Dose Escalation Results from a Phase 2 Study of ACE-083, a Local Muscle Therapeutic, in Patients with Facioscapulohumeral Muscular Dystrophy (FSHD)

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Advisory Board: Sarepta, Biogen, Acceleron, Fulcrum, PTC
Facioscapulohumeral Muscular Dystrophy (FSHD) – Introduction

- FSHD is characterized by slowly progressive weakness in muscles of the face, shoulder, upper arm, lower leg and trunk; can be asymmetric
- Disease is due to contraction/hypomethylation of D4Z4 repeat element on chromosome 4, leading to overexpression of DUX4 in muscle
  - Fewer repeats correlate with more severe disease
- Patient-reported symptoms with high prevalence and impact on quality of life:
  - Arms (biceps brachii)
    - 73% of all patients (71% bilateral)
  - Foot drop (tibialis anterior)
    - 69% of all patients (43% bilateral)

ACE-083 – A Locally-Acting Muscle Therapeutic

- ACE-083 is a locally-acting protein therapeutic in the TGF-β superfamily consisting of a modified form of human follistatin that binds GDF8 (myostatin) plus other negative regulators of skeletal muscle
- Designed to be locally injected in affected muscles to increase muscle mass and strength
- Increased muscle mass demonstrated in healthy volunteers\(^1\)
- Tibialis anterior and biceps were selected as initial muscle targets for a locally acting therapeutic

ACE-083 FSHD 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

Part 1 – 3 mos open-label, N=36

- TA, Biceps
  - 150 mg unilateral
    - N=6/muscle
  - 200 mg unilateral
    - N=6/muscle
- TA 200 mg bilateral
- Biceps 240 mg unilateral
  - N=6/muscle

Part 2 – 6 mos placebo-controlled → 6 mos open-label, N=56

- 6 mos
  - ACE-083
    - 240 mg bilateral
      - N=14/muscle
  - Placebo
    - bilateral
      - N=14/muscle
- 6 mos
  - ACE-083
    - 240 mg bilateral
      - N=14/muscle
Baseline Characteristics
ACE-083 FSHD Study – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TA N=18</th>
<th>Biceps N=18</th>
<th>Overall N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>46 (19-63)</td>
<td>48 (20-69)</td>
<td>46 (19-69)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (44%)</td>
<td>12 (67%)</td>
<td>20 (56%)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (56%)</td>
<td>6 (33%)</td>
<td>16 (44%)</td>
</tr>
<tr>
<td><strong>Duration of symptoms, yr</strong></td>
<td>26 (4-40)</td>
<td>22 (4-55)</td>
<td>25 (4-55)</td>
</tr>
<tr>
<td><strong>D4Z4 fragment size (kb), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤18 (1-3 repeats)</td>
<td>2 (11.8%)</td>
<td>4 (22.2%)</td>
<td>6 (17.1%)</td>
</tr>
<tr>
<td>19-28 (4-6 repeats)</td>
<td>9 (52.9%)</td>
<td>11 (61.1%)</td>
<td>20 (57.1%)</td>
</tr>
<tr>
<td>&gt;28 (&gt;6 repeats)</td>
<td>6 (35.3%)</td>
<td>3 (16.7%)</td>
<td>9 (25.7%)</td>
</tr>
<tr>
<td><strong>MMT MRC grade, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 to 3+</td>
<td>5 (28%)</td>
<td>1 (6%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>4- to 4+</td>
<td>13 (72%)</td>
<td>17 (94%)</td>
<td>30 (83%)</td>
</tr>
<tr>
<td><strong>Total muscle mass, g</strong></td>
<td>69 (36-158)</td>
<td>76 (29-221)</td>
<td></td>
</tr>
<tr>
<td><strong>Fat fraction, %</strong></td>
<td>42 (12-82)</td>
<td>15 (6-79)</td>
<td></td>
</tr>
</tbody>
</table>

*N=17 for TA and N=35 for Overall (one TA patient diagnosed as FSHD2 hence no D4Z4 fragment size)

TA = tibialis anterior; MMT = manual muscle testing; MRC = Medical Research Council
D4Z4 = Region with repeated segments on chromosome 4 that regulates expression of DUX4 gene
Median (range), unless otherwise indicated; muscle data for treated sides only

Preliminary data as of 13 Mar 2019
ICCs estimated using three measurements on different days during the Screening/Baseline period show test-retest reliability.

<table>
<thead>
<tr>
<th>Population</th>
<th>Variable</th>
<th>Mean ± SD</th>
<th>ICC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA patients (n=18)</td>
<td>6-min walk test distance (m)</td>
<td>379.9 ± 117.4</td>
<td>0.98 (0.96, 0.99)</td>
</tr>
<tr>
<td></td>
<td>10m walk/run time (s)</td>
<td>8.1 ± 3.0</td>
<td>0.96 (0.92, 0.98)</td>
</tr>
<tr>
<td></td>
<td>4-stair climb time (s)</td>
<td>4.7 ± 4.1</td>
<td>0.94 (0.89, 0.97)</td>
</tr>
<tr>
<td></td>
<td>FSHD-HI total score</td>
<td>37.2 ± 24.4</td>
<td>0.97 (0.94, 0.99)</td>
</tr>
<tr>
<td></td>
<td>QMT (dorsiflexion MVIC) (N)</td>
<td>70.7 ± 42.0</td>
<td>0.85 (0.73, 0.92)</td>
</tr>
<tr>
<td>Biceps patients</td>
<td>PUL composite time (s)*</td>
<td>19.8 ± 4.9</td>
<td>0.86 (0.75, 0.92)</td>
</tr>
<tr>
<td>(n=18)</td>
<td>FSHD-HI total score</td>
<td>32.1 ± 23.2</td>
<td>0.97 (0.94, 0.98)</td>
</tr>
<tr>
<td></td>
<td>QMT (elbow flexion MVIC) (N)</td>
<td>102.5 ± 50.8</td>
<td>0.97 (0.94, 0.98)</td>
</tr>
</tbody>
</table>

*PUL composite time is sum of 4 timed tests from the middle level domain of the PUL test

ICC=intraclass correlation coefficient; CI=confidence interval; FSHD-HI=facioscapulohumeral muscular dystrophy-health index; N=newton; PUL=performance of upper limb test; QMT=quantitative muscle testing with hand-held dynamometer; SD=standard deviation; TA=tibialis anterior; MVIC=maximum voluntary isometric contraction

Preliminary data as of 13 Mar 2019
Baseline fat fraction was measured by 2-pt Dixon MRI scan for the entire tibialis anterior muscle

Significant correlations were observed for baseline fat fraction (%) and 10mW/R (s)

Baseline timed function tests correlated with each other and with the FSHD-Health Index ambulation subscore

10mW/R = 10-meter walk/run; 6MWD = 6-minute walk test distance; FSHD-HI = FSHD Health Index

Pearson correlation coefficients

$r = 0.60$
$p < 0.01$
$n = 18$

$r = -0.91$
$p < 0.0001$
$n = 18$

$r = -0.59$
$p = 0.01$
$n = 18$

Preliminary data as of 13 Mar 2019
Baseline fat fraction was measured by 2-pt Dixon MRI scan for the entire biceps muscle, and correlated significantly with manual or quantitative muscle strength testing (MMT-MRC grade or hand-held dynamometry, respectively).

Baseline performance of the upper limb (PUL) mid-level timed tests (s) correlated with the FSHD-Health Index total score.

FSHD-HI = FSHD Health Index; MMT = Manual Muscle Testing (MRC Grade); N=newton; PUL = performance of the upper limb; QMT = QMT=quantitative muscle testing with hand-held dynamometer
Pearson correlation coefficients, except FF vs MMT = Spearman correlation coefficient

Preliminary data as of 13 Mar 2019
Part 1 Dose Escalation Results
ACE-083 FSHD Study – Related Adverse Events
Part 1 TA and Biceps Cohorts

- ACE-083 was generally well tolerated in subjects treated for up to 3 months (5 doses)
- No serious adverse events
- Most common adverse events were injection site reactions and myalgia, mostly grade 1-2
  - One related grade 3 event of lower leg intramuscular swelling in the 200 mg TA cohort
- No clinically significant laboratory abnormalities on treatment

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

<table>
<thead>
<tr>
<th></th>
<th>Tibialis Anterior N=18</th>
<th>Biceps N=19*</th>
<th>Overall N=37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain</td>
<td>12 (67%)</td>
<td>5 (26%)</td>
<td>17 (46%)</td>
</tr>
<tr>
<td>Injection site discomfort</td>
<td>5 (28%)</td>
<td>7 (37%)</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>4 (22%)</td>
<td>5 (26%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (28%)</td>
<td>4 (21%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>2 (11%)</td>
<td>6 (32%)</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>3 (17%)</td>
<td>5 (26%)</td>
<td>8 (22%)</td>
</tr>
</tbody>
</table>

*Includes one treated patient who discontinued prior to Study Day 43

Preliminary data as of 13 Mar 2019
Increases in total muscle volume were dose-dependent, with >15% increase observed at doses of 200-240 mg/muscle.
Fat fraction decreased, most notably in tibialis anterior cohorts (which had higher fat fraction at baseline)

**Tibialis Anterior**

- N=9
- N=5
- N=6
- N=6

**Biceps**

- N=11
- N=6
- N=6
- N=6

*excluding MRC grades <3 or >4+

Preliminary data as of 13 Mar 2019
**ACE-083 FSHD Study – Contractile Muscle Volume by MRI**

**Part 1; Percent Change from Baseline to Day 106 (3 Weeks Post Last Dose)**

- Increased muscle volume was due to increase in contractile muscle fraction
  - Contractile Muscle Volume = Total Muscle Volume * \([(100 – \text{Fat Fraction)}) / 100\]

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**Tibialis Anterior**

- N=9
- N=5
- N=6
- N=6

**Biceps**

- N=11
- N=6
- N=6
- N=6

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*Preliminary data as of 13 Mar 2019*

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*excepting MRC grades <3 or >4+*
ACE-083 FSHD Study – Conclusions

- ACE-083, a locally-acting muscle therapeutic acting on myostatin and other muscle inhibitors, was generally well-tolerated when injected in the tibialis anterior or biceps over a 3-month treatment period in patients with FSHD.

- Baseline assessments demonstrated good test-retest reliability (ICC) and linear correlations of fat fraction by MRI with strength and timed function tests, and of timed function tests with each other and the FSHD-HI quality of life PRO.

- Increases in total muscle volume were dose-dependent, with >15% increase observed at doses of 200 to 240 mg/muscle.

- Fat fraction decreased in the tibialis anterior cohorts.

- These results support continued investigation of ACE-083 in neuromuscular diseases.
  - Placebo-controlled Part 2 of this Phase 2 FSHD study is ongoing (NCT02927080).
  - Placebo-controlled Phase 2 study in Charcot-Marie-Tooth disease is ongoing (NCT03124459).
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