

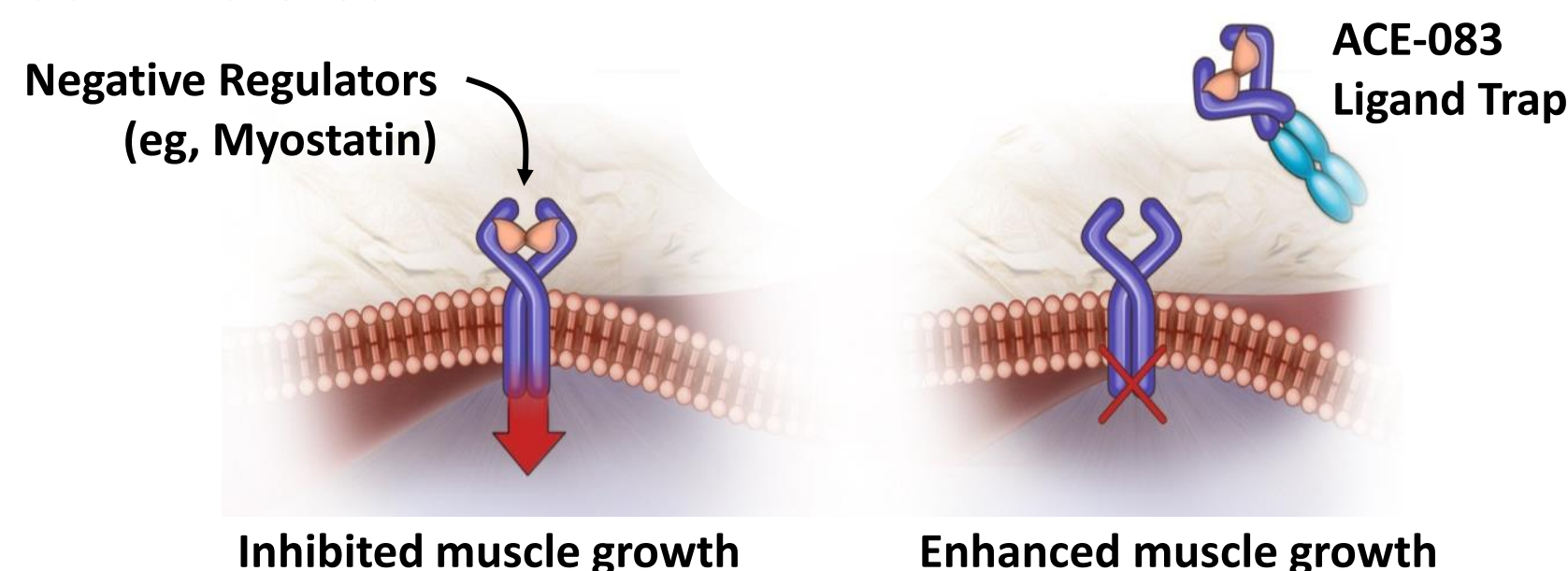
ACE-083, a Locally-Acting TGF-Beta Superfamily Ligand Trap, Increases Muscle Volume of Targeted Muscle: Preliminary Results from a Phase 1 Dose Escalation Study in Healthy Volunteers

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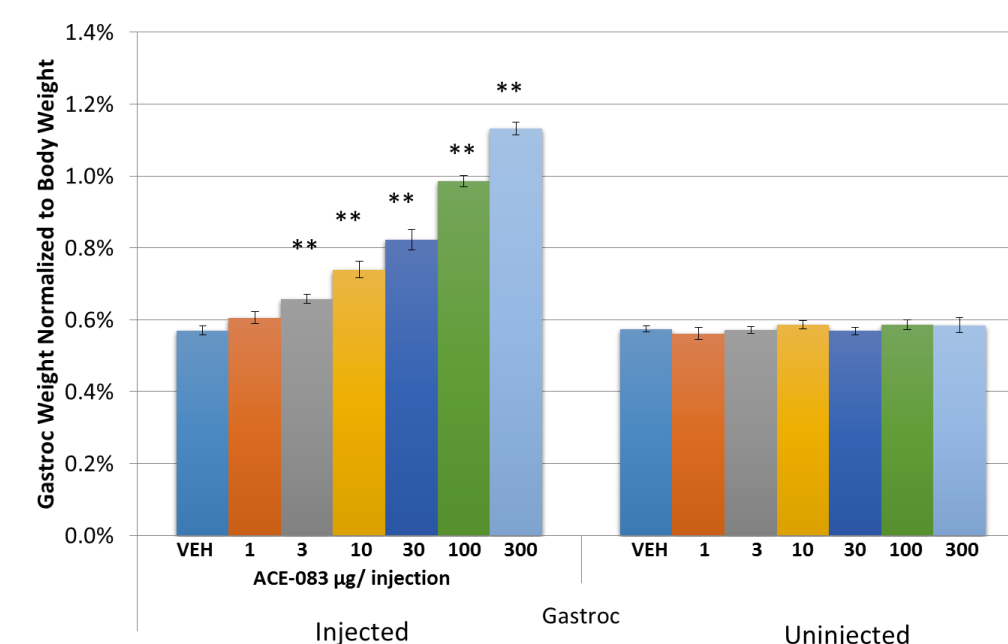
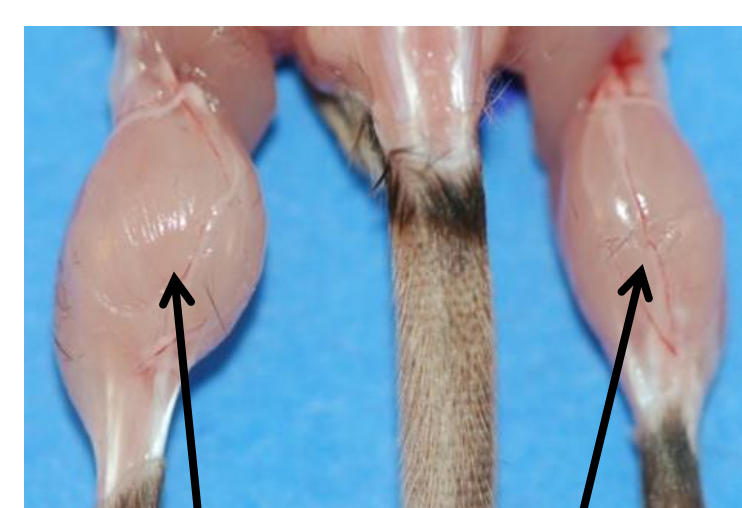
Background

- ACE-083 is a locally acting 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

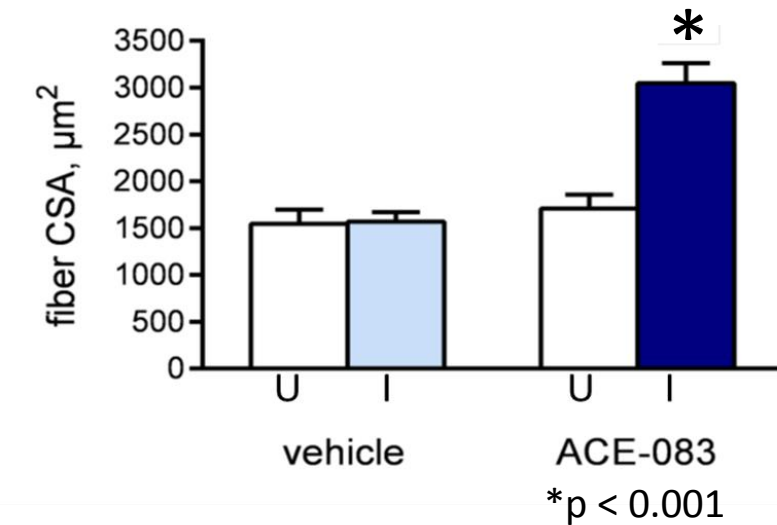
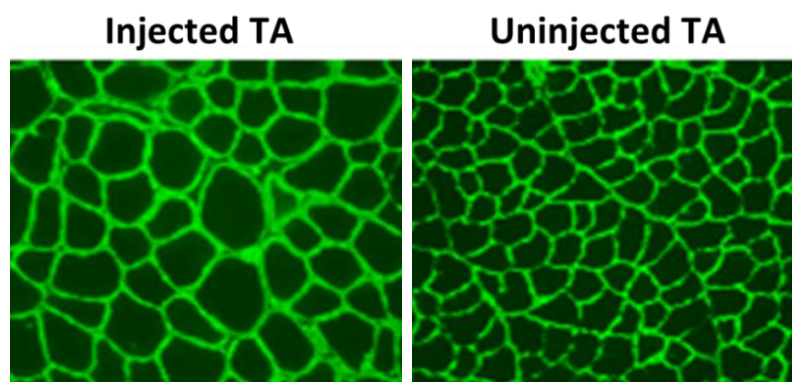


Non-Clinical Studies

- In wild type (WT) mice dosed 2x/week for 1 month into the left gastrocnemius muscle, ACE-083 increased muscle mass locally in target muscle in a dose dependent fashion
- ACE-083 increased muscle fiber cross-sectional area



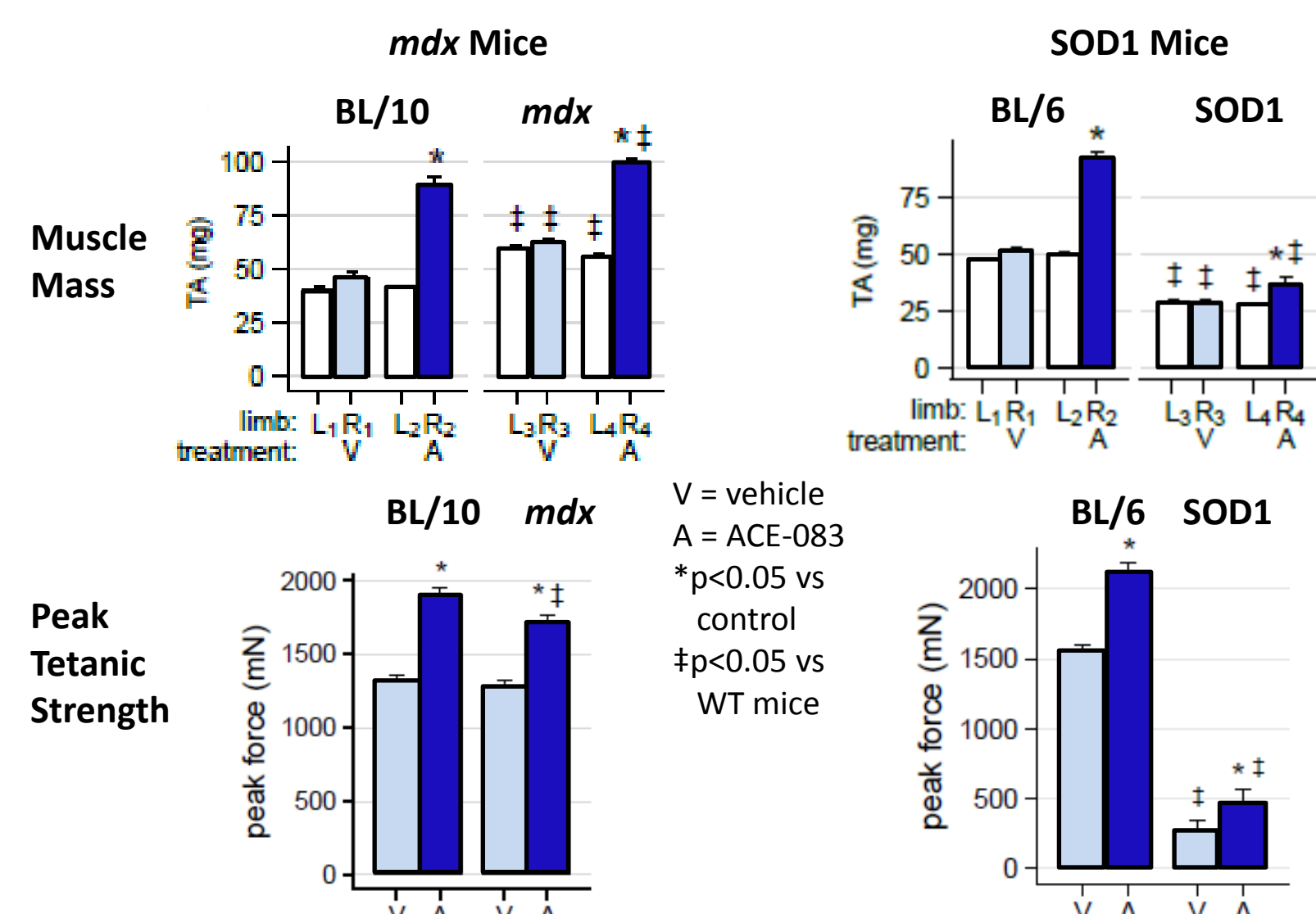
**p<0.05 vs vehicle and vs uninjected leg



TA = tibialis anterior

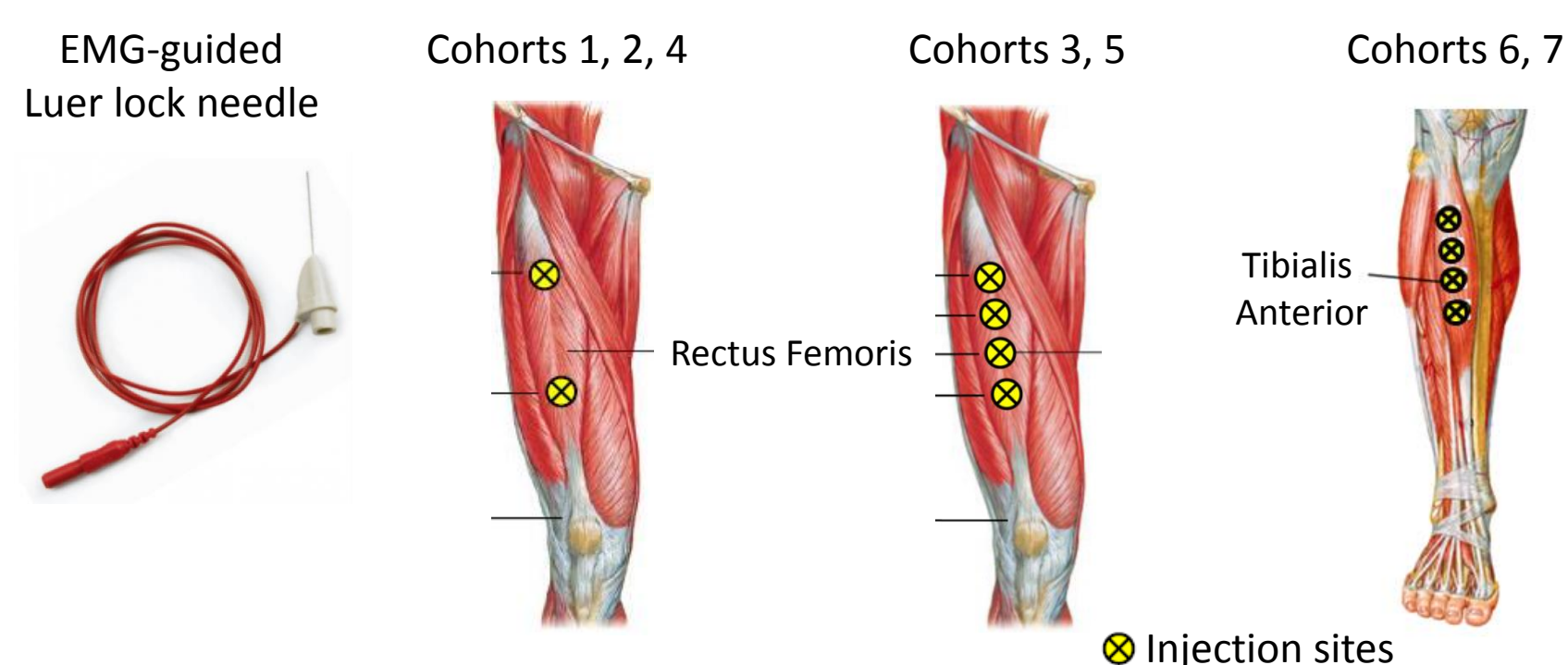
Animal Models

- ACE-083 increased tibialis anterior muscle mass and peak tetanic strength in mouse models of Duchenne muscular dystrophy (*mdx*) and amyotrophic lateral sclerosis (SOD1)



Phase 1 Clinical Study

- Randomized, double-blind, placebo-controlled, dose-ranging study in healthy post-menopausal women
- 1^o Objective: Safety and tolerability of single and multiple doses of ACE-083 as a local muscle injection
- 2^o Objectives: Estimate systemic exposure of ACE-083; evaluate pharmacodynamic effects including muscle volume MRI and muscle strength (fixed and hand-held)



Study Design

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

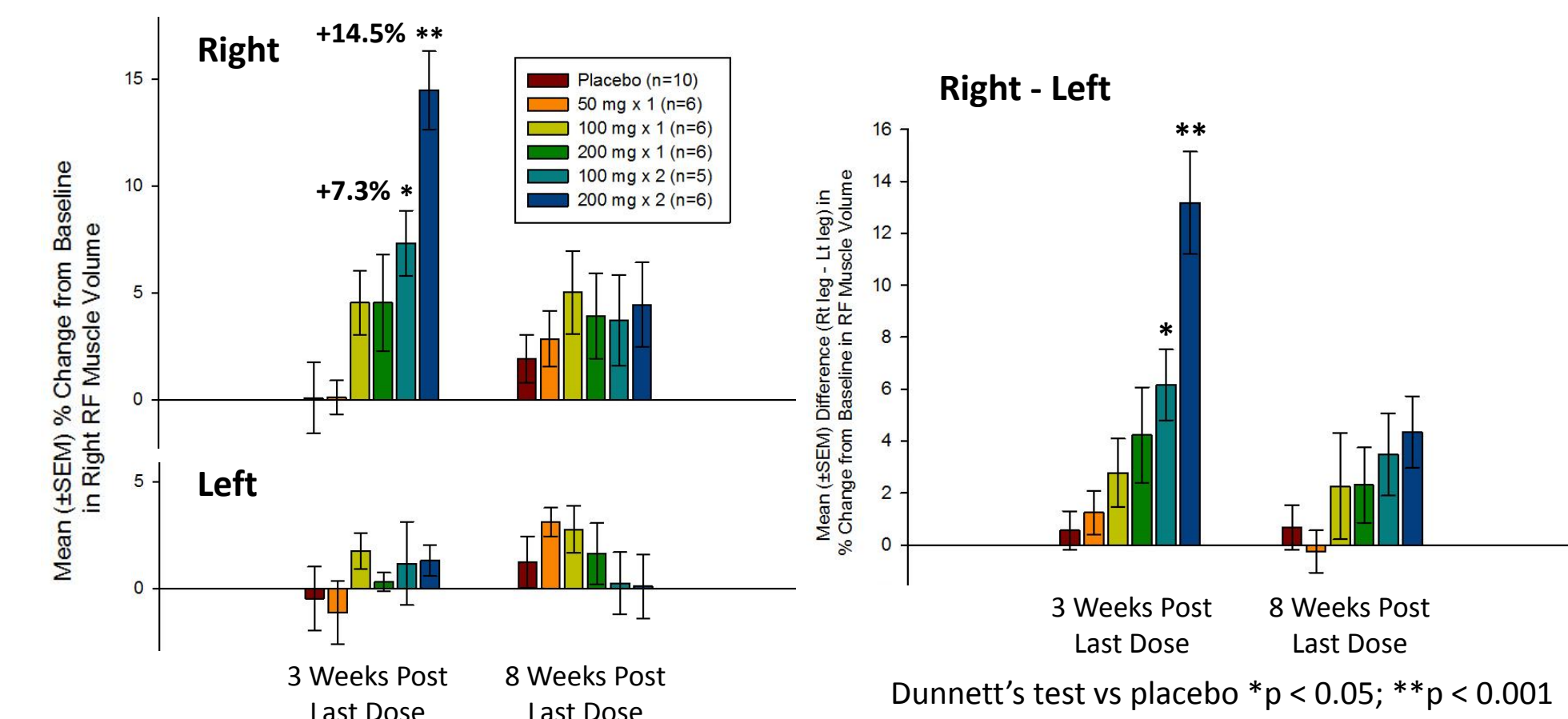
Safety Results (Cohorts 1-5)

- 40 post-menopausal women (97.5% white); median (range) age 56 (45-72) yr; BMI 25.1 (19.2-31.5) kg/m²
- 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 at all dose levels (including placebo); independent of dose or number of injections

Preferred Term n (%)	Placebo (n = 10)	RF Single Dose (mg)			RF Multiple Dose (mg)		ACE-083 (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)

Pharmacodynamic Results (Cohorts 1-5)

- ACE-083 increased rectus femoris (RF) muscle volume (MRI) with no effect on contralateral uninjected muscle
- 3 weeks after last dose, right RF muscle volume increased by 7.3% (*p<0.05) and 14.5% (**p<0.001) in Cohorts 4, 5



- Changes in total quadriceps strength did not correlate with RF muscle volume changes in these healthy subjects

Summary/Conclusions

- ACE-083 is a locally-acting protein therapeutic that acts as a ligand trap for GDF8 (myostatin) and other negative regulators of muscle mass
- ACE-083 injected into RF muscle in healthy volunteers had a favorable safety profile and resulted in dose-dependent and significant increases in RF muscle volume
- These data support further studies in muscle diseases such as facioscapulohumeral muscular dystrophy (FSHD)

References

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- Mulivor et al. International Congress on Neuromuscular Diseases, 2014
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- Glasser et al. Conf. on Cachexia, Sarcopenia & Muscle Wasting, 2015
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clinicaltrials.gov NCT02257489

