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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**ACE-083 Background**

- TGF-β superfamily ligands such as myostatin (GDF8) and activins are known negative regulators 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 protein therapeutic that binds GDF8 and activins and inhibits SMAD 2/3 signaling

**Pre-Clinical Results**

- In wild type (WT) mice, ACE-083 led to increased tibialis anterior (TA) muscle fiber cross-sectional area (CSA)1
- In both WT and the mdx mouse model of Duchenne muscular dystrophy (DMD), local injections of ACE-083 led to dose-dependent increases in muscle mass2,3
- Preclinical studies showed limited systemic exposure, confirming the local activity of specific muscle injections

**A083-01 Study Design**

- A083-01 is an ongoing, single-center, randomized, double-blind, placebo-controlled, dose-ranging study in healthy post-menopausal women
- Primary Objective: Characterize the safety and tolerability of single and repeated doses of ACE-083
- Secondary Objectives: Estimate systemic exposure and evaluate pharmacodynamic effects, including changes in muscle volume as measured on MRI and changes in strength as measured by fixed system and hand-held dynamometry
- Five cohorts of 8 subjects were randomized to ACE-083 (n=6) or matched placebo (n=2), administered as 2 or 4 injections along the length of the right rectus femoris (RF). Two additional cohorts of 9 subjects (6:3) are ongoing with administration to the right TA (Table 1)

**Efficacy Results: Cohorts 1-5 (cont.)**

- **ACE-083 is a locally-acting protein therapeutic that acts as a ligand trap for GDF8 and other negative regulators of muscle mass**
- In preclinical models, local injection of ACE-083 increased muscle mass and force in the injected muscle
- Study A083-01 is an ongoing Phase 1 study evaluating ACE-083 administration into the RF and TA in healthy volunteers (www.clinicaltrials.gov/ct2/show/NCT02257489)
- Results from Cohorts 1-5 of this Phase 1 study demonstrate that local administration of ACE-083 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 myogenic and/or neurogenic diseases, including FSHD and DMD

**References**

1. 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