A Phase 1 Healthy Volunteer Study of ACE-083, a Novel, Locally-Acting Muscle Agent

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Background

- ACE-083 is a locally-acting investigational 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.
- In wild type (WT) mice, local injection of ACE-083 2x/week for 1 month into the left gastrocnemius muscle led to localized, dose-dependent hypertrophy in the target muscle and increases in strength.

Phase 1 Clinical Study Objectives

- Randomized, double-blinded, placebo-controlled, dose-ranging study in healthy post-menopausal women
- Primary objective: Safety and tolerability of single and multiple doses of ACE-083 as a local muscle injection
- Secondary objectives: Estimate systemic exposure of ACE-083; evaluate pharmacodynamic effects including muscle volume by MRI and strength by hand-held dynamometer and fixed system

Study Design

- ACE-083 (or placebo) was administered under EMG guidance using a Myoslect 26G needle as a single dose (day 1) or as two doses (day 1 and day 22) to the right side only
- Each dose was divided into 2 or 4 injections
- Cohorts 1-5: rectus femoris (RF); Cohorts 6-7: tibialis anterior (TA)

Efficacy Results

- At 3 weeks after last dose, ACE-083 increased muscle volume of the right RF up to 14.5% and the right TA up to 8.9% at the highest dose levels tested (p<0.001 vs placebo for each muscle) with no effect in the contralateral uninjected muscle
- Increases in muscle volume correlated with dose administered of ACE-083 in mg/kg of muscle
- No consistent changes were observed in knee extension (RF) or dorsiflexion (TA) strength in these healthy subjects

Safety Results

- 58 post-menopausal women were enrolled into the study
- 42 were treated with ACE-083
  - Median (range) age 56 (45-70) yr; BMI 25.9 (19.2-31.6) kg/m2; 98% white
  - No serious adverse events (AEs), dose-limiting toxicities, or discontinuations due to AE
  - All AEs were grade 1-2, transient, and most commonly injection-site related
  - Similar AE incidence was observed in placebo and active groups

Adverse Events at Least Possibly Related to Study Drug in ≥10% of Subjects

- RF (Cohorts 1-5) vs TA (Cohorts 6-7)
  - Pain in extremity
  - Injection site discomfort
  - Muscle tightness
  - Discomfort
  - Injection site oedema
  - Myalgia
  - Musculoskeletal stiffness
  - Myalgia
  - Injection site reaction
  - Injection site hemorrhage
  - Total discomfort
  - Muscle twitching

Summary/Conclusions

- ACE-083, a locally-acting investigational protein therapeutic that acts as a ligand trap for GDF8 (myostatin) and other negative regulators of muscle mass, was injected into the RF muscle or TA muscle in healthy volunteers.
- ACE-083 had a favorable safety profile and resulted in dose-dependent and significant increases in muscle volume.
- These data support further clinical studies of ACE-083 to potentially improve strength and function in neuromuscular diseases; a phase 2 study in facioscapulohumeral muscular dystrophy (FSHD) will be initiated in 2016.

References

- Mulvih et al. World Muscle Society, 2014
- Mulvih et al. INCMD, 2014
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- Attie et al. INCMD, 2016

% Change in Muscle Volume by MRI

- Rectus Femoris (RF)
- Tibialis Anterior (TA)

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