A Phase 2 study to evaluate ACE-083, a local muscle therapeutic, in patients with FSHD

Chad E Glasser PharmD[1], Ashley Leneus[1], Dawn Wilson[1], Matthew L Sherman, MD[1] and Kenneth M Attie, MD[1]

[1]Acceleron Pharma, Cambridge, MA

FSHD International Research Consortium

Boston, MA
November 2016

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, local injection of ACE-083 2x/wk for 4 wks into the gastrocnemius muscle led to localized, dose-dependent hypertrophy and increases in strength of the target muscle
- In mouse models of myogenic (*mdx*) and neurogenic (SOD1) muscle disease, local injection of ACE–083 into the tibialis anterior 2x/wk for 4 wks increased muscle mass and peak tetanic strength

Phase 1 Healthy Volunteer Clinical Study Design

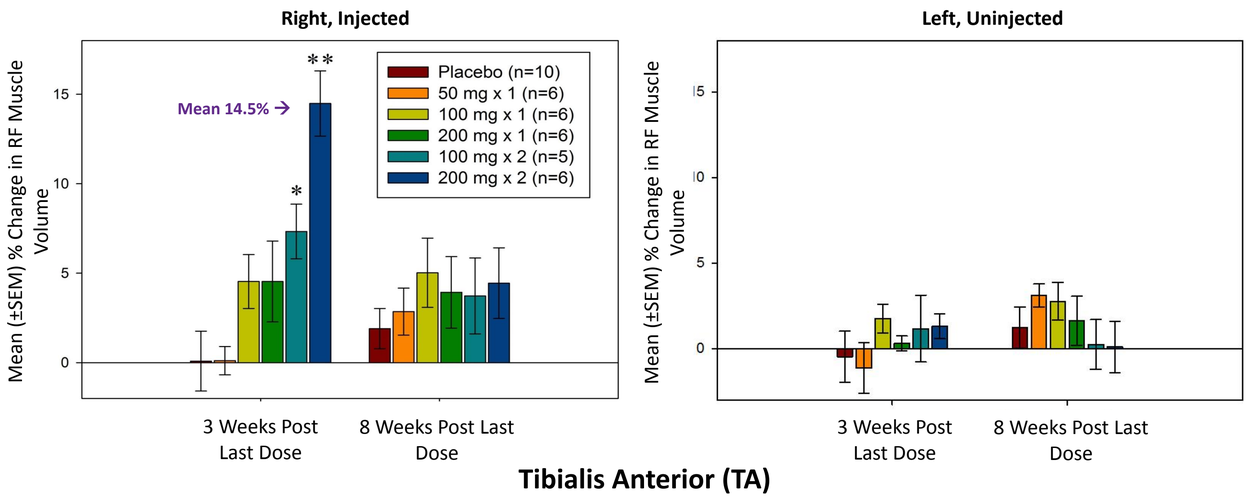
- In a recently completed phase 1, double-blind, placebo-controlled, dose-escalation study in 58 healthy post-menopausal women, ACE-083 was unilaterally injected into the right rectus femoris (RF) or tibialis anterior (TA) muscle under EMG guidance (NCT02257489)
- Cohorts 1-3 tested single doses of 50, 100, and 200mg in the RF; cohorts 4-5 tested two doses (day 1 and day 22) of 100 and 200mg in the RF; 2 to 4 injections/dose
- Cohorts 6-7 tested two doses (day 1 and day 22) of 100 and 150mg in the TA

Efficacy Results

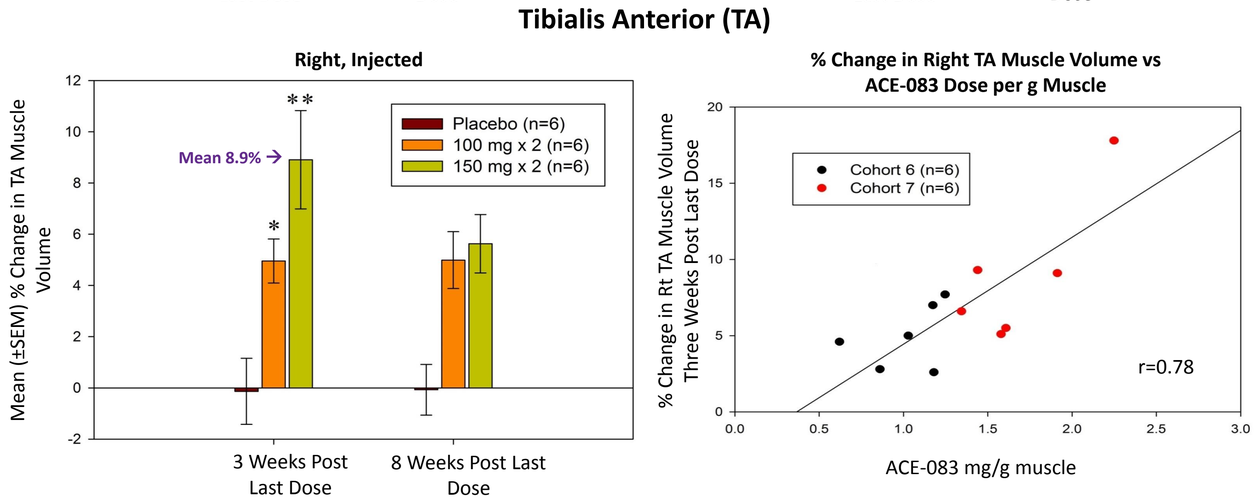
- At 3 weeks after the last dose of ACE-083, mean increases in muscle volume of the right RF and the right TA were 14.5% and 8.9%, respectively, at the highest dose levels tested ($p<0.001$ vs placebo for each muscle) with no effect in the contralateral uninjected muscle
- Increases in muscle volume 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

% Change in Muscle Volume by MRI

Rectus Femoris (RF)



Tibialis Anterior (TA)



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

Safety Results

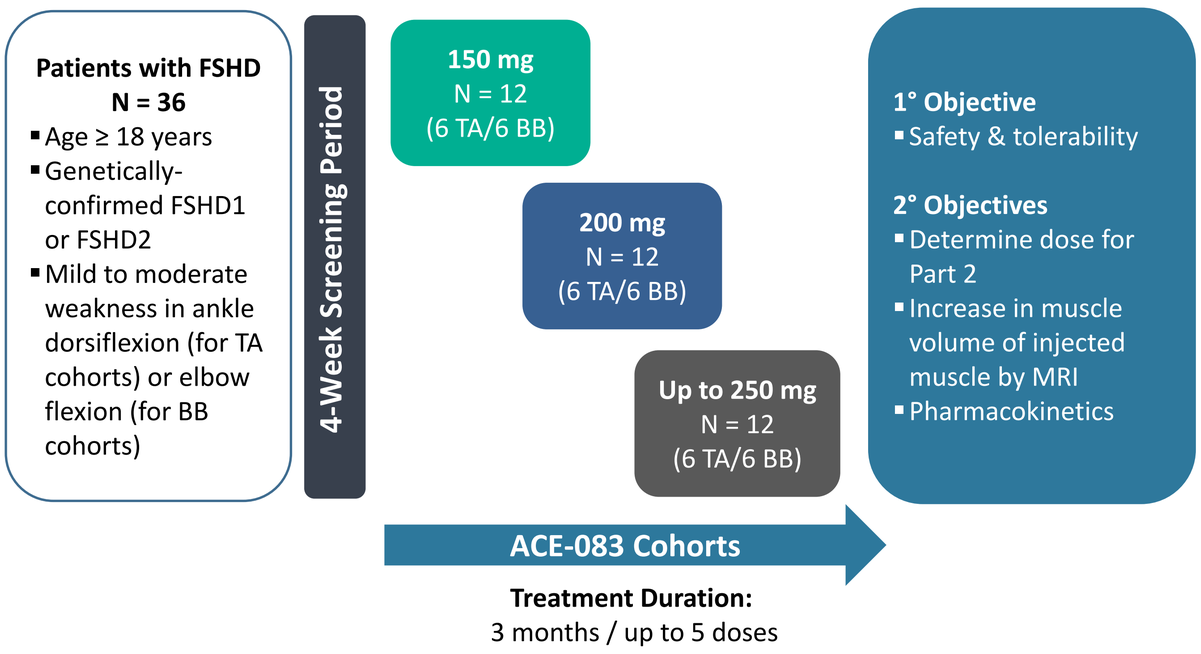
- No serious adverse events (AEs), dose-limiting toxicities, or discontinuations due to AEs
- All AEs were grade 1-2, transient, and most commonly injection-site related
- Similar AE incidence was observed in placebo and active groups

Related Adverse Events in ≥10% of Any Pooled-Active Group in Study A083-01

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)	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

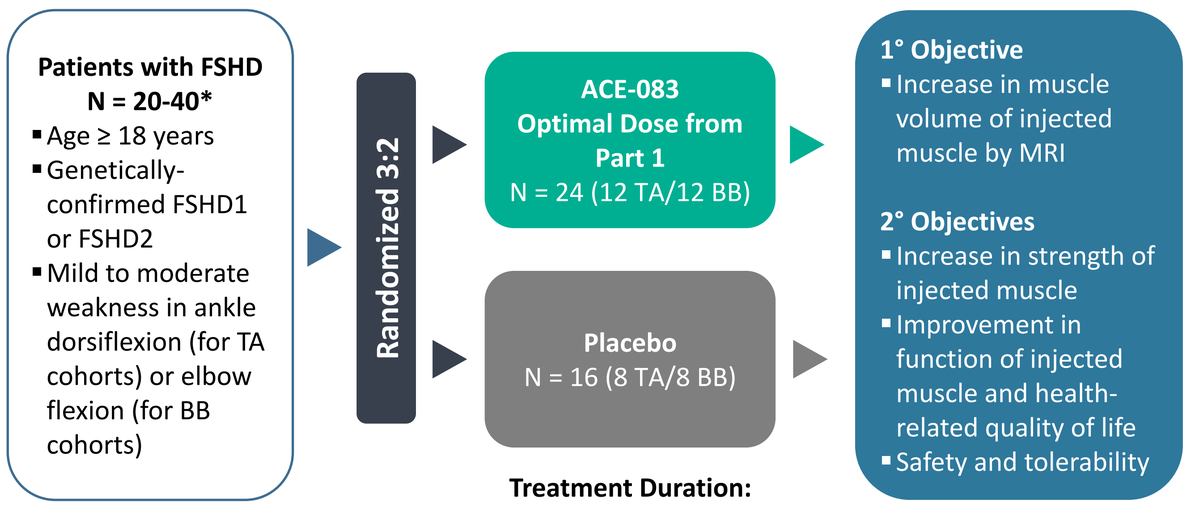
Phase 2 FSHD Clinical Study Design

- **Part 1**: open-label, sequential, dose-escalation cohorts in either the tibialis anterior (TA) or biceps brachii (BB), with objective to identify dose to be used in Part 2



Treatment Duration:
3 months / up to 5 doses

- **Part 2**: randomized, double-blind, placebo-controlled in one or both muscles, tibialis anterior (TA) and biceps brachii (BB) at the dose identified in Part 1



*N=20 if one muscle, N=40 if both muscles

Treatment Duration:
3 months / up to 5 doses

Phase 2 FSHD Clinical Study Assessments

- **Muscle volume**
  - Percent change from baseline in muscle volume of injected muscle by MRI
- **Strength**
  - Percent change from baseline in strength of injected muscle by quantitative muscle testing (fixed system and hand-held dynamometer)
- **Function**
  - TA: 10 meter walk/run, 4-stair climb, 6 minute walk test, gait analysis
  - BB: Performance of Upper Limb (PUL), FSHD-Health Index upper extremity sub-scores
- **Health-related quality of life**
  - FSHD-Health Index (FSHD-HI) questionnaire overall score

Summary/Conclusions

- ACE-083 is a locally-acting agent for the growth and regeneration of muscle
- Its mode of administration is well-suited for FSHD due to the focal involvement of specific muscles, often asymmetrically
- Results of the Phase 1 study in healthy volunteers demonstrated marked, dose-dependent increases in muscle volume by MRI after 1 or 2 doses
- These results support the evaluation of ACE-083 in a phase 2 study in patients with FSHD, targeting both upper arm and lower leg (foot drop) weakness (NCT02927080)

References

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

Sponsored by ACCELERON

clinicaltrials.gov NCT02927080