Preliminary Results from a Phase 2 Study to Evaluate ACE-083, a Local Muscle Therapeutic, in Patients with Facioscapulohumeral Muscular Dystrophy

Jeffrey Statland¹, Anthony Amato², Elena Bravver³, Craig Campbell⁴, Lauren Elman⁵, Nicholas Johnson⁶, Nanette Joyce⁷, Chafic Karam⁸, John T Kissel⁹, Lawrence Korngut¹⁰, Erin O’Ferrall¹¹, Georgios Manousakis¹², Alan Pestrónk¹³, Perry B Shieh¹⁴, Rabi Tawil¹⁵, Ashley Leneus¹⁶, Barry Miller¹⁶, Matthew L Sherman¹⁶, Chad E Glasser¹⁶, Kenneth M Attie¹⁶

¹University of Kansas Medical Center, ²Brigham and Women’s Hospital, ³Carolina’s Healthcare System Neurosciences Institute, ⁴Children’s Hospital London Health Sciences Centre, ⁵University of Pennsylvania, ⁶University of Utah, ⁷University of California Davis Medical Center, ⁸Oregon Health & Science University, ⁹The Ohio State University, ¹⁰University of Calgary, ¹¹Montreal Neurological Institute, ¹²University of Minnesota, ¹³Washington University School of Medicine, ¹⁴University of California, Los Angeles, ¹⁵University of Rochester School of Medicine, ¹⁶Acceleron Pharma

Disclosure: Dr. Statland has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Strongbridge, Acceleron, Regeneron, and Sanofi.
Facioscapulohumeral Muscular Dystrophy (FSHD) – Introduction

- One of the most common muscular dystrophies
  - Worldwide prevalence ~5-7 in 100,000; ~20,000 in US
- Typical presentation in the second to third decade of life
- Two genetic distinct types which converge on a common pathway
  - Both lead to de-repression of *DUX4*, believed to cause disease by toxic gain-of-function
- Characteristic presentation with muscles of face, shoulders, upper arm, then distal lower extremity
  - Biceps
  - Tibialis anterior – foot drop

ACE-083 is a locally-acting protein therapeutic consisting of modified form of human follistatin that binds GDF8 (myostatin) plus other negative regulators of skeletal muscle in the TGF-β superfamily.

- Designed to be locally injected in affected muscles
- Intended to increase muscle mass and strength in diseases with debilitating focal muscle involvement
ACE-083 FSHD Phase 2 Study Design

Part 1 – 3 mos open-label, N=36

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

- Randomize 1:1
- ACE-083 bilateral
  - N = 14/muscle
- Placebo bilateral
  - N = 14/muscle
- ACE-083 bilateral
  - N = 14/muscle
- ACE-083 bilateral
  - N = 14/muscle

Treatment
- ACE-083 injection into tibialis anterior (TA) or biceps, unilaterally or bilaterally, every 3 weeks
ACE-083 FSHD Study – Part 1

**Key Eligibility Criteria**

- **Inclusion**
  - Age ≥ 18 years
  - Genetically-confirmed FSHD1 or FSHD2 in patient or 1st-degree relative
  - Clinical signs/symptoms of FSHD
  - Mild to moderate weakness in ankle dorsiflexion or elbow flexion in the injected muscle

- **Exclusion**
  - Medications potentially affecting muscle strength/function
  - Significant change in physical activity or exercise

**Primary Objective**

- Safety and tolerability

**Secondary/Exploratory Objectives**

- Dose selection for Part 2
- Total muscle volume, intramuscular fat fraction (by Dixon MRI scan)
- Ankle dorsiflexion/elbow flexion strength (QMT)
- Timed function tests, gait analysis
- Quality of life (FSHD-Health Index)
## ACE-083 FSHD Study – Baseline Characteristics
### Part 1 Cohorts 1 and 2

- Median duration of symptoms was 24 years
- Fat fraction (%) was higher in tibialis anterior vs biceps cohorts

<table>
<thead>
<tr>
<th></th>
<th>Tibialis Anterior N=12</th>
<th>Biceps N=12</th>
<th>Overall N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>46 (19-63)</td>
<td>53 (20-69)</td>
<td>47 (19-69)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (50%)</td>
<td>8 (67%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (50%)</td>
<td>4 (33%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td><strong>Duration of symptoms, yr</strong></td>
<td>26 (4-35)</td>
<td>22 (4-55)</td>
<td>24 (4-55)</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>3 (25%)</td>
<td>0 (0%)</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>4- to 4+</td>
<td>9 (75%)</td>
<td>12 (100%)</td>
<td>21 (87.5%)</td>
</tr>
<tr>
<td><strong>Total muscle mass, g</strong></td>
<td>72 (35-160)</td>
<td>89 (37-223)</td>
<td></td>
</tr>
<tr>
<td><strong>Fat fraction, %</strong></td>
<td>36 (12-82)</td>
<td>14 (6-79)</td>
<td></td>
</tr>
</tbody>
</table>

MMT = manual muscle testing; MRC = Medical Research Council
Median (range), unless otherwise indicated; muscle data for treated sides only

Preliminary data as of 28 March 2018
Primary Endpoint: Safety
ACE-083 FSHD Study – Safety Summary
Part 1 Cohorts 1 and 2

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

### Related* Adverse Events Occurring in ≥10% of Patients Overall

<table>
<thead>
<tr>
<th>Preferred Term, n(%)</th>
<th>TA N=12</th>
<th>Biceps N=13^</th>
<th>Overall N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 AE</td>
<td>9 (75%)</td>
<td>10 (77%)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>9 (75%)</td>
<td>3 (23%)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Injection site discomfort</td>
<td>2 (17%)</td>
<td>5 (39%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>2 (17%)</td>
<td>3 (23%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (17%)</td>
<td>3 (23%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>1 (8%)</td>
<td>3 (23%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>1 (8%)</td>
<td>2 (15%)</td>
<td>3 (12%)</td>
</tr>
</tbody>
</table>

*Possibly or probably related to ACE-083
^Includes one treated patient who discontinued prior to Study Day 43

Preliminary data as of 28 March 2018
Secondary Endpoints: Imaging
ACE-083 FSHD Study – Percent Change in Total Muscle Volume (TMV)
Part 1 Cohorts 1 and 2

- Increases in TMV in treated muscle observed at Day 106 (3 weeks post last dose) shown below
- Dose-dependent response on treated side for 150 mg, 200 mg

Preliminary data as of 28 March 2018
Decrease in fat fraction in treated TA muscle observed at Day 106 (3 weeks post last dose) shown below

Preliminary data as of 28 March 2018
ACE-083 FSHD Study – Contractile Muscle Volume

- Contractile muscle volume (CMV) is a measure of viable, functional muscle
- Derived from total muscle volume (TMV) minus intramuscular fat, as measured by Dixon MRI scan*
- Represents available functional muscle for activity of local muscle therapeutic
- Preliminarily, correlations were observed for baseline contractile muscle with strength by manual muscle testing

*CMV = [TMV * (100 – fat fraction)] / 100
ACE-083 FSHD Study – Conclusions

- ACE-083, a locally-acting muscle therapeutic, acting on myostatin *plus* other inhibitors, was safe and generally well-tolerated over a 3-month treatment period in patients with FSHD injected in the tibialis anterior or biceps brachii
  - One dose-limiting toxicity was seen in the 200 mg TA cohort
- Increases in total muscle volume were dose-dependent, with 15-20% increase observed at higher dose levels
- Fat fraction decreased, most notably in tibialis anterior cohorts
- These results support continued investigation of ACE-083 in neuromuscular diseases
  - Placebo–controlled Part 2 of FSHD study now enrolling (NCT02927080)
  - Separate Phase 2 study is ongoing in Charcot-Marie-Tooth disease (NCT03124459)
The authors wish to thank the patients and their families for their participation and contributions as well as the following team members:

**Sub-Investigators:** Richard Barohn, MD, Benjamin Brooks, MD, Russell Butterfield, MD, Nizar Chahin, MD, Mazen Dimachkie, MD, Miriam Freimer, MD, Melanie Glenn, MD, Stanley Iyadurai, MD, Omar Jawdat, MD, Eric Logigian, MD, Samantha LoRusso, MD, Craig McDonald, MD, Erin O’Ferrall, MD, Mamatha Pasnoor, MD, Rodney Li Pi Shan, MD, Amro Shino, MD, Francy Shu, MD, Chris Weihl, MD, Eugenio Zapata, MD

**Evaluators:** Melissa Currence, Xi Dong, Lauren Draper, Katy Eichinger, Keegan Fitzgerald, Julaine Florence, Patricia Flynn, Molly Grames, Laura Herbelin, Scott Holsten, Brandi Johnson, Wendy Koesters, Jose Martinez, Melissa McIntyre, Alina Nicorici, Crystal O’Conner, Stephanie Poelker, Mohammed Sanjak, Cheryl Scholtes, Catherine Siener, Christy Skura

**Clinical Site Coordinators:** Colleen Anthonisen, Sonya Aziz-Zaman, Natalya Burlakova, Megan Christ, Bryant Gordon, Bridget Hoskins, Kianoush Kamali, Cynthia Lary, Leann Lewis, Jennifer Mabry, Ayla McCalley, Jennifer Petzke, Lisa Ranzinger, Kristen Roe, Alison Newell-Sturdivant, Linda Schimoeller

**MedPace:** Emily Birkmeyer, Shanshan Cui, Megan Kolthoff, Chad Leslie, Taylor Meece, Stephanie Porter, Georgiana Salyers, Richard Scheyer, MD, Wendy van den Branden

**Acceleron:** Leah Leahy, Stephanie D’Eon, Jade Sun, Saba Qamar, Connie Slocum, Carrie Barron, Shuree Harrison, Thienhhu Nguyen, Suada Celikovic

**VirtualScopics, VirtuSense, ATOM, University of Rochester** (Chad Heatwole), ERT