# ACE-083, a Locally-Acting Muscle Agent, Increases Muscle Volume in Healthy Volunteers

Kenneth M Attie, MD[1], Chad E Glasser[1], Michael R Gartner, MD[2], Brian L Boes, MD[3], R Scott Pearsall[1], Xiaosha Zhang[1], Jade Sun[1], Brian Vidal[1], Ashley Bellevue[1], Monty Hankin[1], and Matthew L Sherman, MD[1]

*[1]Acceleron Pharma, Cambridge, MA; [2]Celerion, Lincoln, NE; [3]Bryan Health, Lincoln, NE*

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## Background

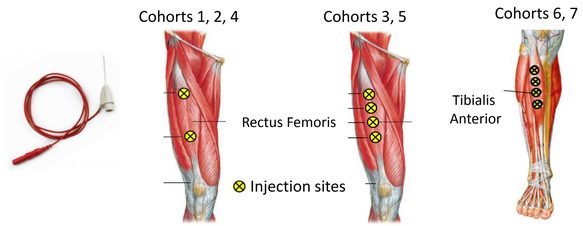
- ACE-083 is a locally-acting investigational protein therapeutic that binds GDF8 (myostatin) and other ligands in the TGF-β superfamily that negatively regulate skeletal muscle.
- ACE-083 was designed to increase muscle mass and strength selectively in the muscle into which the drug is administered.
- 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.
- In mouse models of both myogenic and neurogenic disease, local injection of ACE-083 into the tibialis anterior 2x/week for 4 weeks increased muscle mass as well as peak tetanic strength.

## Phase 1 Clinical Study Objectives

- Randomized, double-blind, 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 handheld dynamometer and fixed system

## Study Design

- ACE-083 (or placebo) was administered under EMG guidance using a MyoJect 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)




| Injected Muscle | Cohort | Dosing Day(s) | Dose (mg) | # Injections mL per Dose | # Subjects | |
|---|---|---|---|---|---|---|
| | | | | | ACE-083 | Placebo |
| Rectus Femoris | 1 | 1 | 50 | 2 x 0.75 | 6 | 2 |
| | 2 | 1 | 100 | 2 x 1.0 | 6 | 2 |
| | 3 | 1 | 200 | 4 x 1.0 | 6 | 2 |
| | 4 | 1, 22 | 100 | 2 x 1.0 | 6 | 2 |
| | 5 | 1, 22 | 200 | 4 x 1.0 | 6 | 2 |
| Tibialis Anterior | 6 | 1, 22 | 100 | 4 x 0.5 | 6 | 3 |
| | 7 | 1, 22 | 150 | 4 x 0.75 | 6 | 3 |
| | | | | Total: | 42 | 16 |

## Safety Results

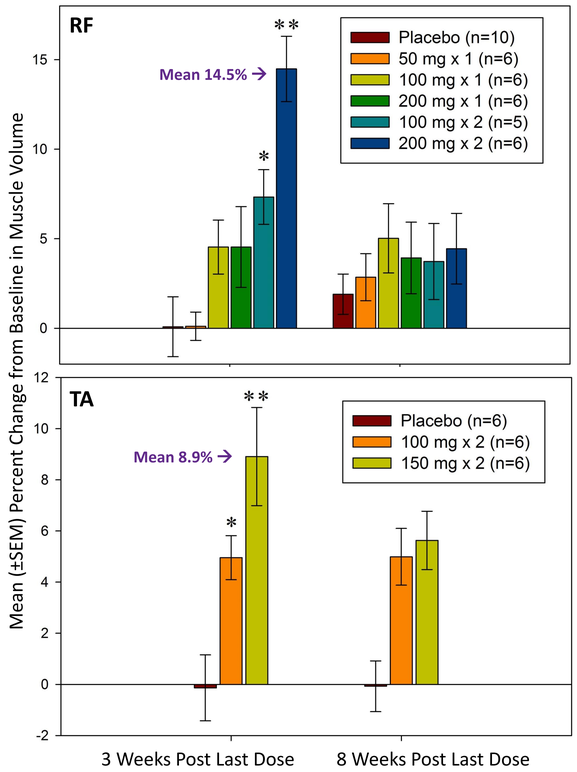
- 58 post-menopausal women were enrolled into the study
- 42 were treated with ACE-083
  - Median (range) age 56 (45-70) yr; BMI 25.9 (19.2-31.6) kg/m$^2$; 98% white
- No serious adverse events, dose-limiting toxicities, or discontinuations due to adverse events (AEs)
- All AEs were grade 1-2, transient,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

| Preferred Term n (%) | RF (Cohorts 1-5) | | TA (Cohorts 6-7) | |
|---|---|---|---|---|
| | Placebo (n=10) | ACE-083 (n=30) | Placebo (n=6) | ACE-083 (n=12) |
| Pain in extremity | 2 (20) | 7 (23) | 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) |
| Arthralgia | 1 (10) | 3 (10) | 4 (67) | 2 (17) |
| Musculoskeletal stiffness | 1 (10) | 4 (13) | 1 (17) | 2 (17) |
| Myalgia | 0 | 7 (23) | 0 | 2 (17) |
| Injection site reaction | 1 (10) | 5 (17) | 0 | 1 (8) |
| Injection site hemorrhage | 0 | 5 (17) | 0 | 1 (8) |
| Limb discomfort | 2 (20) | 3 (10) | 0 | 1 (8) |
| Muscle twitching | 3 (30) | 8 (27) | 0 | 0 |

## Efficacy Results

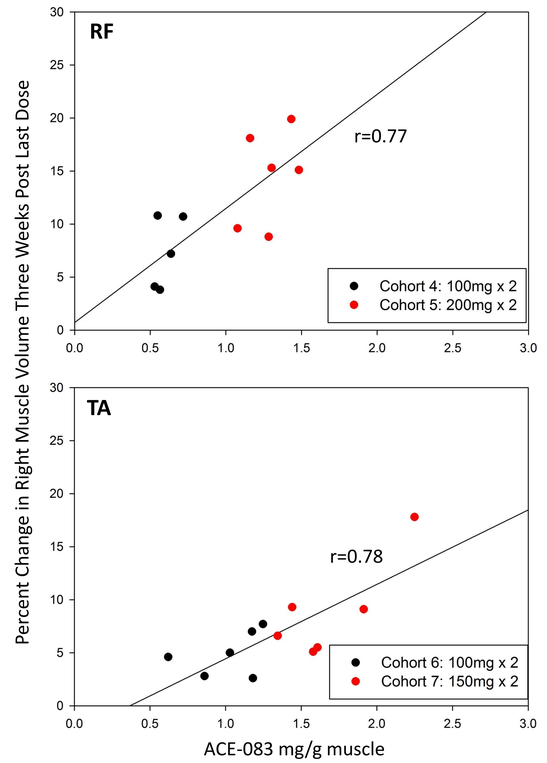
- At 3 weeks after last dose, ACE-083 increased muscle volume of the right RF up to 14.5% and the right TA up to 8.9% at the highest dose levels tested ($p<0.001$ vs placebo for each muscle) with no effect in the contralateral uninjected muscle.
- Increases in muscle volume correlated with dose administered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

### Percent Change in Volume of Injected (Right) Muscle




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

### Correlation Between Muscle Volume Increases and ACE-083 Dose




NOTE: 1 subject in Cohort 7 only received one dose of ACE-083, on Study Day 1

## 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 such as facioscapulohumeral muscular dystrophy (FSHD).

## References

- Mulivor et al. World Muscle Society, 2014
- Mulivor et al. International Congress on Neuromuscular Diseases, 2014
- Pearsall et al. World Muscle Society, 2015
- Glasser et al. Conf. on Cachexia, Sarcopenia, and Muscle Wasting, 2015
- Pearsall et al. MDA Clinical Conference, 2016

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