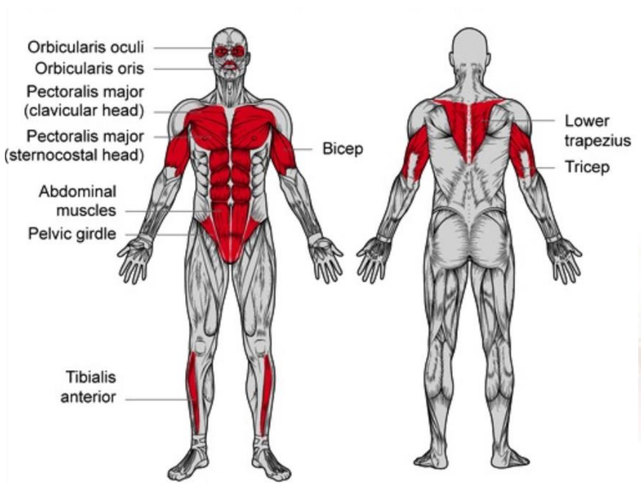


Figure 1: Clinical Presentation of FSHD[1]

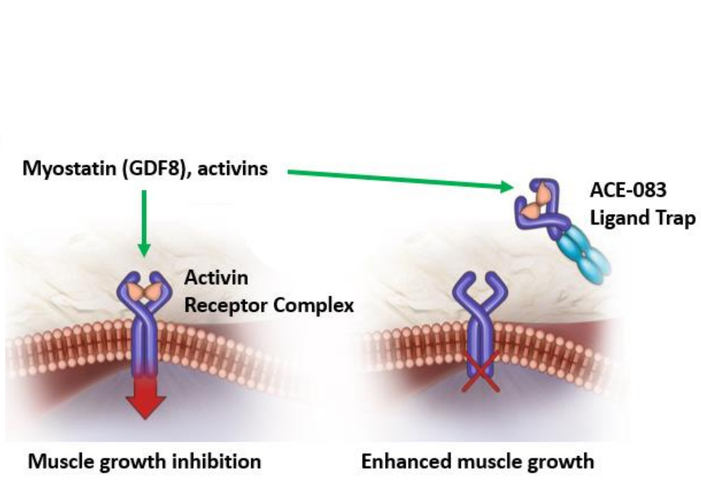
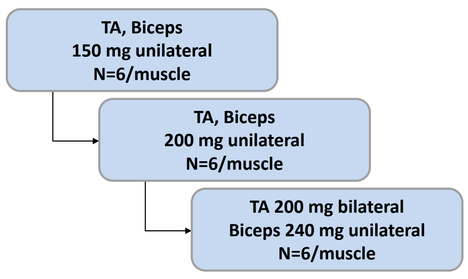


Figure 2: ACE-083 Mechanism of Action

- Patient-reported symptoms[2] with high prevalence and impact on quality of life:
  - Impaired gait and mobility due to foot drop, reported in 69% of patients
  - Biceps weakness reported in 73% of patients
- 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
- Increased muscle mass demonstrated in healthy volunteers[3] and patients with FSH muscular dystrophy[4]
- Tibialis anterior and biceps were selected as key targets for a locally acting muscle therapeutic in FSHD

Phase 2 Study in FSHD

Part 1 – *3 mos open-label, N=36*



Part 2 – *6 mos placebo-controlled → 6 mos open-label, N=56*

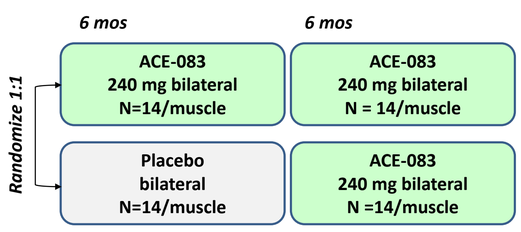


Figure 3: Study Design

Treatment:

- ACE-083 injection into tibialis anterior (TA) or biceps muscle, unilaterally or bilaterally, every 3 weeks

Key Eligibility Criteria for Part 1:

- Age ≥ 18 years
- Genetically-confirmed FSHD1 or FSHD2, or, genetically-confirmed first-degree relative and clinical signs/symptoms of FSHD
  - Mild to moderate weakness in ankle dorsiflexion or elbow flexion in the injected muscle
  - No concomitant medications potentially affecting muscle strength/function

Phase 2 Study Part 1 Results

Table 1: Demographics and Baseline Disease Characteristics

	Tibialis Anterior N=18	Biceps N=18	Overall N=36
Age, yr	46 (19-63)	48 (20-69)	46 (19-69)
Gender, n (%)			
Male	8 (44%)	12 (67%)	20 (56%)
Female	10 (56%)	6 (33%)	16 (44%)
Duration of symptoms, yr	26 (4-40)	22 (4-55)	25 (4-55)
MMT MRC grade, n (%)			
3 to 3+	5 (28%)	1 (6%)	6 (17%)
4- to 4+	13 (72%)	17 (94%)	30 (83%)
Total muscle mass, g	69 (36-158)	76 (29-221)	
Fat fraction, %	42 (12-82)	15 (6-79)	

MMT = manual muscle testing; MRC = Medical Research Council
Median (range), unless otherwise indicated

Safety Results

Table 2: Possibly or Probably Related Adverse Events in ≥ 10% of Patients Overall

	Tibialis Anterior N=18	Biceps N=19*	Overall N=37
Injection site pain	12 (67%)	6 (32%)	18 (49%)
Injection site discomfort	5 (28%)	7 (37%)	12 (32%)
Injection site erythema	4 (22%)	5 (26%)	9 (24%)
Myalgia	5 (28%)	4 (21%)	9 (24%)
Injection site bruising	2 (11%)	6 (32%)	8 (22%)
Injection site swelling	3 (17%)	5 (26%)	8 (22%)

*Includes one treated patient who discontinued prior to Study Day 43

- ACE-083 was generally well tolerated in subjects treated for up to 3 months (5 doses)
- No serious adverse events; most adverse events were mild or moderate (grades 1-2)
  - One related grade 3 event of lower leg intramuscular swelling in the 200 mg TA cohort
- Most common adverse events were injection site reactions and myalgia
- No clinically significant laboratory abnormalities on treatment

Preliminary data as of 24July2018

Imaging Results

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

Figure 4: Total Muscle Volume (Percent Change)

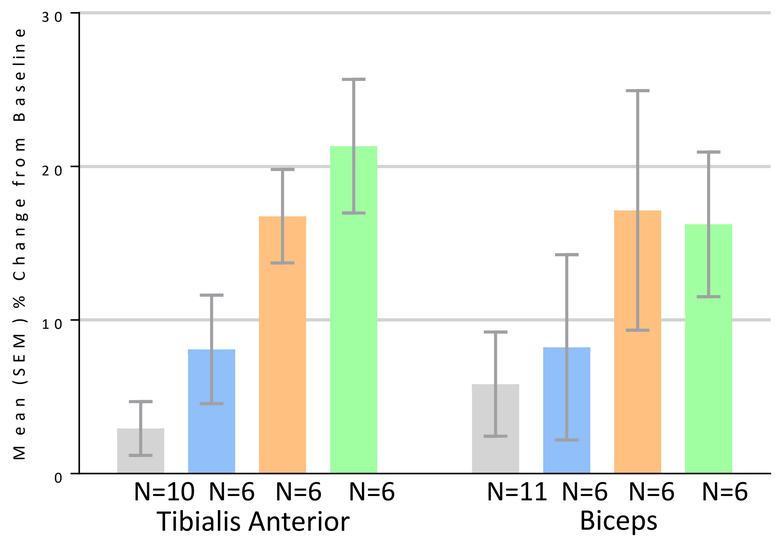


Figure 5: Fat Fraction, % (Absolute Change)

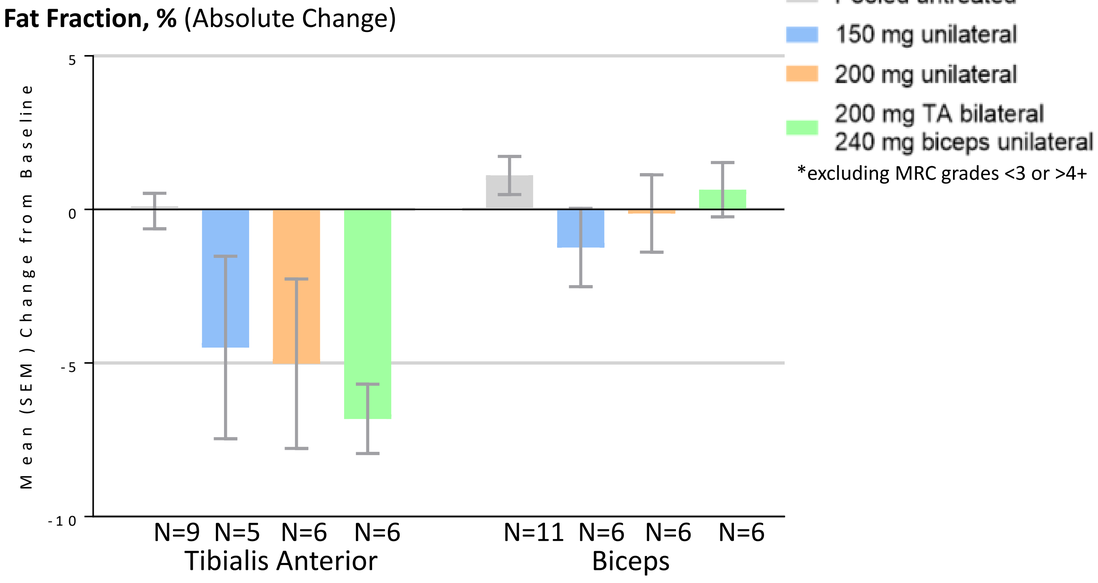
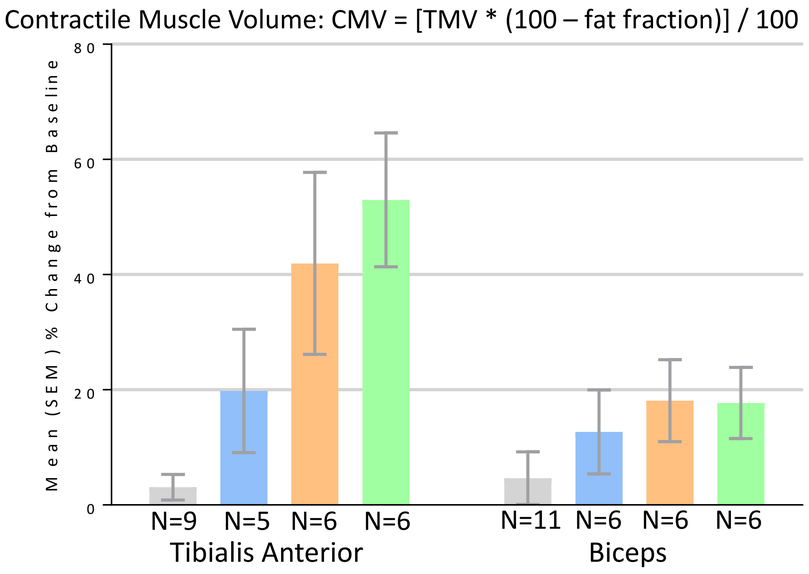


Figure 6: Contractile Muscle Volume (Percent Change)

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



Summary/Conclusions

- ACE-083, a locally-acting muscle therapeutic acting on myostatin *plus* other inhibitors, was safe and generally well-tolerated when injected in the tibialis anterior or biceps brachii over a 3-month treatment period in patients with FSHD
- Increases in total muscle volume were dose-dependent, with >15% increase observed at doses of 200 to 240 mg/muscle
- Fat fraction decreased, most notably in tibialis anterior cohorts with higher baseline values
- These results support continued investigation of ACE-083 in neuromuscular diseases
  - Placebo-controlled Part 2 of this Phase 2 FSHD study now enrolling (NCT02927080)
  - Placebo-controlled Part 2 of a Phase 2 study in Charcot-Marie-Tooth disease now enrolling (NCT03124459) [Poster #339]

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[1]*Lek A et al. Trends Mol Med 2015; 21 (5): 295-306*
[2]*Nguyen T, et al. MDA Scientific Conference 2017*
[3]*Glasser CE, et al. Muscle Nerve. 2018; 57:921-9264*
[4]*Statland J, et al. American Academy of Neurology 2018*

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For trial updates and list of sites, please go to:
clinicaltrials.gov NCT02927080