Results of a Phase 2 Double-Blind Placebo-Controlled Study of a Local Muscle Therapeutic, ACE-083, in Subjects with Charcot-Marie-Tooth (CMT) Disease

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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

- 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

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)


CMT = Charcot-Marie-Tooth; TA = tibialis anterior
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
- Locally increased muscle mass demonstrated in healthy volunteers\(^1\) and patients with FSHD\(^2\) and CMT\(^3\)
- Tibialis anterior and biceps were selected as initial muscle targets for a locally acting therapeutic

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\[\text{CMT} = \text{Charcot-Marie-Tooth}; \text{FSHD} = \text{facioscapulohumeral muscular dystrophy}; \text{GDF} = \text{growth differentiation factor}; \text{TGF-β} = \text{transforming growth factor-beta}\]
ACE-083 CMT Phase 2 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, ≤ 500 meters

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

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
- Placebo
  - N=20
- 6 months
  - ACE-083 240 mg
    - N=20
  - ACE-083 240 mg
    - N=20
ACE-083 CMT Study - Part 2 Endpoints

Endpoints measured at Study Day 190 compared to baseline vs placebo control group

**Primary Endpoint:**
- Improvement from baseline to Day 190 (percent change) in total and contractile muscle volume (TMV, CMV, by MRI) with ACE-083 as compared with placebo

**Secondary Endpoints:**
Improvement from baseline to Day 190 in:
- Functional tests: 6-minute walk test, 10-meter walk/run, Berg balance scale, CMTES2
- Patient-reported outcomes (PRO): CMT-Heath Index (CMT-HI) total and selected subscale scores
- Ankle dorsiflexion strength (MVIC by hand-held dynamometry and MMT-MRC Grade)
- Fat fraction (FF, by MRI)

CMTES2 = CMT Examination Score v2; MMT = manual muscle testing; MRC = Medical Research Council; MVIC = maximum voluntary isometric contraction
Statistical Analysis Populations and Methods

Statistical Analysis Populations:

- **Per Protocol Set**: All patients randomized who received at least one dose of study drug (includes placebo) with no major protocol violations
- **Safety Set**: All patients randomized who received at least one dose of study drug (includes placebo)

Statistical Methods:

**Efficacy** (Imaging, Functional [6MWD, 10mW/R], Strength [MVIC, MMT], CMT-HI):

- ANCOVA of Day 190 percent change (raw change for fat fraction, CMT-HI, MMT) from baseline
- Least squares (LS) mean with p-value and 90% confidence interval (CI) of treatment group effect
- Treatment group effect (ACE-083 vs. Placebo) tested using a two-sided, 0.10 significance level

**Safety**: Adverse events, laboratory tests, anti-drug antibody, vital signs, and ECG data were reviewed and summarized; summary of adverse events will be shown

6MWD = 6-minute walk distance; 10mW/R = 10 meter walk/run; MVIC = maximum voluntary isometric contraction; MMT = manual muscle testing; MRC = Medical Research Council; CMT-HI = Charcot-Marie-Tooth Health Index; ANCOVA = analysis of covariance; SEM = standard error of the mean
Baseline Characteristics, Part 2
### ACE-083 CMT Study – Baseline Characteristics, Part 2

**Per Protocol Set**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 20)</th>
<th>ACE-083 (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>49.0 (20-71)</td>
<td>46.0 (19-67)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (35%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (65%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td><strong>CMT disease diagnosis, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT1</td>
<td>17 (85%)</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>CMTX</td>
<td>3 (15%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td><strong>Form of CMT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demyelinating</td>
<td>14 (70%)</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>Axonal</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Mixed demyelinating and axonal</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td><strong>Duration since onset of symptoms (years)</strong></td>
<td>29.5 (1-64)</td>
<td>24.5 (2-49)</td>
</tr>
<tr>
<td><strong>Strength, ankle dorsiflexion MMT, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (MRC Grade 4 to 4+)</td>
<td>8 (40%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Moderate (MRC Grade 3 to 4-)</td>
<td>12 (60%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td><strong>Fat fraction (%)</strong></td>
<td>29.4 (10.2-53.9)</td>
<td>23.8* (10.2-65.9)</td>
</tr>
<tr>
<td><strong>Total muscle mass (g)</strong></td>
<td>56.3 (31.2-148.0)</td>
<td>74.6* (44.3-215.3)</td>
</tr>
</tbody>
</table>

*Continuous data are presented as median (min - max). Per Protocol Set = all patients randomized who received at least one dose of study drug with no major protocol violations.

MMT = manual muscle testing; MRC = Medical Research Council

Data as of 14 Feb 2020
Imaging Results, Part 2
ACE-083 treatment achieved a 13.5% greater increase in total muscle volume (TMV by MRI) \((p=0.01)\) and a 23.3% greater increase in contractile muscle volume (CMV) vs placebo \((p=0.02)\)

- **CMV = TMV * [(100 – Fat Fraction)] / 100**

### Table: Imaging Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LS Mean (SEM)</th>
<th>Difference (ACE-083 – Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=20)</td>
<td>ACE-083 (N=20)</td>
</tr>
<tr>
<td>Percent change in TMV</td>
<td>2.2 (4.1)</td>
<td>15.8 (4.3)</td>
</tr>
<tr>
<td>Percent change in CMV</td>
<td>1.7 (7.9)</td>
<td>24.9 (8.6)</td>
</tr>
<tr>
<td>Raw change in Fat Fraction (%)</td>
<td>1.0 (1.8)</td>
<td>-2.1 (1.9)</td>
</tr>
</tbody>
</table>

CI = confidence interval; LS = least squares; SEM = standard error of the mean
Mean (SEM) Percent Change in Contractile Muscle Volume (MRI)

Data as of 14 Feb 2020
Strength/Function/PRO Results, Part 2
### CMT Study Results, Part 2 Placebo-Controlled Phase (to Day 190)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LS Mean (SEM)</th>
<th>Difference (ACE-083 – Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=20)</td>
<td>ACE-083 (N=20)</td>
</tr>
<tr>
<td>Raw change in ankle dorsiflexion MMT decimal score</td>
<td>-0.1 (0.1)</td>
<td>0.2 (0.1)</td>
</tr>
<tr>
<td>% change in ankle dorsiflexion MVIC</td>
<td>-4.2 (19.8)</td>
<td>30.9 (19.9)</td>
</tr>
<tr>
<td>Percent change in 6MWD</td>
<td>5.9 (4.0)</td>
<td>9.0 (3.8)</td>
</tr>
<tr>
<td>Percent change in 10mW/R time</td>
<td>-10.4 (4.7)</td>
<td>-8.7 (4.6)</td>
</tr>
<tr>
<td>Raw change CMT-HI total score</td>
<td>-0.2 (3.3)</td>
<td>-2.2 (3.1)</td>
</tr>
<tr>
<td>Raw change CMT-HI activities subscale score</td>
<td>-4.9 (4.8)</td>
<td>3.5 (4.9)</td>
</tr>
<tr>
<td>Raw change CMT-HI fatigue subscale score</td>
<td>3.0 (5.1)</td>
<td>-6.7 (5.0)</td>
</tr>
</tbody>
</table>

6MWD = 6-minute walk distance; 10mW/R = 10 meter walk/run; CI = confidence interval; CMT-HI = Charcot-Marie-Tooth Health Index; LS = least squares; SEM = standard error of the mean; MMT = manual muscle test; MVIC = maximum voluntary isometric contraction
Mean (SEM) Change in Ankle Dorsiflexion Strength

**MVIC**

**MMT**

Double-blind

Open-label

SEM = standard error of the mean; MVIC = maximum voluntary isometric contraction; MMT = manual muscle test; LS = Least-squares

*LS mean difference (ACE-083 vs. Placebo) = 0.30; p = 0.03*
Mean (SEM) Percent Change in 6MWD, 10mW/R

SEM = standard error of the mean; 6MWD = 6-minute walk distance; 10mW/R = 10 meter walk/run

Data as of 14 Feb 2020
Mean (SEM) Absolute Change in CMT-HI Total Score

Data as of 14 Feb 2020
Safety Results, Part 2
ACE-083 CMT Study – Adverse Events, Part 2

- ACE-083 was generally well tolerated during the double-blind period (to Day 190)
- Majority of AEs were mild/moderate; no drug-related serious adverse events

### Possibly or Probably Related AEs Occurring in ≥10% Patients Treated with ACE-083 in the Double-Blind Period

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Double-Blind Period</th>
<th>Open-Label ACE-083</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=21 n (%)</td>
<td>ACE-083 N=23 n (%)</td>
</tr>
<tr>
<td>At least 1 related TEAE</td>
<td>11 (52.4%)</td>
<td>16 (69.6%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>1 (4.8%)</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2 (9.5%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>2 (9.5%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (9.5%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>1 (4.8%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>(4.8%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>0</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Injection site discomfort</td>
<td>4 (19.0%)</td>
<td>4 (17.4%)</td>
</tr>
<tr>
<td>Injection site warmth</td>
<td>2 (9.5%)</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>0</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>0</td>
<td>3 (13.0%)</td>
</tr>
</tbody>
</table>

Note: 4 patients who received at least 1 dose in the double-blind period discontinued prior to the start of the open-label period  
Data as of 14 Feb 2020
ACE-083 CMT Study – Conclusions

- Consistent with previous clinical studies, ACE-083 treatment resulted in statistically significant muscle volume increases and was generally well tolerated.

- The placebo-controlled part of this study met the primary endpoint of statistically significant differences in TMV and CMV percent change between ACE-083 and placebo at study day 190 (6 months):
  - 13.5% greater increase in total muscle volume by MRI (p=0.01)
  - 23.3% greater increase in contractile muscle volume (p=0.02)

- Ankle dorsiflexion strength increased by manual muscle testing by 1 level (p=0.03); no statistically significant improvement by dynamometry.

- No statistically significant differences in motor function tests or CMT-HI total score:
  - There was a trend for improvement in fat fraction by MRI and CMT-HI fatigue score.

- Adverse events (non-ISR) more common in ACE-083 group included myalgia, pain in extremity, arthralgia, joint swelling, and musculoskeletal stiffness.

- A learning effect was observed for the motor function tests, supporting consideration of a run-in period and appropriate control arm in future neuromuscular studies.

Data as of 14 Feb 2020
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