An Ongoing Phase 2 Study Evaluating the Safety, Efficacy, and Pharmacokinetics of ACE-083 in Patients with CMT1 and CMTX

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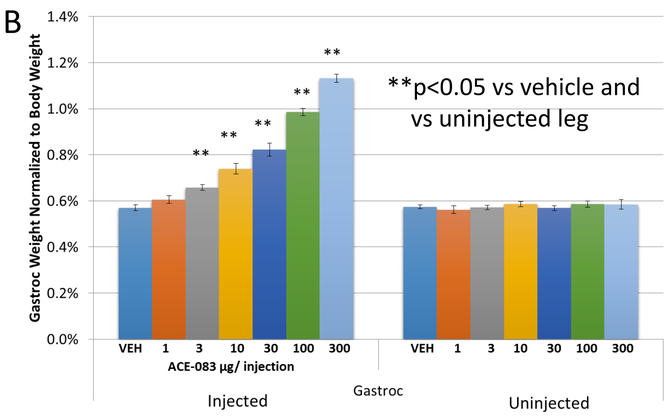
Background

- ACE-083 is a locally-acting investigational protein therapeutic that blocks GDF8 (myostatin) and other TGF-β superfamily inhibitors of skeletal muscle growth; it is designed to increase muscle mass and strength selectively in the muscle into which the drug is administered
- In wild type (WT) mice (Fig 1), local injection of ACE-083 2x/wk for 4 wks into the gastrocnemius muscle led to localized (Fig 1A), dose-dependent (Fig 2B) hypertrophy and increases in strength of the target muscle
- In mouse models of myogenic (*mdx*) and neurogenic (SOD1, CMT) muscle disease, local injection of ACE–083 into the tibialis anterior 2x/wk for 4 wks increased muscle mass and peak tetanic strength

Figure 1: Effect of ACE-083 on Muscle Size in Wild Type Mice

A

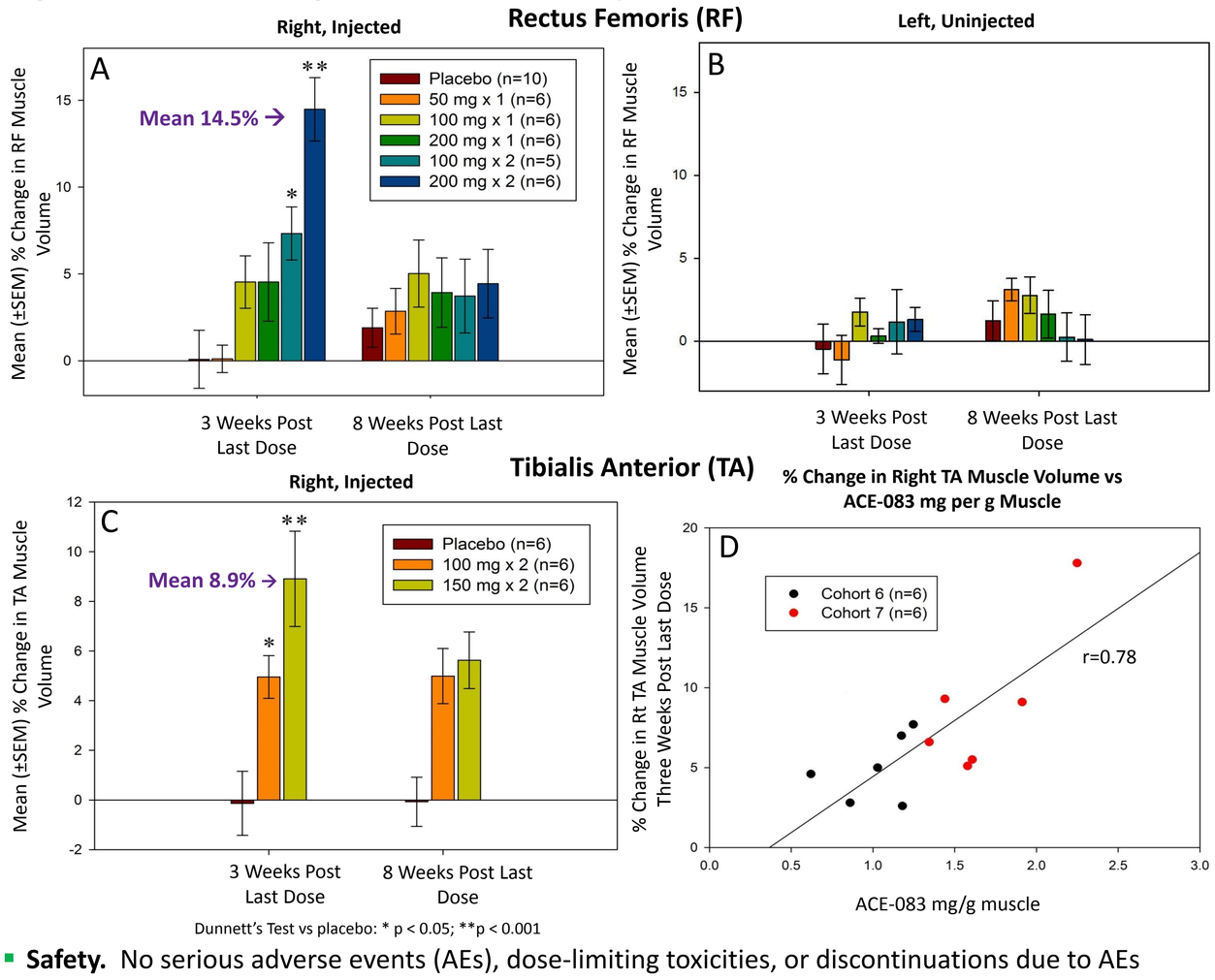
B



Phase 1 Healthy Volunteer Study Results

- In a phase 1, double-blind, placebo-controlled, dose-escalation study in 58 healthy post-menopausal women, ACE-083 was unilaterally injected into the right rectus femoris (RF) or tibialis anterior (TA) muscle under EMG guidance for one or two doses (Day 1 and Day 22) (NCT02257489)
- At 3 weeks after the last dose of ACE-083, mean increases in muscle volume of the right RF and the right TA were 14.5% (Fig 2A) and 8.9% (Fig 2C), respectively, at the highest dose levels tested ($p<0.001$ vs placebo for each muscle) with no effect in the contralateral uninjected muscle (Fig 2B)
- Increases in muscle volume correlated with dose administered of ACE-083 in mg/g of muscle (Fig 2D)
- No consistent changes were observed in knee extension (RF) or dorsiflexion (TA) strength in these healthy subjects

Figure 2: Percent Change in Muscle Volume by MRI



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

- **Safety.** No serious adverse events (AEs), dose-limiting toxicities, or discontinuations due to AEs
- All AEs were grade 1-2, transient, and most commonly injection-site related
- AE incidence was similar in placebo, ACE-083 groups; myalgia and injection site hemorrhage were more frequent in ACE-083 arms

Table 1: Related Adverse Events in ≥10% of ACE-083 RF or TA Group in Phase 1 Study

Preferred Term n (%)	Rectus Femoris		Tibialis Anterior	
	Placebo (N=10)	ACE-083 (N=30)	Placebo (N=6)	ACE-083 (N=12)
Pain in extremity	2 (20)	6 (20)	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)
Musculoskeletal stiffness	1 (10)	1 (3)	1 (17)	2 (17)
Arthralgia	0	1 (3)	4 (67)	2 (17)
Injection site reaction	1 (10)	5 (17)	0	1 (8)
Limb discomfort	2 (20)	3 (10)	0	1 (8)
Injection site hemorrhage	0	4 (13)	0	1 (8)
Myalgia	0	3 (10)	0	1 (8)
Muscle twitching	3 (30)	8 (27)	0	0

Phase 2 CMT Clinical Study Design

- Key Inclusion Criteria:
  - Patients age ≥ 18 yr with clinical signs/symptoms of CMT1 or CMTX, genetically confirmed for patient or first-degree relative
  - Mild to moderate weakness in left and right ankle dorsiflexion as determined by Medical Research Council (MRC) manual muscle testing (MMT) score (4- to 4+)
- Treatment: ACE-083 injected locally, bilaterally into TA every 3 weeks X 5 doses (3 months)

Figure 3: Phase 2 CMT Study Design

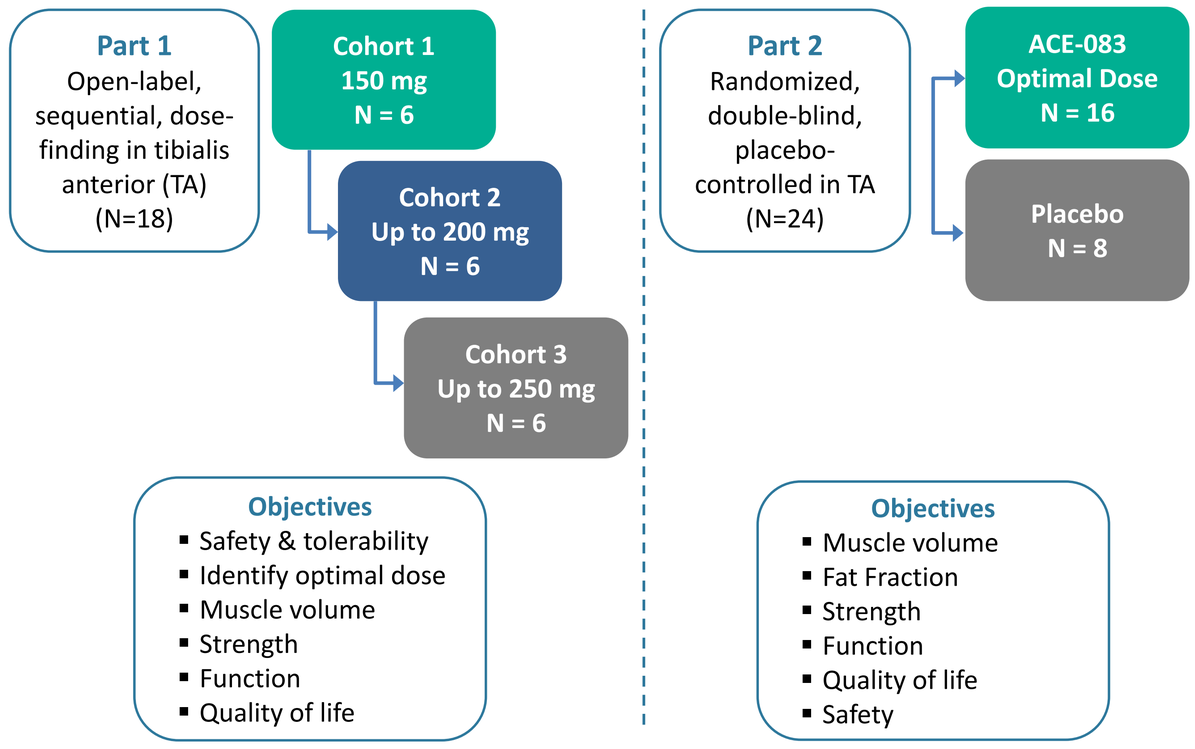
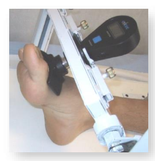


Table 2: Study Assessments and Endpoints

	Study Assessment	Pharmacodynamic Endpoint
Imaging	• Muscle Volume (MRI) • Fat Fraction (MRI)	• Percent change in muscle volume/ IM fat of injected muscle
Strength	• Hand-Held Dyna-myometry (with fixation device) 	• Percent change in strength of injected muscle by quantitative muscle testing
Function	• 6MWT • 10m walk/run • Berg Balance Scale • Gait analysis	• Change/percent change in functional parameters
Investigator-/ Patient-Reported Outcomes	• CMTES2 • CMT-HI (QoL)	• Change in CMT Examination Score (Version 2) • Change in CMT Health Index score

Summary/Conclusions

- ACE-083 is a locally-acting protein therapeutic that promotes muscle growth
- Its mechanism of action is well-suited for mild-moderate CMT due to the focal involvement of specific muscles
- Results of a phase 1 study in healthy volunteers demonstrated that ACE-083 was generally safe and well-tolerated and resulted in marked, dose-dependent increases in muscle volume by MRI after 1 or 2 doses
- These results support the evaluation of ACE-083 in an ongoing phase 2 study in patients with CMT, targeting ankle dorsiflexion weakness (foot drop), as well as in study of patients with FSHD
- Please refer to poster P3_72 (Li J et al.) entitled "ACE-083, A Locally-Acting GDF/Activin Ligand Trap, Augments Dorsiflexor Muscle Function in a Murine Model of CMT Disease"

References/Acknowledgements

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

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For trial updates and list of sites, please go to:
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