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

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)

Study Design

- **Study Design**: Estimate systemic exposure of ACE-083; evaluate pharmacodynamic effects including muscle volume MRI and muscle strength (fixed and hand-held)
- **Pharmacodynamic Results**: ACE-083 increased rectus femoris (RF) muscle volume (MRI) with no effect on contralateral un.injected muscle
- **Phase 1 Clinical Study**: Randomized, double-blind, placebo-controlled, dose-ranging study in healthy post-menopausal women
- **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**

Non-Clinical Studies

- ACE-083 increased muscle fiber cross-sectional area

Pharmacodynamic Results (Cohorts 1-5)

- **ACE-083 increased rectus femoris (RF) muscle volume (MRI) with no effect on contralateral un injected 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**

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**

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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