Results of the Dose-Escalation Portion of a Phase 2 Study of ACE-083, a Local Muscle Therapeutic, in Patients with Charcot-Marie-Tooth (CMT) Disease

Florian P Thomas¹, Michael Shy², David Herrmann³, Jeffrey Statland⁴, David Walk⁵, Colin Quinn⁶, Nicholas Johnson⁷, SH Subramony⁸, Chafic Karam⁹, Tahseen Mozaffar¹⁰, Chad E Glasser¹¹, Barry Miller¹¹, Ashley Leneus¹¹, Robert K Zeldin¹¹, Kenneth M Attie¹¹

¹Hackensack UMC and Hackensack Meridian School of Medicine, ²University of Iowa, ³University of Rochester Medical Center, ⁴University of Kansas Medical Center, ⁵Dept. of Neurology, University of Minnesota, ⁶University of Pennsylvania, ⁷University of Utah, ⁸University of Florida, ⁹Oregon Health & Science University, ¹⁰University of California Irvine, ¹¹Acceleron Pharma
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Charcot-Marie-Tooth (CMT) Disease – Introduction

- CMT is the most common inherited peripheral neuropathy, with an incidence of 1 in 2500\(^1\)
- CMT is a slowly progressive neuropathy that causes predominantly distal arm and leg weakness, motor and sensory nerve loss, and foot and ankle deformities
  - Tibialis anterior (TA) weakness is a cardinal manifestation of disease, with virtually all patients developing weak ankle dorsiflexion, often early in their disease course
  - Weakness of the TA muscle causes foot drop, impairs ambulation, and increases the risk of falls
- CMT has substantial unmet medical need with no drug therapies currently available
  - Orthotics and bracing can be helpful, but compromise gait mechanics and may lead to muscle atrophy and discomfort

CMT Pathophysiology\(^2\)

Damage to peripheral nerves results in distal sensory disruption and muscle atrophy

- \(>80\) genes identified
- Several sub-types (CMT 1, 2, 4 and X)
- Initially affects myelin sheath (eg, Type 1) or nerve axon (eg, Type 2)

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\(^1\) and patients with FSH muscular dystrophy\(^2\).
- Tibialis anterior and biceps were selected as initial muscle targets for a locally acting therapeutic.

ACE-083 CMT Study Design

Key Eligibility Criteria:
- Age ≥ 18 years
- Genetically-confirmed CMT1 or CMTX, or, genetically-confirmed first-degree relative and clinical signs/symptoms of CMT1 or CMTX
- Left and right ankle dorsiflexion weakness
- 6-minute walk distance ≥ 150 meters

Treatment:
- ACE-083 injection into tibialis anterior (TA) muscle bilaterally every 3 weeks

Assessments and Selected Outcome Measures:
- Safety and tolerability
- Total and contractile muscle volume (TMV, CMV), fat fraction (FF) by 2-pt Dixon MRI
- Strength by hand-held dynamometry and manual muscle testing
- 6-minute walk test, 10m walk/run
- CMT-Health Index

Part 1 – 3 mos open-label ACE-083
- Cohort 1
  ACE-083 150 mg
  N=6
- Cohort 2
  ACE-083 200 mg
  N=6
- Cohort 3
  ACE-083 240 mg
  N=6

Part 2 – 6 mos placebo-controlled → 6 mos open-label
- Randomize 1:1
- 6 months
  - ACE-083 240 mg
    N=20
- 6 months
  - ACE-083 240 mg
    N = 20
  - Placebo
    N=20
  - ACE-083 240 mg
    N =20
Baseline Characteristics
# ACE-083 CMT Study – Baseline Characteristics, Part 1

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 150 mg N=6</th>
<th>Cohort 2 200 mg N=6</th>
<th>Cohort 3 240 mg N=6</th>
<th>Overall N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>35 (23-62)</td>
<td>39 (18-61)</td>
<td>52 (31-58)</td>
<td>48 (18-62)</td>
</tr>
<tr>
<td>Gender, n (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td>2 (33%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td>4 (67%)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>Duration of symptoms, yr</td>
<td>31 (14-61)</td>
<td>30 (6-51)</td>
<td>12 (2-25)</td>
<td>23 (2-61)</td>
</tr>
<tr>
<td>CMT subtype, n (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT1A</td>
<td>4 (67%)</td>
<td>5 (83%)</td>
<td>2 (33%)</td>
<td>11 (61%)</td>
</tr>
<tr>
<td>CMT1B</td>
<td>1 (17%)</td>
<td>0</td>
<td>3 (50%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>CMTX1</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Total muscle mass, g</td>
<td>66 (38-87)</td>
<td>70 (40-85)</td>
<td>92 (73-141)</td>
<td>78 (38-141)</td>
</tr>
<tr>
<td>Fat fraction, %</td>
<td>29 (10-45)</td>
<td>31 (15-37)</td>
<td>27 (9-44)</td>
<td>30 (9-45)</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>418 (236-588)</td>
<td>381 (324-501)</td>
<td>459 (265-620)</td>
<td>411 (236-620)</td>
</tr>
</tbody>
</table>

6MWD = 6-minute-walk distance  
Median (range), unless otherwise indicated
ACE-083 CMT Study – Baseline Correlations, Part 1 Patients

- Baseline 6MWD correlated with 10mW/R and the CMT-HI Mobility Subscore

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

Preliminary data as of 18 March 2019
Part 1 Dose Escalation Results
ACE-083 CMT Study – Related Adverse Events, Part 1

- ACE-083 was generally well tolerated in subjects treated for up to 3 months (5 doses)
  - Most common adverse events were injection site reactions, muscle spasms, and myalgia
  - Most adverse events were mild or moderate (grades 1-2)
- No clinically significant laboratory abnormalities on treatment

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

<table>
<thead>
<tr>
<th>Preferred Term, n(%)</th>
<th>Cohort 1 150 mg (N=6)</th>
<th>Cohort 2 200 mg (N=6)</th>
<th>Cohort 3 240 mg (N=6)</th>
<th>Overall N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site discomfort</td>
<td>3 (50%)</td>
<td>2 (33%)</td>
<td>3 (50%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>1 (17%)</td>
<td>2 (33%)</td>
<td>2 (33%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>2 (33%)</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1 (17%)</td>
<td>2 (33%)</td>
<td>1 (17%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (33%)</td>
<td>0</td>
<td>2 (33%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>1 (17%)</td>
<td>0</td>
<td>1 (17%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>1 (17%)</td>
<td>0</td>
<td>1 (17%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Muscle tightness</td>
<td>1 (17%)</td>
<td>0</td>
<td>1 (17%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

Preliminary data as of 18 March 2019
ACE-083 CMT Study – Total Muscle Volume, Part 1
Percent Change from Baseline to Day 106 (3 weeks post last dose)

(Average of right and left sides)
Intramuscular fat fraction was measured by 2-pt Dixon MRI scan of the entire tibialis anterior muscle.

Preliminary data as of 18 March 2019
ACE-083 CMT Study – Contractile Muscle Volume, Part 1
Percent Change from Baseline to Day 106 (3 weeks post last dose)

- Contractile Muscle Volume = Total Muscle Volume * [(100 – Fat Fraction)] / 100

Preliminary data as of 18 March 2019
ACE-083 CMT Study – Conclusions, Part 1

- ACE-083, a locally-acting muscle therapeutic, acting on myostatin *plus* other inhibitors of muscle growth, had a favorable safety profile and was generally well-tolerated over a 3-month treatment period in patients with CMT injected in the tibialis anterior (TA).

- Baseline 6MWD correlated with 10m Walk/Run and CMT-HI Mobility Subscore.

- Changes observed in pharmacodynamic outcome measures at 3 weeks post last dose:
  - Mean % increases of >12% total muscle volume and >15% contractile muscle volume
  - Mean absolute decrease in fat fraction of >3% in the 200 mg and 240 mg group

- These results support continued investigation of ACE-083 in neuromuscular diseases:
  - Placebo-controlled Part 2 of this Phase 2 CMT study is now enrolling (NCT03124459)
  - Placebo-controlled Part 2 of a separate Phase 2 in FSHD study is ongoing (NCT02927080)
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