A Phase 1 Dose Escalation Study of ACE-083, a Locally-Acting Muscle Therapeutic, in Healthy Volunteers

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Background

- Myostatin (GDF8) is a member of the TGF-β superfamily and is a known negative regulator 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 investigational protein therapeutic that acts as a ligand trap for GDF8 and other negative regulators of muscle mass.

Preclinical Rationale

- ACE-083 has been evaluated in both wild-type (WT) C57BL/10 mice and the *mdx* model of Duchenne muscular dystrophy (DMD).
- In wild-type mice, local injection of ACE-083 into the left gastrocnemius (twice weekly x 4 wks, Fig. 1) or tibialis anterior (TA) muscle (twice weekly x 3 wks) led to localized hypertrophy as well as a dose-dependent increases in muscle mass[1] (Fig. 2) and absolute force[2] (Fig. 3).
- ACE-083 also selectively increased muscle mass in the injected muscle of *mdx* mice[3] (Fig. 4 and 5).
- Together these data support the clinical evaluation of ACE-083 in human subjects.

ACE-083 in Wild Type Mice

Fig. 1: ACE-083 Increased Gastrocnemius Muscle Mass in WT Mice by Hypertrophy Without Hyperplasia

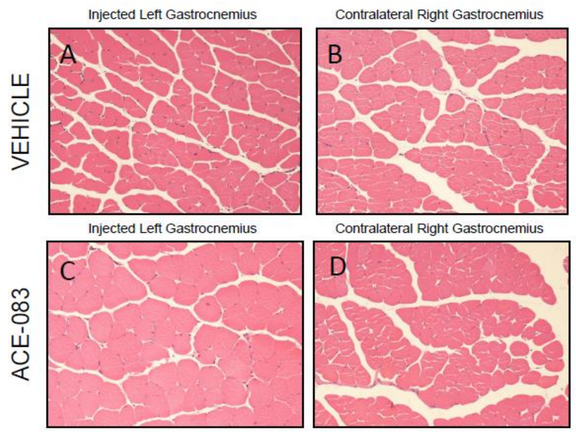


Fig. 2: ACE-083 Led to Significant Dose-Dependent Percent Increases in Gastrocnemius Muscle Mass in WT Mice

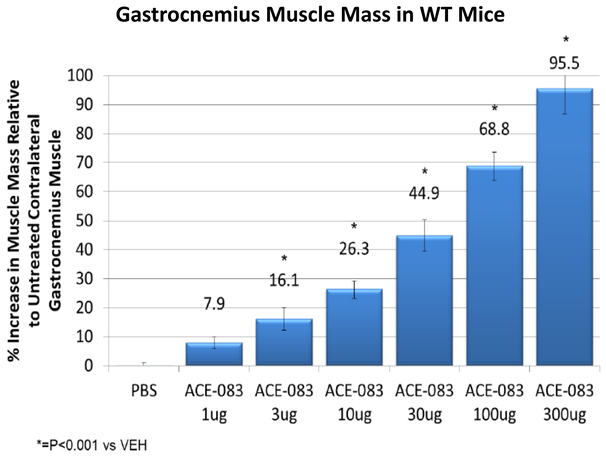
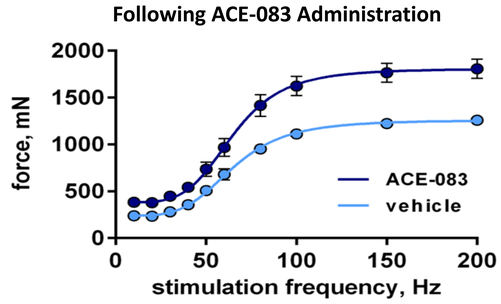


Fig. 3: Increase in Absolute Force of the Tibialis Anterior of WT Mice Following ACE-083 Administration



Absolute force was greater for the ACE-083 TA at all stimulation frequencies compared to vehicle treated TA. The force at 65 ± 3 Hz (the inflexion point of the curve) was 41% greater in ACE-083 vs vehicle treated TA.

ACE-083 in Wild Type and *mdx* (DMD Model) Mice

Fig. 4: ACE-083 Increased Gastrocnemius Muscle Mass Locally in Both WT and *mdx* Mice

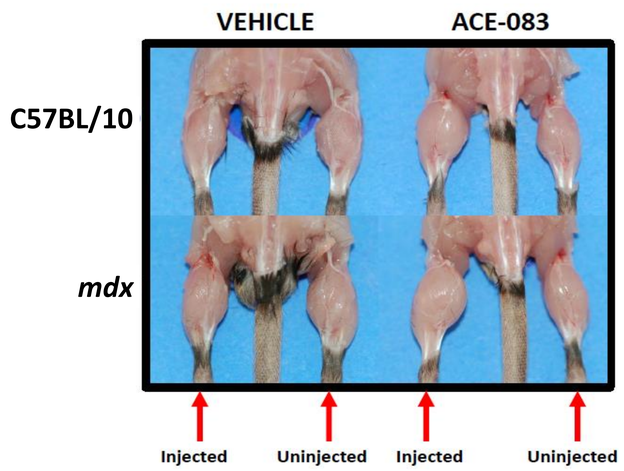
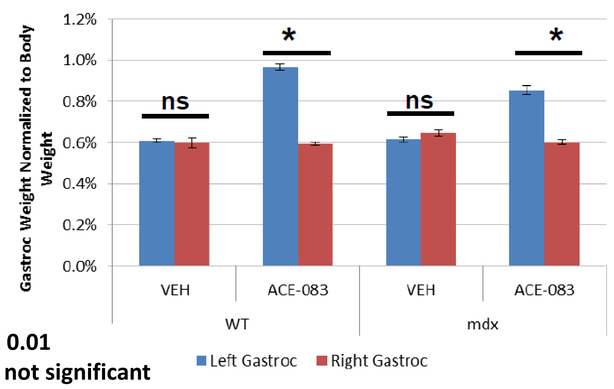


Fig. 5: ACE-083 Increased Muscle Mass in the Injected, but not in the Uninjected Leg in WT and *mdx* Mice



*p ≤ 0.01
ns = not significant

A083-01 Phase 1 Study Methods

- A083-01 is an ongoing single-center, randomized, double-blind, placebo-controlled, dose escalation study in healthy post-menopausal women.
- **Primary Objective:**
  - Characterize safety and tolerability of single and repeated doses of ACE-083.
- **Secondary Objectives:**
  - Estimate systemic exposure.
  - Evaluate pharmacodynamic effects, including changes in muscle volume as measured on MRI and changes in strength as measured by hand-held dynamometer and Biodex fixed system.
- Seven cohorts of 8 subjects each will be randomized to receive ACE-083 (n=6) or placebo (n=2 or 3), administered as 2 or 4 injections along the length of the right rectus femoris (RF, cohorts 1-5) or right tibialis anterior (TA, cohorts 6-7) (Table 1)

Table 1: Dosing Levels and Dosing Days for Cohorts 1-7

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

Fig. 6: ACE-083 Approximate RF Injection Sites for Cohorts 1, 2 and 4 (A) and Cohorts 3 and 5 (B)

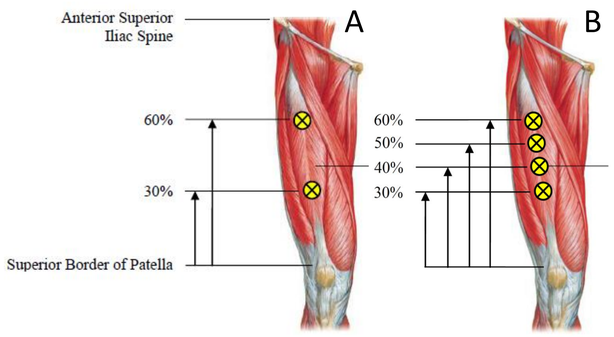
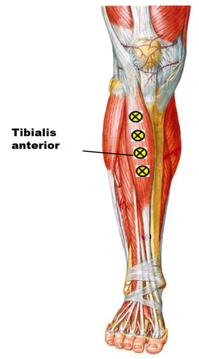


Fig. 7: ACE-083 Approximate TA Injection Sites for Cohorts 6 and 7



- MRIs were collected pre-dose as well as 3 weeks and 8 weeks post-last dose (Table 2)

Table 2: MRI Assessments in Relation to Dosing

Number of Doses	Assessment	Day 1	Day 22	Day 43	Day 57	Day 78
Single Dose	Dosing	X				
	MRI	X (pre-dose)	X		X	
Multiple Doses	Dosing	X	X			
	MRI	X (pre-dose)		X		X

Conclusions

- ACE-083 is a locally-acting investigational protein therapeutic that acts as a ligand trap for GDF8 and other negative regulators of muscle mass
- Mouse models have shown that local injection of ACE-083 increases muscle mass and force in the injected muscle
- A083-01 is an ongoing Phase 1 study evaluating ACE-083 administration into the RF and TA in healthy volunteers

References

1. 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
2. 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
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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