A Phase 1 Healthy Volunteer Study of ACE-083, a Novel, Locally-Acting Muscle Agent

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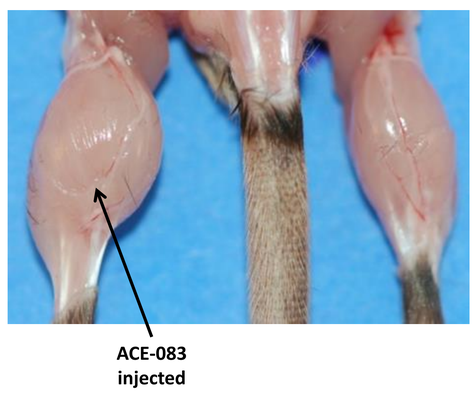
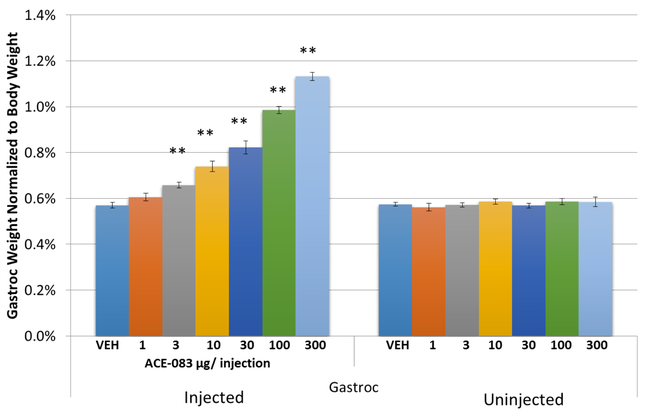
Background

- ACE-083 is a locally-acting investigational protein therapeutic that binds GDF8 (myostatin) and other ligands in the TGF-β superfamily that negatively regulate skeletal muscle.
- ACE-083 was designed to increase muscle mass and strength selectively in the muscle into which the drug is administered.
- In wild type (WT) mice, local injection of ACE-083 2x/week for 1 month into the left gastrocnemius muscle led to localized, dose-dependent hypertrophy in the target muscle and increases in strength.





**p<0.05 vs vehicle and vs uninjected leg

- In mouse models of both myogenic (*mdx*) and neurogenic (SOD1) disease, local injection of ACE-083 into the tibialis anterior 2x/week for 4 weeks increased muscle mass as well as peak tetanic strength.

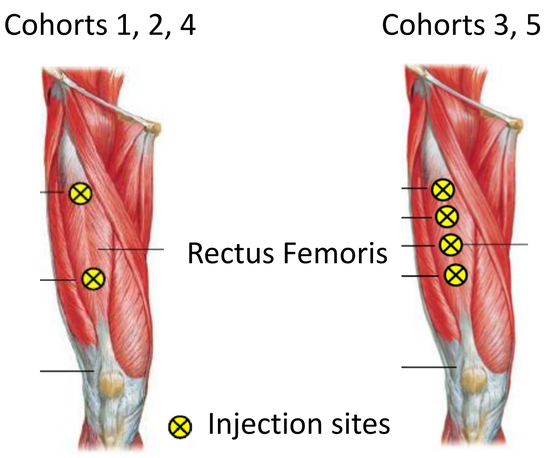
Phase 1 Clinical Study Objectives

- Randomized, double-blind, placebo-controlled, dose-ranging study in healthy post-menopausal women
- Primary objective: Safety and tolerability of single and multiple doses of ACE-083 as a local muscle injection
- Secondary objectives: Estimate systemic exposure of ACE-083; evaluate pharmaco-dynamic effects including muscle volume by MRI and strength by handheld dynamometer and fixed system

Study Design

- ACE-083 (or placebo) was administered under EMG guidance using a MyoJect 26G needle as a single dose (day 1) or as two doses (day 1 and day 22) to the right side only
- Each dose was divided into 2 or 4 injections
- Cohorts 1-5: rectus femoris (RF); Cohorts 6-7: tibialis anterior (TA)

Injected Muscle	Cohort	Dosing Day(s)	Dose (mg)	# Injections mL per Dose	# Subjects	
					ACE-083	Placebo
Rectus Femoris	1	1	50	2 x 0.75	6	2
	2	1	100	2 x 1.0	6	2
	3	1	200	4 x 1.0	6	2
	4	1, 22	100	2 x 1.0	6	2
	5	1, 22	200	4 x 1.0	6	2
Tibialis Anterior	6	1, 22	100	4 x 0.5	6	3
	7	1, 22	150	4 x 0.75	6	3
				Total:	**42**	**16**



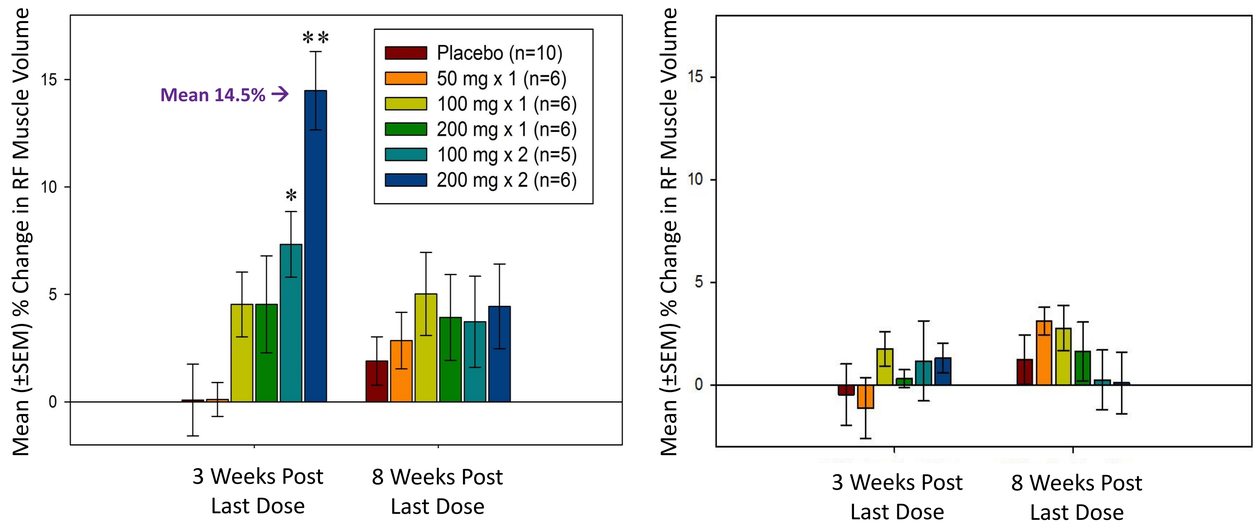
Efficacy Results

- At 3 weeks after last dose, ACE-083 increased muscle volume of the right RF up to 14.5% and the right TA up to 8.9% at the highest dose levels tested ($p<0.001$ vs placebo for each muscle) with no effect in the contralateral uninjected muscle
- Increases in muscle volume correlated with dose administered of ACE-083 in mg/g of muscle
- No consistent changes were observed in knee extension (RF) or dorsiflexion (TA) strength in these healthy subjects

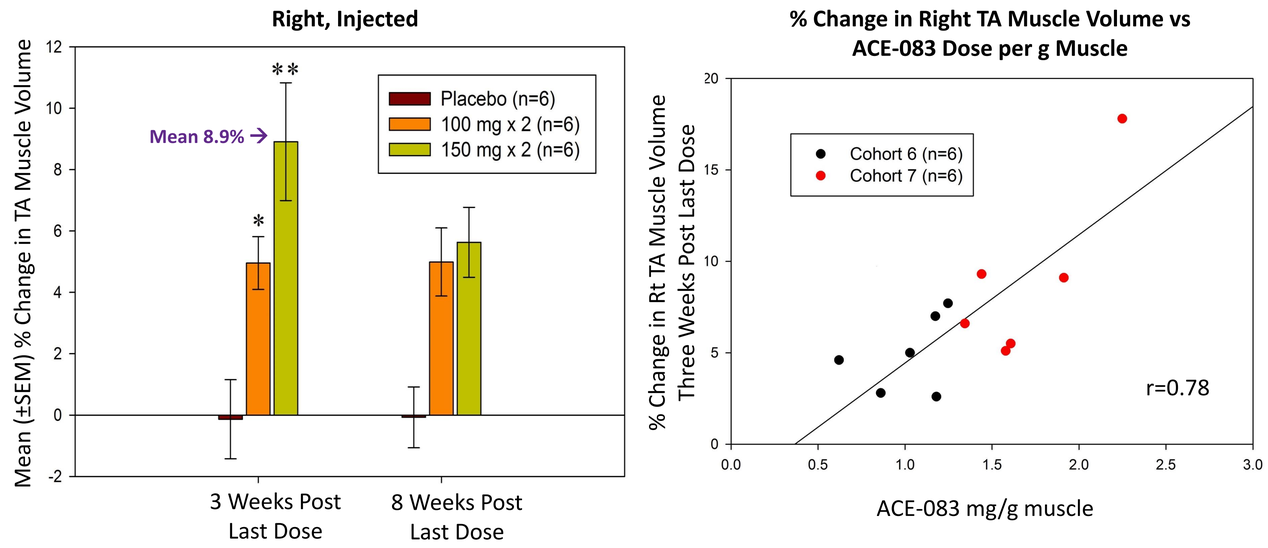
Efficacy Results (cont.)

% Change in Muscle Volume by MRI

Rectus Femoris (RF)



Tibialis Anterior (TA)



Dunnett's Test vs placebo: * $p < 0.05$; ** $p < 0.001$

Safety Results

- 58 post-menopausal women were enrolled into the study
- 42 were treated with ACE-083
  - Median (range) age 56 (45-70) yr; BMI 25.9 (19.2-31.6) kg/m^2; 98% white
- No serious adverse events (AEs), dose-limiting toxicities, or discontinuations due to AE
- All AEs were grade 1-2, transient, and most commonly injection-site related
- Similar AE incidence was observed in placebo and active groups

Adverse Events at Least Possibly Related to Study Drug in ≥10% of Subjects

Preferred Term n (%)	RF (Cohorts 1-5)		TA (Cohorts 6-7)	
	Placebo (n=10)	ACE-083 (n=30)	Placebo (n=6)	ACE-083 (n=12)
Pain in extremity	2 (20)	7 (23)	5 (83)	12 (100)
Injection site pain	10 (100)	27 (90)	6 (100)	11 (92)
Injection site discomfort	1 (10)	4 (13)	3 (50)	4 (33)
Muscle tightness	1 (10)	2 (7)	2 (33)	4 (33)
Injection site warmth	2 (20)	1 (3)	1 (17)	3 (25)
Discomfort	0	0	2 (33)	3 (25)
Injection site oedema	0	0	1 (17)	3 (25)
Arthralgia	1 (10)	3 (10)	4 (67)	2 (17)
Musculoskeletal stiffness	1 (10)	4 (13)	1 (17)	2 (17)
Myalgia	0	7 (23)	0	2 (17)
Injection site reaction	1 (10)	5 (17)	0	1 (8)
Injection site hemorrhage	0	5 (17)	0	1 (8)
Limb discomfort	2 (20)	3 (10)	0	1 (8)
Muscle twitching	3 (30)	8 (27)	0	0

Summary/Conclusions

- ACE-083, a locally-acting investigational protein therapeutic that acts as a ligand trap for GDF8 (myostatin) and other negative regulators of muscle mass, was injected into the RF muscle or TA muscle in healthy volunteers.
- ACE-083 had a favorable safety profile and resulted in dose-dependent and significant increases in muscle volume.
- These data support further clinical studies of ACE-083 to potentially improve strength and function in neuromuscular diseases; a phase 2 study in facioscapulohumeral muscular dystrophy (FSHD) will be initiated in 2016.

References

- Mulivor et al. World Muscle Society, 2014
- Mulivor et al. ICNMD, 2014
- Pearsall et al. World Muscle Society, 2015
- Glasser et al. Conf. on Cachexia, Sarcopenia, 2015
- Pearsall et al. MDA Clinical Conference, 2016
- Attie et al. ICNMD, 2016

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