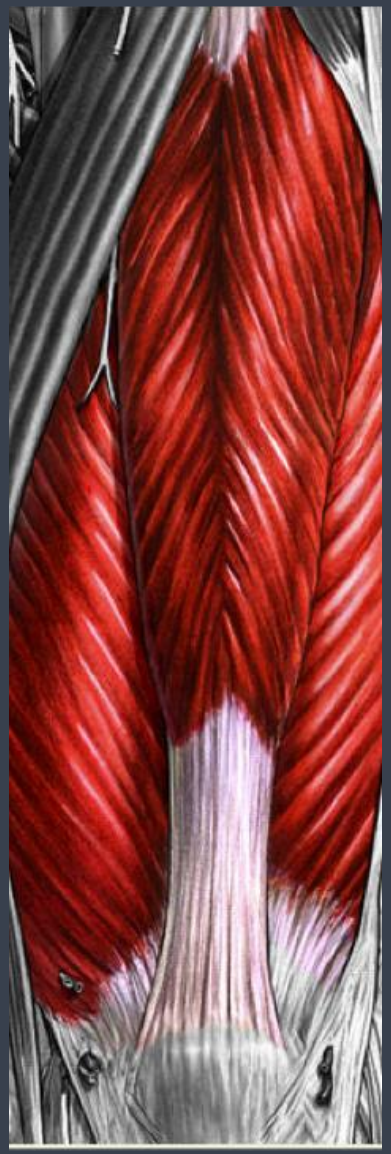

Phase 1 dose escalation study of ACE-083 in healthy volunteers: Preliminary results for a locally acting muscle therapeutic

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ACCELERON

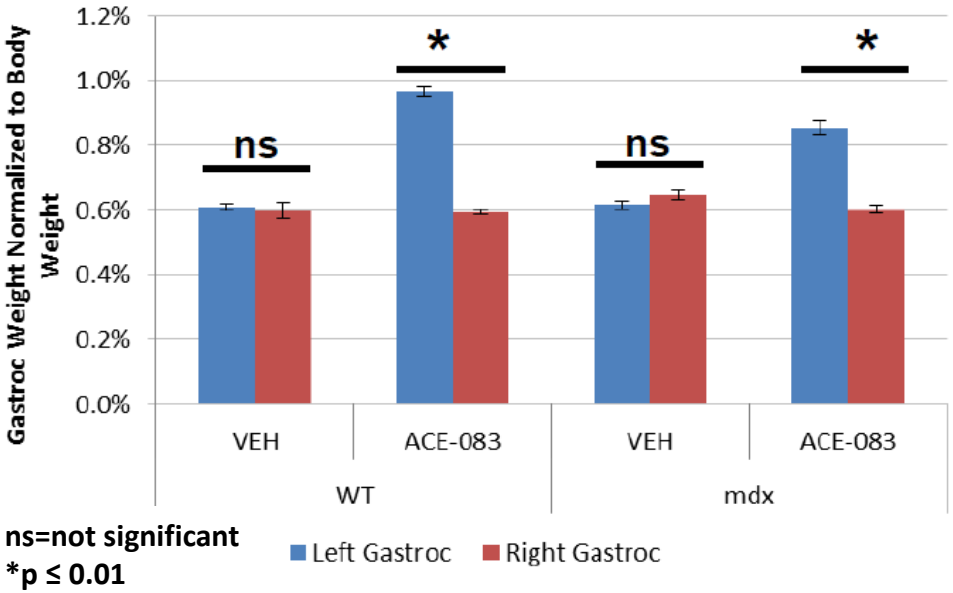
ACE-083 Background

- ACE-083 is a locally acting protein therapeutic that binds GDF8 (myostatin) and activins among other negative regulators of skeletal muscle growth
- ACE-083 was designed to increase muscle mass and strength selectively in the muscle into which the drug is administered

ACE-083 Pre-Clinical Results

- In both wild type (WT) and the *mdx* mouse model of Duchenne muscular dystrophy (DMD), local injection of ACE-083 led to localized muscle hypertrophy as well as dose-dependent increases in muscle mass[1,2]

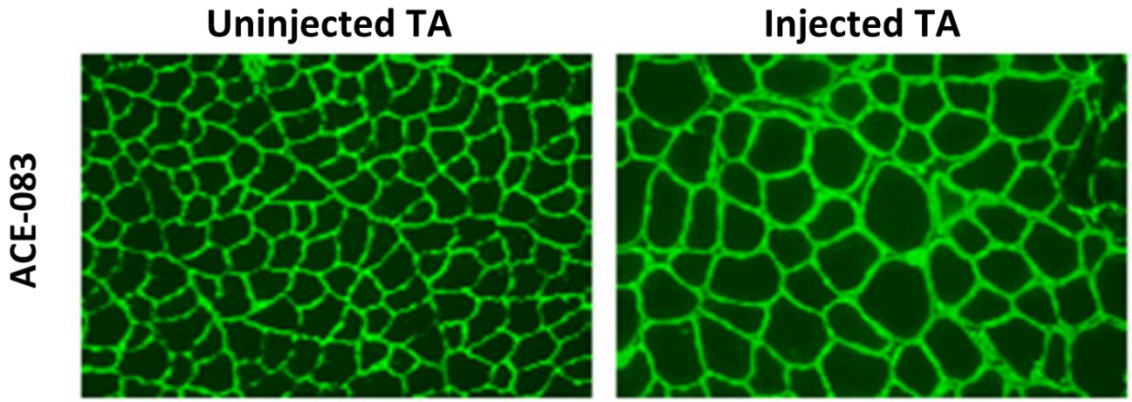
ACE-083 Increased Muscle Mass in the Injected (L), but not in the Uninjected (R), Leg in WT and *mdx* Mice

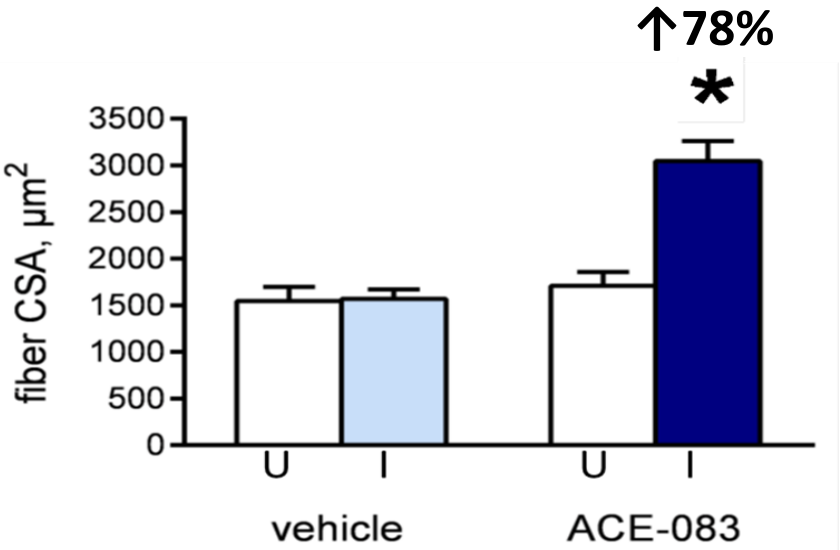


ns=not significant
***p ≤ 0.01**

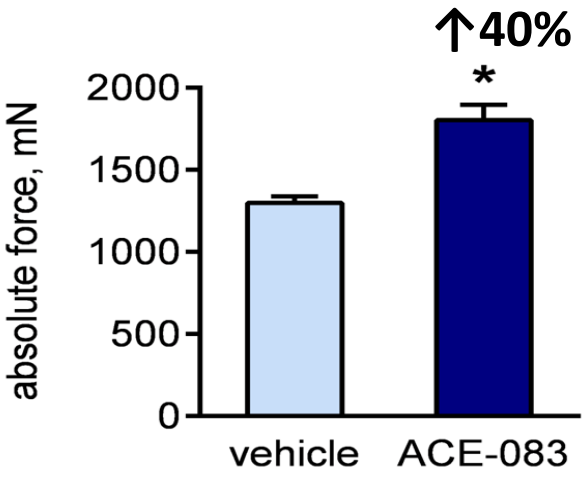
[1]Mulivor et al. 13th International Congress on Neuromuscular Diseases, 2014
[2]Mulivor et al. 19th International Congress of the World Muscle Society, 2014

ACE-083 Administration Led to an Increase in Fiber CSA and Peak Tetanic Force of the Tibialis Anterior (TA) in WT Mice[3]





*p = ≤ 0.001



*p = ≤ 0.05

[3]Pearsall et al. International Congress of the World Muscle Society, 2015

A083-01: A Phase 1 Study in Healthy Volunteers

Study Description

- An ongoing randomized, double-blind, placebo-controlled, dose-ranging study in healthy post-menopausal women

Objectives of the Study

- Primary: To characterize the safety and tolerability of single and repeated doses of ACE-083 as a local muscle injection
- Secondary: To estimate systemic exposure and evaluate the pharmacodynamic (PD) effects of ACE-083
  - Changes in muscle volume measured on MRI
  - Changes in strength as measured by Biodex fixed system and hand-held dynamometer

A083-01 Study Design

Number of Doses	Cohort	Dosing Day(s)	Dose Level (mg)	Injected Muscle	Injections per Dose	ACE-083 Subjects	Placebo Subjects	Status
Single Dose	1	1	50	RF	2	6	2	Completed
	2	1	100	RF	2	6	2	
	3	1	200	RF	4	6	2	
Multiple Doses	4	1, 22	100	RF	2	6	2	
	5	1, 22	200	RF	4	6	2	
	6	1, 22	100	TA	4	6	3	Ongoing
	7	1, 22	150	TA	4	6	3	
Total Number of Subjects (Planned):						**42**	**16**	

RF: rectus femoris, TA: tibialis anterior

NCT02257489

Data as of 26Aug2015

Pharmacodynamic Assessments

- MRI was obtained pre-dose (Day 1) as well as 3 weeks (Day 22 or 43) and 8 weeks (Day 57 or Day 78) post last dose

Number of Doses	Assessment	Day 1	Day 22	Day 43	Day 57	Day 78
Single Dose	Dosing	X				
	MRI	X	X		X	
Multiple Doses	Dosing	X	X			
	MRI	X		X		X

- Strength was assessed by Biodex fixed system at 3 and 8 weeks post last dose
- A handheld dynamometer was also used to evaluate strength weekly throughout the treatment period

Safety Results: Cohorts 1-5

- Forty post-menopausal women (97.5% white) with a median age of 56 (range: 45-72 yrs) and median body mass index (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

Data as of 26Aug2015

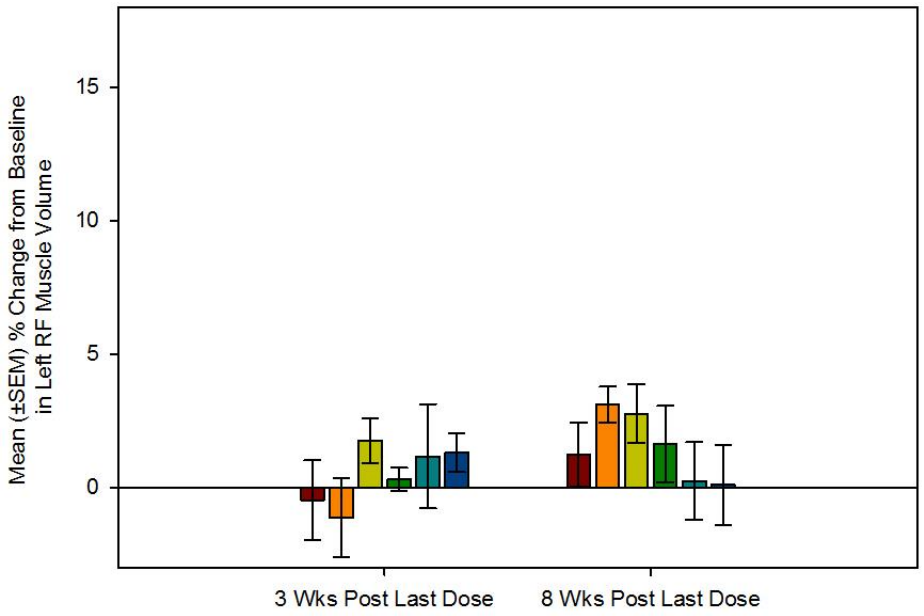
Adverse Events at Least Possibly Related to Study Drug Occurring in ≥ 10% (3 or more) ACE-083 Treated Subjects

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)	
Injection 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)
Injection 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)
Injection site discomfort	1 (10)	0	1 (17)	0	3 (50)	0	4 (13)
Injection 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)

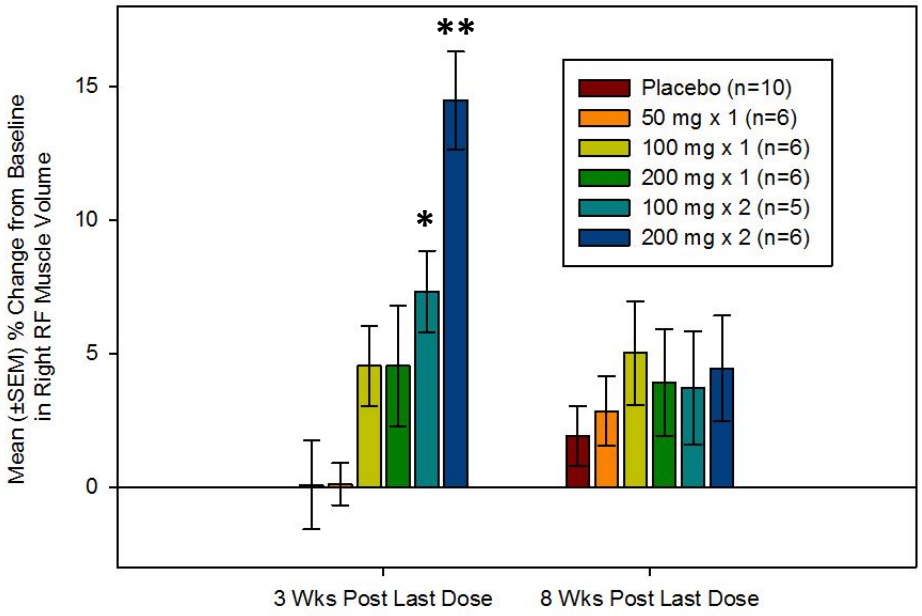
Data as of 26Aug2015

ACE-083 Produced Significant Increases in Muscle Volume by MRI in the Injected Muscle with No Effect on the Uninjected Muscle

No Treatment
(Left Rectus Femoris)



ACE-083 Treated
(Right Rectus Femoris)



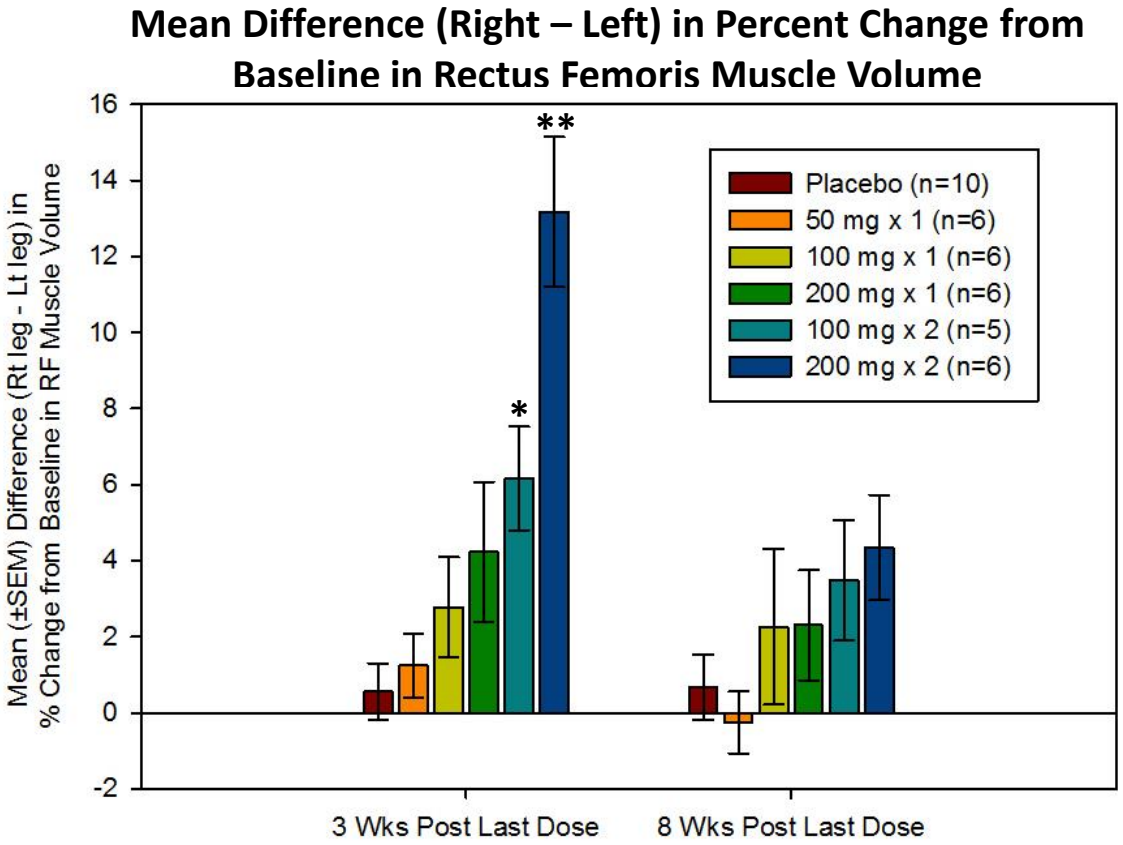
NOTE: Significance level in comparison to placebo using Dunnett's Test: *p = < 0.05; ** p= < 0.001

- Changes in the left uninjected RF muscle were used to control for MRI variability

- Three weeks after the last dose of ACE-083, the right RF muscle volume increased from baseline by 7.3% ($p<0.05$) and 14.5% ($p<0.001$) in Cohorts 4 and 5, respectively

Data as of 26Aug2015

A Dose-Dependent Increase in RF Muscle Volume was Observed Following Local Administration of ACE-083



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

- In Cohorts 2-5, RF volume remains increased, though attenuated, at 8 weeks post last dose

Data as of 26Aug2015

Changes in Strength Following ACE-083 Administration

- Changes in strength did not correlate with muscle volume changes in these healthy subjects
- RF muscle accounted for only ~13% (range: 10-16%) of the total quadriceps muscle volume in these healthy subjects
- Ongoing cohorts evaluating administration of ACE-083 into the tibialis anterior (TA) will evaluate dorsiflexion strength

Conclusions

- ACE-083 is a locally-acting protein therapeutic that acts as a ligand trap for myostatin and other negative regulators of muscle mass
- A083-01 is an ongoing Phase 1 study evaluating ACE-083 administration into the RF and TA in healthy volunteers
- ACE-083 injected 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 muscle diseases, such as Facioscapulohumeral muscular dystrophy (FSHD) and Duchenne Muscular Dystrophy

Acknowledgements

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