Phase 1 dose escalation study of ACE-083 in healthy volunteers: Preliminary results for a locally acting muscle therapeutic

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ACE-083 Background

- ACE-083 is a locally acting protein therapeutic that binds GDF8 (myostatin) and activins among other negative regulators of skeletal muscle growth
- ACE-083 was designed to increase muscle mass and strength selectively in the muscle into which the drug is administered
ACE-083 Pre-Clinical Results

- In both wild type (WT) and the *mdx* mouse model of Duchenne muscular dystrophy (DMD), local injection of ACE-083 led to localized muscle hypertrophy as well as dose-dependent increases in muscle mass\(^1,2\)

\(^1\)Mulivor et al. 13\(^{th}\) International Congress on Neuromuscular Diseases, 2014
\(^2\)Mulivor et al. 19\(^{th}\) International Congress of the World Muscle Society, 2014
ACE-083 Administration Led to an Increase in Fiber CSA and Peak Tetanic Force of the Tibialis Anterior (TA) in WT Mice

\[\text{↑78\%} \quad \text{(*p = < 0.001)}\]

\[\text{↑40\%} \quad \text{(*p = < 0.05)}\]

A083-01: A Phase 1 Study in Healthy Volunteers

Study Description

- An ongoing randomized, double-blind, placebo-controlled, dose-ranging study in healthy post-menopausal women

Objectives of the Study

- **Primary**: To characterize the safety and tolerability of single and repeated doses of ACE-083 as a local muscle injection
- **Secondary**: To estimate systemic exposure and evaluate the pharmacodynamic (PD) effects of ACE-083
  - Changes in muscle volume measured on MRI
  - Changes in strength as measured by Biodex fixed system and hand-held dynamometer
## A083-01 Study Design

<table>
<thead>
<tr>
<th>Number of Doses</th>
<th>Cohort</th>
<th>Dosing Day(s)</th>
<th>Dose Level (mg)</th>
<th>Injected Muscle</th>
<th>Injections per Dose</th>
<th>ACE-083 Subjects</th>
<th>Placebo Subjects</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Dose</td>
<td>1</td>
<td>1</td>
<td>50</td>
<td>RF</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>100</td>
<td>RF</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td>200</td>
<td>RF</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Multiple Doses</td>
<td>4</td>
<td>1, 22</td>
<td>100</td>
<td>RF</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1, 22</td>
<td>200</td>
<td>RF</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1, 22</td>
<td>100</td>
<td>TA</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>1, 22</td>
<td>150</td>
<td>TA</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Total Number of Subjects (Planned):</strong></td>
<td><strong>42</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>16</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RF: rectus femoris, TA: tibialis anterior

NCT02257489

Data as of 26Aug2015
Pharmacodynamic Assessments

- MRI was obtained pre-dose (Day 1) as well as 3 weeks (Day 22 or 43) and 8 weeks (Day 57 or Day 78) post last dose

- Strength was assessed by Biodex fixed system at 3 and 8 weeks post last dose

- A handheld dynamometer was also used to evaluate strength weekly throughout the treatment period

<table>
<thead>
<tr>
<th>Number of Doses</th>
<th>Assessment</th>
<th>Day 1</th>
<th>Day 22</th>
<th>Day 43</th>
<th>Day 57</th>
<th>Day 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Dose</td>
<td>Dosing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Multiple Doses</td>
<td>Dosing</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

- Number of Doses

- Assessment

- Day 1

- Day 22

- Day 43

- Day 57

- Day 78
Safety Results: Cohorts 1-5

- Forty post-menopausal women (97.5% white) with a median age of 56 (range: 45-72 yrs) and median body mass index (BMI) of 25.1 (range: 19.2-31.5 kg/m²) were enrolled into the study.

- There were 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.

- Injection site pain was documented at all dose levels (including placebo) and was independent of dose or number of injections.

Data as of 26Aug2015
## Adverse Events at Least Possibly Related to Study Drug Occurring in ≥ 10% (3 or more) ACE-083 Treated Subjects

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo Treated (n = 10)</th>
<th>Single Dose (mg)</th>
<th>Multiple Dose (mg)</th>
<th>ACE-083 Treated (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>50 (n=6)</td>
<td>100 (n=6)</td>
<td>200 (n=6)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>10 (100)</td>
<td>5 (83)</td>
<td>5 (83)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Muscle twitching</td>
<td>3 (30)</td>
<td>0</td>
<td>1 (17)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (10)</td>
<td>1 (17)</td>
<td>0</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (10)</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>2 (20)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injection site discomfort</td>
<td>1 (10)</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Limb discomfort</td>
<td>2 (20)</td>
<td>0</td>
<td>0</td>
<td>3 (50)</td>
</tr>
</tbody>
</table>

Data as of 26Aug2015
ACE-083 Produced Significant Increases in Muscle Volume by MRI in the Injected Muscle with No Effect on the Uninjected Muscle

No Treatment
(Left Rectus Femoris)

- Changes in the left uninjected RF muscle were used to control for MRI variability

ACE-083 Treated
(Right Rectus Femoris)

- Three weeks after the last dose of ACE-083, the right RF muscle volume increased from baseline by 7.3% (p<0.05) and 14.5% (p<0.001) in Cohorts 4 and 5, respectively

Data as of 26Aug2015
A Dose-Dependent Increase in RF Muscle Volume was Observed Following Local Administration of ACE-083

In Cohorts 2-5, RF volume remains increased, though attenuated, at 8 weeks post last dose.

NOTE: Significance level in comparison to placebo using Dunnett’s Test:
*p = < 0.05; ** p = < 0.001
Changes in Strength Following ACE-083 Administration

• Changes in strength did not correlate with muscle volume changes in these healthy subjects
• RF muscle accounted for only ~13% (range: 10-16%) of the total quadriceps muscle volume in these healthy subjects
• Ongoing cohorts evaluating administration of ACE-083 into the tibialis anterior (TA) will evaluate dorsiflexion strength
Conclusions

- ACE-083 is a locally-acting protein therapeutic that acts as a ligand trap for myostatin and other negative regulators of muscle mass
- A083-01 is an ongoing Phase 1 study evaluating ACE-083 administration into the RF and TA in healthy volunteers
- ACE-083 injected into the RF muscle is associated with a favorable safety profile and resulted in dose-dependent and significant increases in RF muscle volume
- These encouraging data support further studies of ACE-083 in a variety of muscle diseases, such as Facioscapulohumeral muscular dystrophy (FSHD) and Duchenne Muscular Dystrophy
Acknowledgements

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