ACE-083, a locally-acting TGF-beta superfamily ligand trap, increases muscle volume of targeted muscle: Preliminary results from a Phase 1 dose escalation study in healthy volunteers

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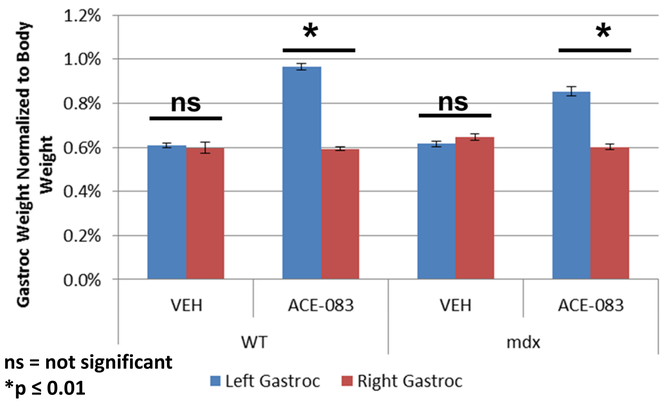
ACE-083 Background

- TGF-β superfamily ligands such as myostatin (GDF8) and activins are known negative regulators of muscle growth
- GDF8 signals through the activin receptor type IIB (ActRIIB) to induce SMAD 2/3 phosphorylation and translocation to the nucleus to regulate gene transcription
- ACE-083 is a locally-acting protein therapeutic that binds GDF8 and activins and inhibits SMAD 2/3 signaling

Pre-Clinical Results

- In wild type (WT) mice, ACE-083 led to increased tibialis anterior (TA) muscle fiber cross-sectional area (CSA)[1]
- In both WT and the *mdx* mouse model of Duchenne muscular dystrophy (DMD), local injections of ACE-083 led to dose-dependent increases in muscle mass[2,3] (Figure 1)

Figure 1: ACE-083 Increased Muscle Mass in the Injected (L), but not in the Uninjected (R), Leg in WT and *mdx* Mice



ns = not significant
*p ≤ 0.01

- In WT mice, ACE-083 increased peak tetanic force by 40% and muscle fiber CSA by 78% in the injected muscle measured ex vivo
- Preclinical studies showed limited systemic exposure, confirming the local activity of specific muscle injections

A083-01 Study Design

- A083-01 is an ongoing, single-center, randomized, double-blind, placebo-controlled, dose-ranging study in healthy post-menopausal women
- **Primary Objective:** Characterize the safety and tolerability of single and repeated doses of ACE-083
- **Secondary Objectives:** Estimate systemic exposure and evaluate pharmacodynamic effects, including changes in muscle volume as measured on MRI and changes in strength as measured by fixed system and hand-held dynamometry
- Five cohorts of 8 subjects were randomized to ACE-083 (n=6) or matched placebo (n=2), administered as 2 or 4 injections along the length of the right rectus femoris (RF). Two additional cohorts of 9 subjects (6:3) are ongoing with administration to the right TA (Table 1)

Figure 2: ACE-083 Approximate RF Injection Sites for Cohorts 1, 2 and 4 (A) and Cohorts 3 and 5 (B)

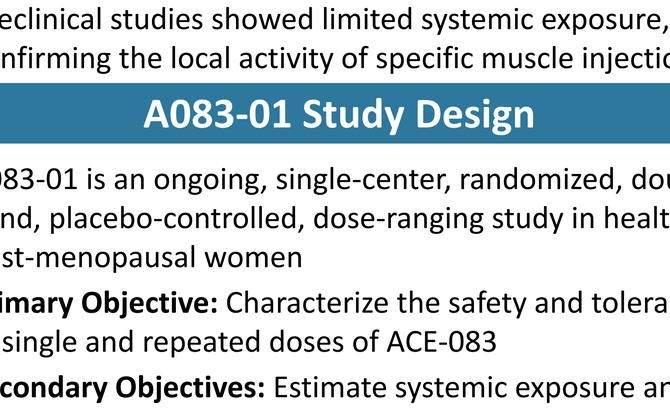
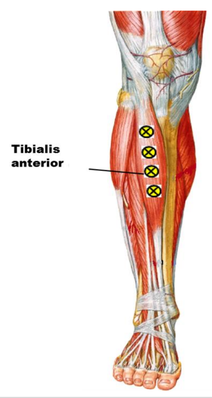


Figure 3: ACE-083 Approximate TA Injection Sites for Cohorts 6 and 7



A083-01 Dosing and Assessments

Table 1: Dosing Administration Details by Cohort

# of Doses	Cohort	Dose Level (mg)	Muscle	Injections per Dose	# Subjects ACE-083: Placebo
Single Dose (Day 1)	1	50	RF	2	6:2
	2	100	RF	2	6:2
	3	200	RF	4	6:2
Multiple Doses (Day 1, 22)	4	100	RF	2	6:2
	5	200	RF	4	6:2
	6*	100	TA	4	6:3
	7*	150	TA	4	6:3
Total # of ACE-083 vs. Placebo treated subjects					42:16

*ongoing cohorts; RF: rectus femoris, TA: tibialis anterior

- MRI was obtained pre-dose as well as 3 and 8 weeks post last dose
- Strength was assessed by Biodex fixed system at 3 and 8 weeks post last dose
- A handheld dynamometer (micro FET) was used to assess strength weekly

Safety Results: Cohorts 1-5

- Forty post-menopausal women (97.5% white) with a median age of 56 (range: 45-72 yrs) and median BMI of 25.1 (range: 19.2-31.5 kg/m^2) were enrolled into the study
- There were no serious adverse events, dose-limiting toxicities, or discontinuations due to adverse events (AEs)
- All AEs were grade 1-2, transient, and most commonly injection site related
- Injection site pain was documented at all dose levels (including placebo) and was independent of dose or number of injections
- Myalgia and injection site hemorrhage were reported in 20% and 13% of ACE-083-treated subjects compared to 10% and 0% of placebo-treated subjects respectively.
- Other frequent related AEs were similar in both groups (Table 2)

Table 2: Adverse Events at Least Possibly Related to Study Drug Occurring in ≥ 10% (3 or more) ACE-083-Treated Subjects

Preferred Term n (%)	Placebo Treated (n =10)	Single Dose (mg)			Multiple Dose (mg)		ACE-083 Treated (n=30)
		50 (n=6)	100 (n=6)	200 (n=6)	100 (n=6)	200 (n=6)	
Inj site pain	10 (100)	5 (83)	5 (83)	6 (100)	5 (83)	6 (100)	27 (90)
Muscle twitching	3 (30)	0	1 (17)	2 (33)	3 (50)	2 (33)	8 (27)
Myalgia	1 (10)	1 (17)	0	2 (33)	1 (17)	2 (33)	6 (20)
Inj site reaction	1 (10)	0	0	1 (17)	1 (17)	3 (50)	5 (17)
Pain in extremity	2 (20)	0	0	0	3 (50)	1 (17)	4 (13)
Inj site discomfort	1 (10)	0	1 (17)	0	3 (50)	0	4 (13)
Inj site hemorrhage	0	1 (17)	0	1 (17)	0	2 (33)	4 (13)
Limb discomfort	2 (20)	0	0	3 (50)	0	0	3 (10)

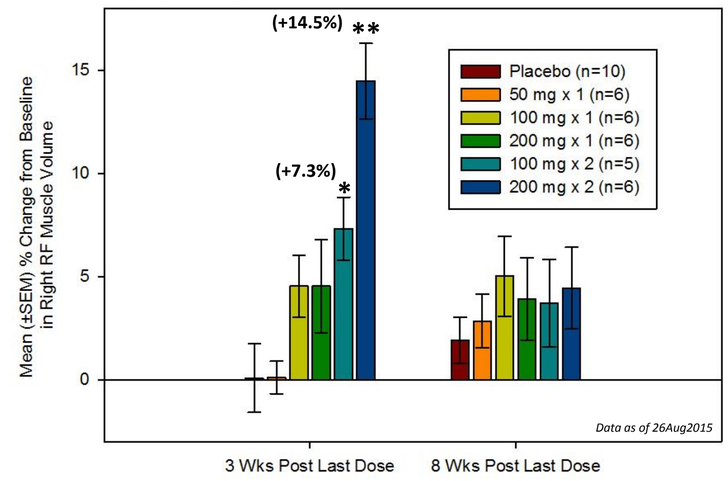
Data as of 26Aug2015

Efficacy Results: Cohorts 1-5

- A dose-dependent increase in the right RF muscle volume by MRI was observed following local administration of ACE-083 (Figure 4)
- Three weeks after the last dose of ACE-083, the right RF muscle volume was significantly increased from baseline by 7.3% (p= <0.05) and 14.5% (p=<0.001) in Cohorts 4 and 5, respectively
- Changes in the left uninjected RF muscle (Figure 5) were used to control for MRI variability; changes in right RF minus left RF muscle volume are depicted in Figure 6
- In Cohorts 2-5, RF volume remained increased, though attenuated, at 8 weeks post last dose
- Strength increases did not consistently correlate with muscle volume increases in these healthy subjects
  - RF muscle accounted for only ~13% (range: 10-16%) of the total quadriceps muscle volume in these subjects

Efficacy Results: Cohorts 1-5 (cont.)

Figure 4: Mean Percent Change from Baseline in Right (Injected) Rectus Femoris Muscle Volume



Significance level in comparison to placebo using Dunnett's Test:
* p= < 0.05; ** p= < 0.001

Figure 5: Mean Percent Change from Baseline in Left (Uninjected) Rectus Femoris Muscle Volume

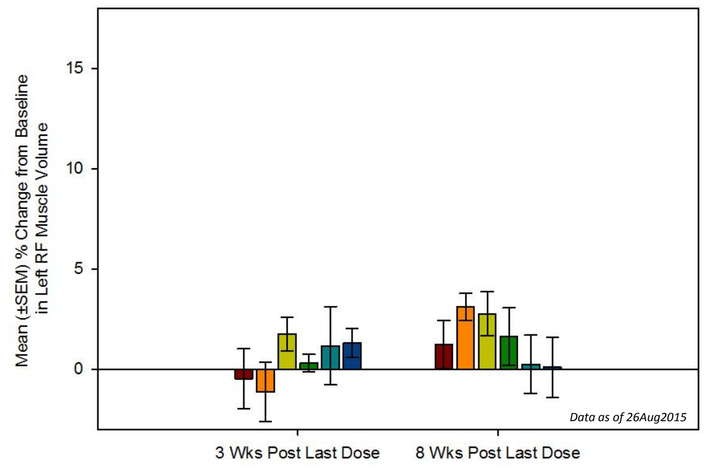
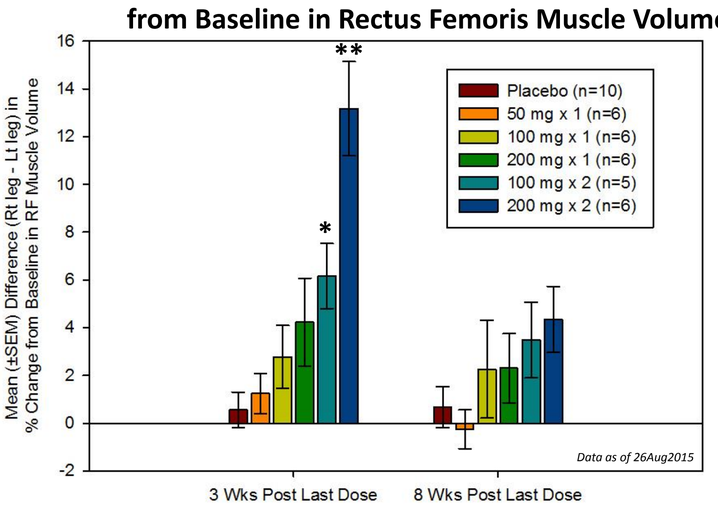


Figure 6: Mean Difference (Right – Left) in Percent Change from Baseline in Rectus Femoris Muscle Volume



Mean difference in % RF volume change 3 weeks after the last dose in placebo was +0.6% compared to ACE-083 treated subjects in cohorts 1-5: +1.2%, +2.8%, +4.2%, +6.2%, and +13.2% respectively. Significance level in comparison to placebo using Dunnett's Test: * p= < 0.05; ** p= < 0.001

Conclusions

- ACE-083 is a locally-acting protein therapeutic that acts as a ligand trap for GDF8 and other negative regulators of muscle mass
- In preclinical models, local injection of ACE-083 increased muscle mass and force in the injected muscle
- Study A083-01 is an ongoing Phase 1 study evaluating ACE-083 administration into the RF and TA in healthy volunteers (www.clinicaltrials.gov/ct2/show/NCT02257489)
- Results from Cohorts 1-5 of this Phase 1 study demonstrate that local administration of ACE-083 into the RF muscle is associated with a favorable safety profile and resulted in dose-dependent and significant increases in RF muscle volume
- These encouraging data support further studies of ACE-083 in a variety of myogenic and/or neurogenic diseases, including FSHD and DMD

References

1. Pearsall et al. ACE-083 Increases Muscle Hypertrophy and Strength in C57BL/6 Mice. 20th International Congress of the World Muscle Society; October 1, 2015
2. Mulivor et al. A Modified Cysteine Knot Ligand Trap of the TGF-β Superfamily, ACE-083, Increases Muscle Mass Locally in Mice. 13th International Congress on Neuromuscular Diseases; July 7, 2014
3. Mulivor et al. ACE-083, a Ligand Trap for Members of the TGF-β Superfamily, Increases Muscle Mass Locally in a Mouse Model of Duchenne Muscular Dystrophy. 19th International Congress of the World Muscle Society; October 9, 2014

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