2020
FSHD Connect Classroom

Lessons Learned from the Phase 2 Study of ACE-083, a Locally-Acting Myostatin Inhibitor, in FSHD

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Disclosure Statement of Financial Interest

Dr. Attie:
Employee, shareholder: *Acceleron Pharma*

Dr. Statland:
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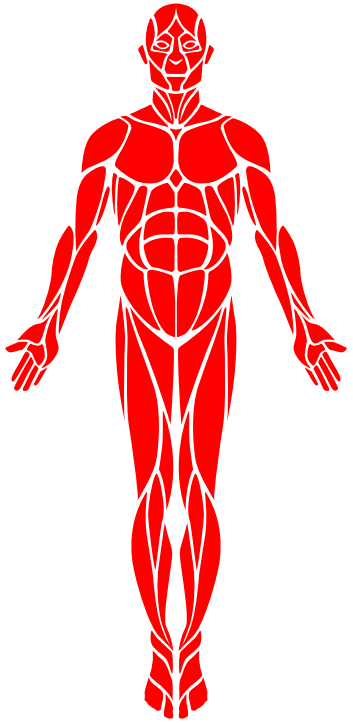
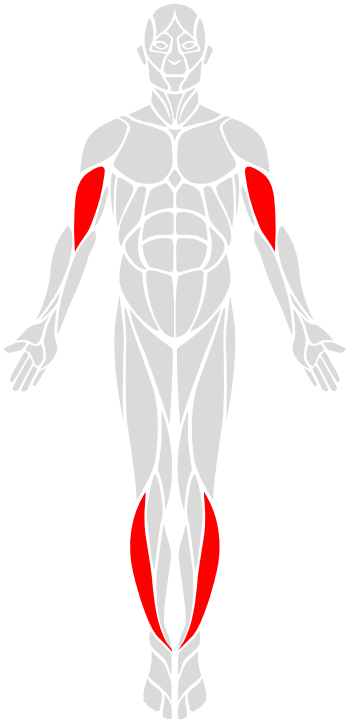
Advisory Board: *Acceleron Pharma, Avidity, Biogen, Dyne, Fulcrum, Sarepta, PTC*

Acceleron Pharma's Investigative Drugs Targeting Muscle



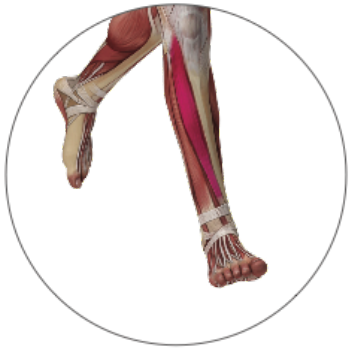
ACE-031, ACE-2494
Systemic Agents



ACE-083
Locally-acting Agent

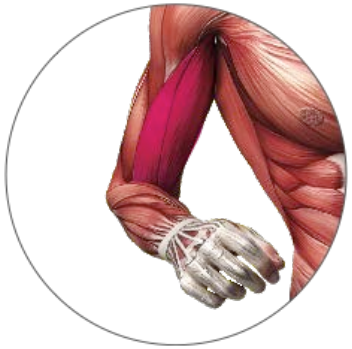
ACE-083 Targeted Biceps and Tibialis Anterior Weakness in FSHD

- Atrophy and weakness of these muscles can have a profound impact on activities of daily living and overall quality of life



Weakness of the Tibialis Anterior (TA)

- Causes foot drop
- Impairs mobility/walking
- Increases risk of falls



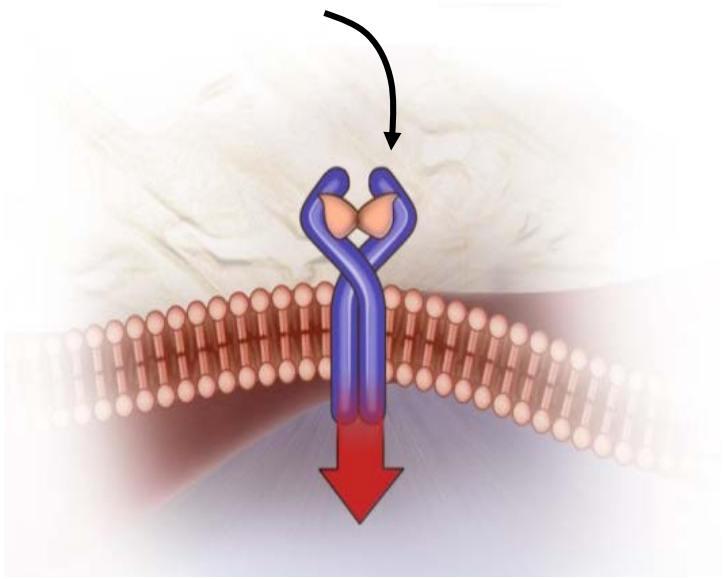
Weakness of the biceps brachii (BB)

- Limits ability to carry or lift objects
- Reduces ability to maintain personal hygiene
- Impairs ability to feed oneself

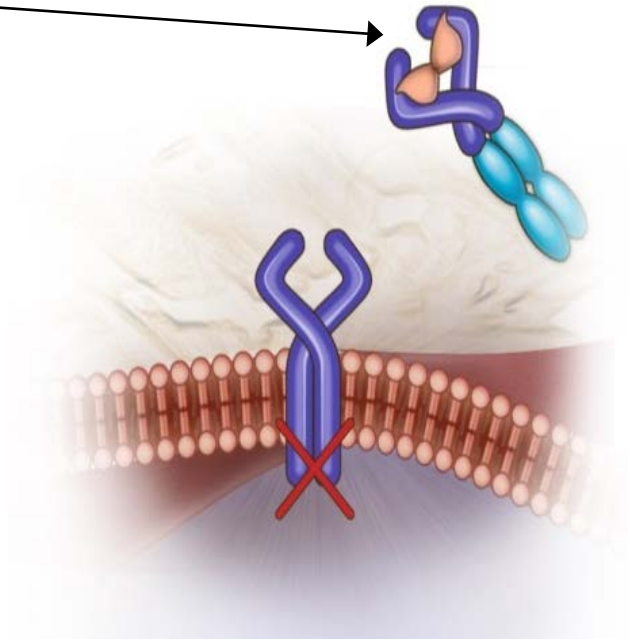
ACE-083: A Locally-Acting “Myostatin-Inhibitor” Muscle Therapeutic

Protein ligands in the TGF-β family including GDFs (myostatin) and activins

ACE-083, a modified version of a natural ligand trap, follistatin



Receptors on muscle cells



Muscle growth inhibited

Enhanced muscle growth

ACE-083 FSHD Phase 2 Study Design

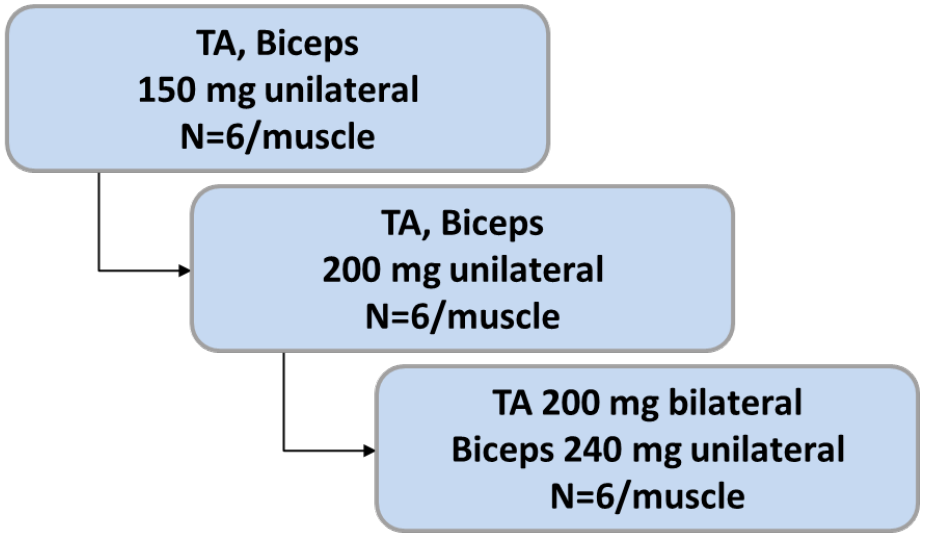
Key Eligibility Criteria

- Age ≥ 18 years
- Genetically-confirmed FSHD1 or FSHD2, or, genetically-confirmed first-degree relative and clinical signs/symptoms of FSHD
  - Mild to moderate weakness in ankle dorsiflexion or elbow flexion in the injected muscle
  - No concomitant medications potentially affecting muscle strength/function

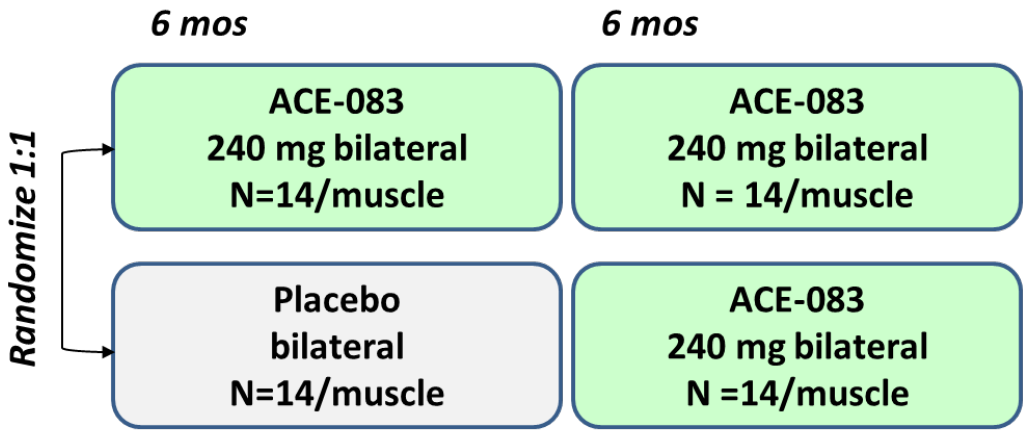
Treatment

- ACE-083 injection into tibialis anterior (TA) or biceps muscle, unilaterally or bilaterally, every 3 weeks (total N=92)

Part 1 – Dose-ranging



Part 2 – Double-blind, placebo controlled



ACE-083 FSHD Study – Part 2 Endpoints

Primary Endpoint

Improvement in muscle volume, as measured by MRI in the biceps and tibialis anterior groups

Secondary Endpoints

Biceps: reduction of fat fraction in muscle (by MRI), improvement in performance of upper limb (PUL) test, FSHD-Heath Index (FSHD-HI, a patient-reported outcome, PRO), strength

Tibialis Anterior: reduction of fat fraction in muscle, improvement in 6-minute-walk test, 10m walk/run, 4-stair climb, FSHD-HI , strength

Baseline Characteristics, Part 2

ACE-083 FSHD Study – Baseline Characteristics, Part 2

	Biceps Brachii		Tibialis Anterior	
	Placebo n=14	**ACE-083 n=14**	**Placebo n=14**	**ACE-083 n=13**
Age (years)	42.5 (21 – 65)	47.5 (28 – 68)	43.5 (18 – 62)	54.0 (31 – 70)
Gender, n (%) **Male** **Female**	 11 (78.6%) 3 (21.4%)	 10 (71.4%) 4 (28.6%)	 7 (50%) 7 (50%)	 6 (46.1%) 7 (53.9%)
Fat fraction (%)	13.4 (5.2 – 87.5) (n=13)	28.2 (1.7 – 73.9)	21.7 (2.9 – 69.3)	26.1 (8.3 – 74.6)
FSHD disease type, n (%) **FSHD1** **FSHD2**	 13 (92.9%) 1 (7.1%)	 14 (100%) 0	 12 (85.7%) 2 (14.3%)	 11 (84.6%) 2 (15.4%)
D4Z4 fragment size (kb), n (%) **≤18 (1-3 repeats)** **19-28 (4-6 repeats)** **>28 (>6 repeats)**	 3 (23.1%) 7 (53.8%) 3 (23.1%)	 4 (28.6%) 8 (57.1%) 2 (14.3%)	 3 (25.0%) 6 (50.0%) 3 (25.0%)	 1 (9.1%) 7 (63.6%) 3 (27.3%)
Duration since onset of symptoms (years)	20.5 (5 – 50)	21.5 (4 – 42)	19.5 (2 – 44)	24.0 (4 – 62)
Strength, MMT, n (%) **mild** **moderate**	 9 (64.3%) 5 (35.7%)	 9 (64.3%) 5 (35.7%)	 7 (50.0%) 7 (50.0%)	 8 (61.5%) 5 (38.5%)
Total muscle mass (g)	102.6 (15.5 – 240.3)	80.1 (30.0 – 223.5)	78.3 (19.8 – 214.2)	87.6 (47.4 – 124.9)

Continuous data are presented as median (min - max). Per Protocol Set used, i.e., all patients randomized who received at least one dose of study drug with no major protocol violations
D4Z4 = Region with repeated segments on chromosome 4 that regulates expression of *DUX4* gene; MMT = manual muscle testing; MRC – Medical Research Council;
Mild = MRC grades 4- to 4+; Moderate = MRC grades 3 to 4-

Data as of 25 Nov 2019

Imaging Results, Part 2

MRI Results, Part 2 Placebo-Controlled Phase: Marked Increases in Muscle

- ACE-083 treatment achieved a 16.4% greater increase in total muscle volume (TMV) than placebo in the biceps group, and 9.5% greater increase in the TA group
- Increases in contractile muscle volume (CMV) were even larger: 23.3%, 18.4%
- Significant reduction in intramuscular fat fraction (FF) was observed in the TA group

	LS Mean (SEM)		Difference (ACE-083 – Placebo)	
			LS Mean (SEM)	p-value
Biceps Group:	**Placebo N=14**	**ACE-083 N=14**		
% change in TMV	2.7 (2.81)	19.1 (2.82)	16.4 (4.03)	<0.0001
% change in CMV	2.6 (5.16)	25.8 (5.45)	23.3 (7.59)	0.002
Change in FF	1.0 (0.96)	-0.2 (0.98)	-1.3 (1.36)	0.36
TA Group:	**Placebo N=14**	**ACE-083 N=13**		
% change in TMV	4.3 (2.72)	13.8 (2.85)	9.5 (3.88)	0.01
% change in CMV	5.6 (4.90)	24.0 (5.20)	18.4 (7.01)	0.01
Change in FF	-0.3 (0.89)	-3.1 (0.95)	-2.7 (1.30)	0.04

CMV = contractile muscle volume; FF = fat fraction; LS mean = least squares mean; SEM = standard error of mean; TMV = total muscle volume
Contractile Muscle Volume = Total Muscle Volume * [(100 – Fat Fraction)] / 100

Data as of 25 Nov 2019

Strength, Function and PRO Results, Part 2

Functional and PRO Results: Only Upper Limb Measures Trended Better after 6 Months

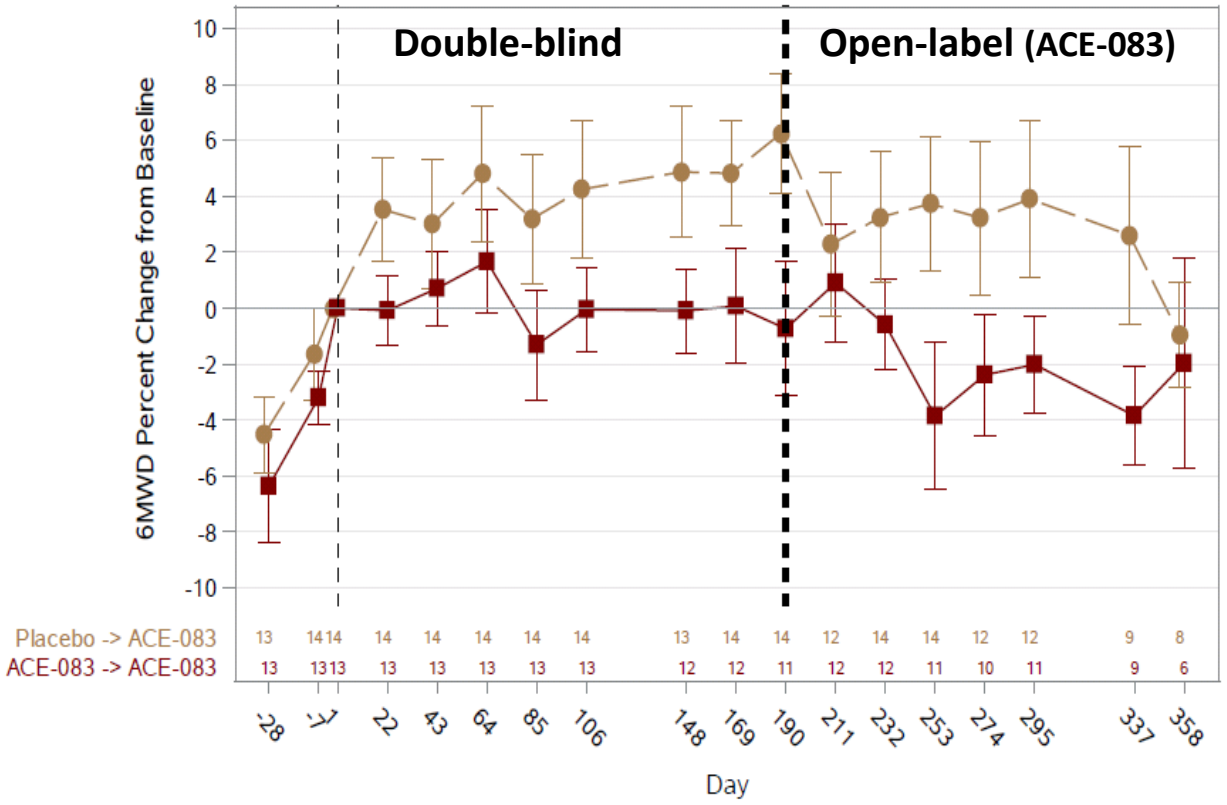
	LS Mean (SEM)		Difference (ACE-083 – Placebo)	
			LS Mean (SEM)	p-value
Biceps Group:	**Placebo N=14**	**ACE-083 N=14**		
% change in PUL Mid-Level Domain Score	-1.2 (1.2)	1.7 (1.2)	2.9 (1.7)	0.09
Change in FSHD-HI (PRO) Total Score	2.3 (2.41)	2.1 (2.61)	-0.1 (3.62)	0.98
Change in FSHD-HI Shoulder/Arm Subscale Score	0.92 (3.83)	-3.81 (4.05)	-4.7 (5.60)	0.40
Tibialis Anterior Group:	**Placebo N=14**	**ACE-083 N=13**		
% change in 6MWT distance	8.6 (2.76)	3.3 (2.94)	-5.3 (4.07)	0.19
% change in 10mW/R time	-8.6 (3.35)	-3.9 (3.59)	4.7 (4.97)	0.35
% change in 4-stair ascend time	-5.2 (4.07)	-4.8 (4.32)	0.5 (6.03)	0.94
Change in FSHD-HI Total Score	2.5 (2.35)	0.5 (2.53)	-2.0 (3.46)	0.57
Change in FSHD-HI Mobility/Ambulation Subscale Score	0.1 (2.94)	-0.9 (3.20)	-1.0 (4.34)	0.82

6MWT = 6-minute walk test; 10mW/R = 10-meter walk/run; CI = confidence interval; FSHD-HI = FSHD Health Index; LS = least squares; PRO = patient-reported outcome; PUL = performance of the upper limb test; QoL = quality of life; SEM = standard error of mean.

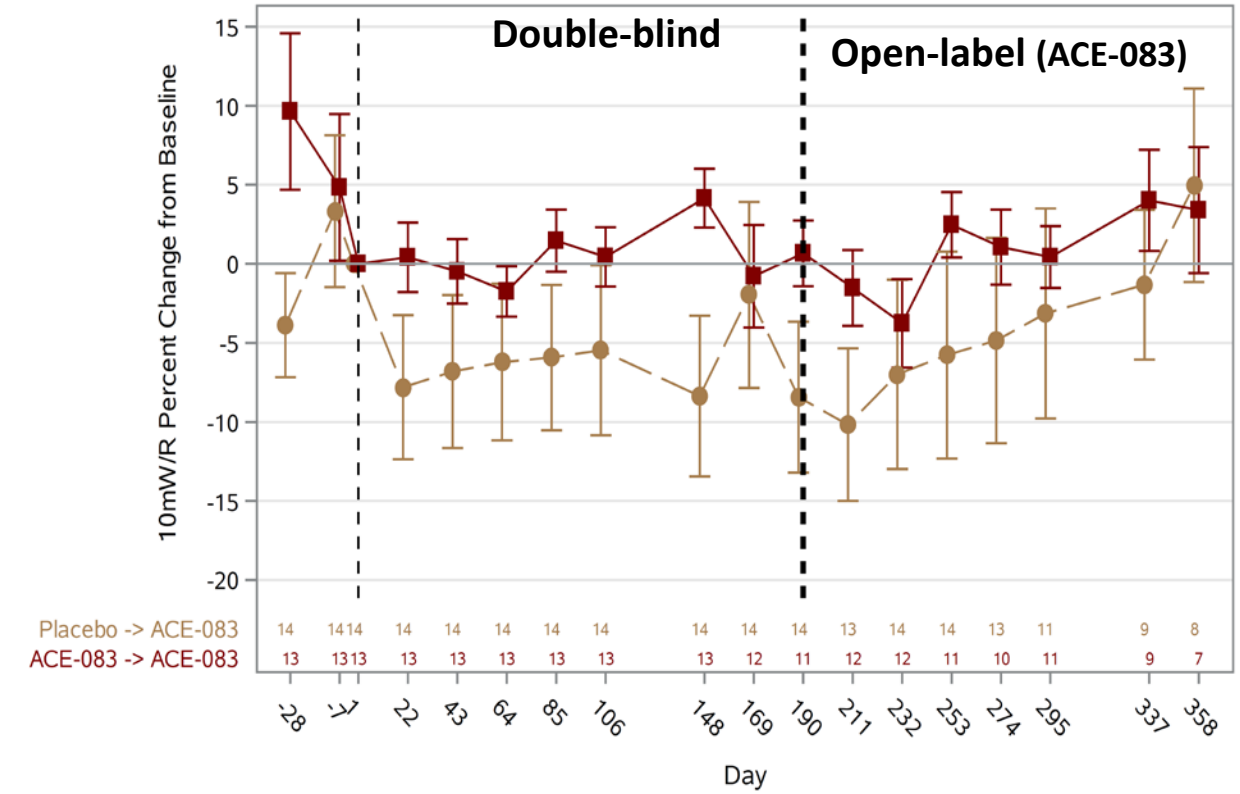
Data as of 25 Nov 2019

6MWT and 10mW/R Showed Minimal Change in ACE-083 TA Group

6MWT Distance



10mW/R Time



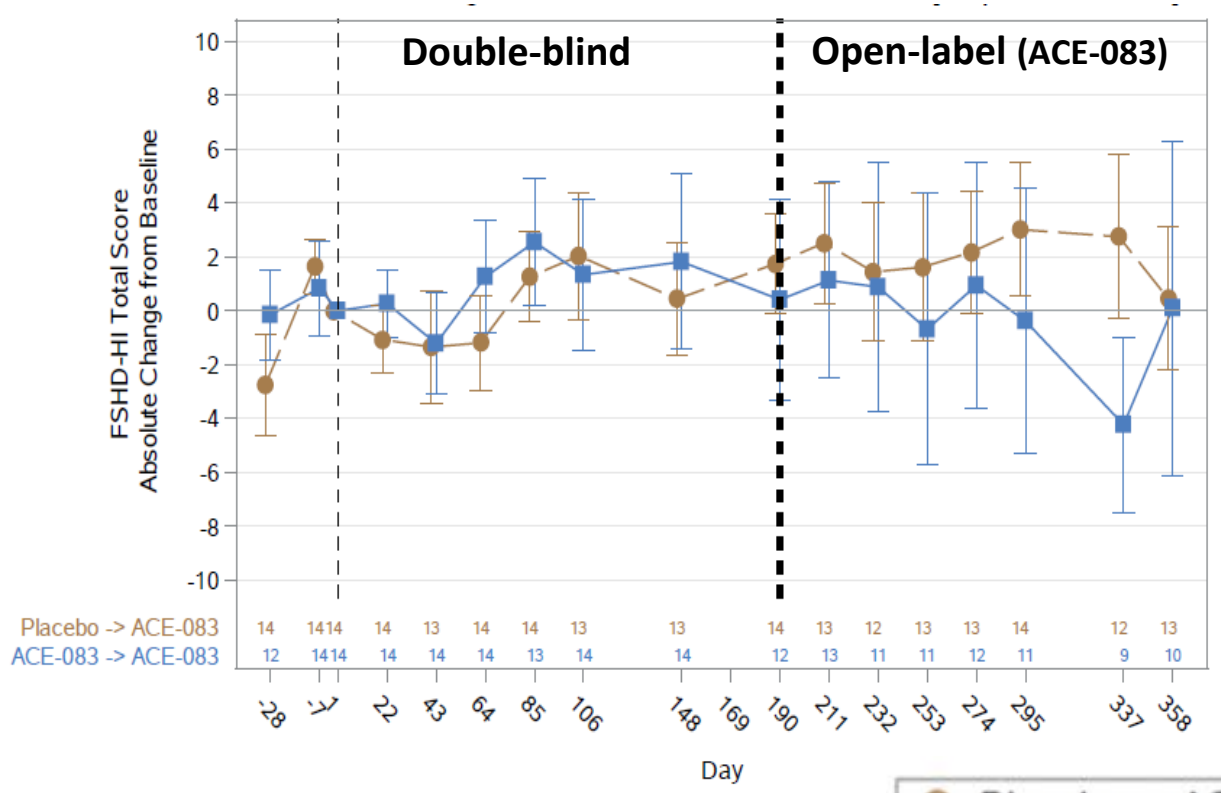
Placebo -> ACE-083 ACE-083 -> ACE-083

6MWD = 6-minute walk distance; 10mW/R = 10-meter walk/run.

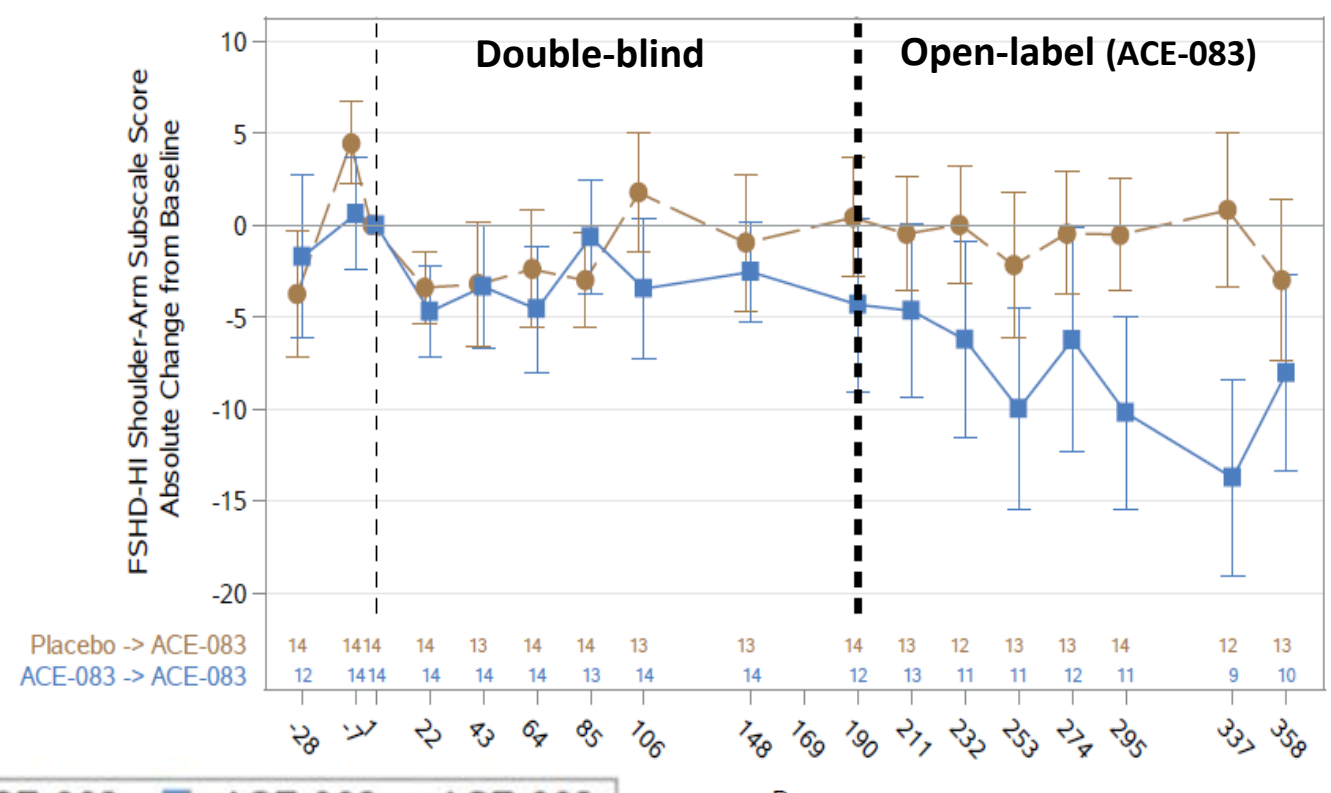
Data as of 25 Nov 2019

Shoulder/Arm Function Subscale of PRO Trended Better in ACE-083 Biceps Group

FSHD-HI Total Score



FSHD-HI Shoulder Arm Subscale Score



FSHD-HI = FSHD Health Index
PRO = patient-reported outcomes

Data as of 25 Nov 2019

Safety Results for ACE-083 FSHD Phase 2 Study, Part 2

- ACE-083 was generally well tolerated in both Biceps and TA groups
- Majority of adverse events were mild/moderate and were primarily injection site reactions
- There were no drug-related serious adverse events; one patient discontinued due to paresthesia in TA group

Possibly or Probably Related Adverse Events Occurring in ≥10% Patients Overall

	Biceps Brachii			Tibialis Anterior		
	Placebo-Controlled Phase		Open-label	Placebo-Controlled Phase		Open-label
	Placebo (N=15) n (%)	ACE-083 (N=14) n (%)	ACE-083 (N=26) n (%)	Placebo (N=15) n (%)	ACE-083 (N=14) n (%)	ACE-083 (N=27) n (%)
At least 1 related TEAE	5 (33.3%)	10 (71.4%)	12 (46.2%)	8 (53.3%)	10 (71.4%)	12 (44.4%)
Injection site erythema	3 (20%)	3 (21.4%)	7 (26.9%)	0	6 (42.9%)	1 (3.7%)
Injection site pruritus	1 (6.7%)	2 (14.3%)	3 (11.5%)	0	5 (35.7%)	1 (3.7%)
Injection site pain	4 (26.7%)	4 (28.6%)	4 (15.4%)	4 (26.7%)	3 (21.4%)	6 (22.2%)
Injection site warmth	0	1 (7.1%)	2 (7.7%)	1 (6.7%)	3 (21.4%)	2 (7.4%)
Injection site discomfort	0	2 (14.3%)	2 (7.7%)	1 (6.7%)	2 (14.3%)	3 (11.1%)
Joint swelling	0	0	0	0	2 (14.3%)	0
Myalgia	0	4 (28.6%)	1 (3.8%)	1 (6.7%)	2 (14.3%)	1 (3.7%)
Injection site bruising	4 (26.7%)	4 (28.6%)	6 (23.1%)	2 (13.3%)	1 (7.1%)	1 (3.7%)
Injection site swelling	0	2 (14.3%)	5 (19.2%)	0	1 (7.1%)	1 (3.7%)
Peripheral swelling	0	2 (14.3%)	0	0	1 (7.1%)	0

Data as of 25 Nov 2019

ACE-083 FSHD Phase 2 Study – Conclusions

- In the placebo-controlled part of the study, there were statistically significant differences in muscle volume percent change between ACE-083 and placebo in both the TA and Biceps groups
  - An improvement in fat fraction was also seen in the TA group
- ACE-083 treatment did not result in statistically significant improvements in the functional or quality of life tests in either the TA or Biceps group, as compared to placebo
  - A trend for improvement in the FSHD-HI Shoulder/Arm Subscale Score in the Biceps group was observed primarily in the second 6 months (uncontrolled phase of study)
- A significant learning/placebo effect was observed, particularly for the motor function tests in the TA group; this was not observed for the quality of life questionnaire
- Recommendations: Future studies in FSHD should consider including a run-in period before treatment, as well as a placebo-treated control arm, to aid interpretation of study results

Myostatin Inhibitors Evaluated in Clinical Trials for Neuromuscular Diseases

Company	Drug	Mechanism	Indications	Status
Acceleron	ACE-031	Receptor ligand trap	DMD	Discontinued, safety
Acceleron	ACE-2494	Receptor ligand trap	FSHD	Discontinued, safety
Acceleron	ACE-083	Follistatin ligand trap, local	FSHD, CMT	Discontinued, efficacy
Biogen	BIIB110	Receptor ligand trap	SMA, ALS	Active
Novartis	Bimagrumab	Antibody to receptor	sIBM	Discontinued, safety/efficacy
Regeneron	REGN 2477+1033	Antibodies to GDFs, activins	sIBM	Discontinued, safety
Wyeth	MYO-029	Antibody to GDFs	DMD, FSHD	Discontinued, efficacy
Lilly	Landogrozumab	Antibody to GDFs	Sarcopenia	Discontinued, efficacy
Pfizer	Domagrozumab	Antibody to GDFs	DMD, LGMD	Discontinued, efficacy
Roche	RO7239361	Adnectin to GDFs	DMD	Discontinued, efficacy
Scholar Rock	SRK-015	Antibody to latent GDF8	SMA	Active

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Thank you!