A Phase 2 study to evaluate ACE-083, a local muscle therapeutic, in patients with FSHD

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Background

- ACE-083 is a locally-acting investigational protein therapeutic that blocks GDF8 (myostatin) and other TGF-β superfamily inhibitors of skeletal muscle growth; it is designed to increase muscle mass and strength selectively in the muscle in which the drug is administered.
- In wild type (WT) mice, local injection of ACE-083 2x/wk for 4 wks into the gastrocnemius muscle led to localized, dose-dependent hypertrophy and increases in strength of the target muscle.
- In mouse models of myogenic (mdx) and neurogenic (SOD1) muscle disease, local injection of ACE-083 into the tibialis anterior 2x/wk for 4 wks increased muscle mass and peak tetanic strength.

Phase 1 Healthy Volunteer Clinical Study Design

- In a recently completed phase 1, double-blind, placebo-controlled, dose-escalation study in 58 healthy post-menopausal women, ACE-083 was unilaterally injected into the right rectus femoris (RF) or tibialis anterior (TA) muscle under EMG guidance (NCT02257489).
- Cohorts 1-3 tested single doses of 50, 100, and 200mg in the RF; cohorts 4-5 tested two doses (1 day and day 22) of 100 and 200mg in the RF; 2 to 4 injections/dose.
- Cohorts 6-7 tested two doses (1 day and day 22) of 100 and 150mg in the TA.

Efficacy Results

- At 3 weeks after the last dose of ACE-083, mean increases in muscle volume of the right RF and the right TA were 14.5% and 8.9%, respectively, at the highest dose levels tested (p<0.001 vs placebo for each muscle) with no effect in the contralateral uninjected muscle.
- Increases in muscle volume correlated with dose administered of ACE-083 in mg/g of muscle.
- No consistent changes were observed in knee extension (RF) or dorsiflexion (TA) strength in these healthy subjects.

Safety Results

- No serious adverse events (AEs), dose-limiting toxicities, or discontinuations due to AEs.
- All AEs were grade 1-2, transient, and most commonly injection-site related.
- Similar AE incidence was observed in placebo and active groups.

References

- Mullivor et al. World Muscle Society, 2014
- Mullivor et al. ICMHD, 2014
- Pearsall et al. World Muscle Society, 2015
- Glasser et al. Conf. on cachexia, sarcopenia, 2015
- Pearsall et al. MDA Clinical Conference, 2016
- Attie et al. ICMHD, 2016

Phase 2 FSHD Clinical Study Assessments

- Muscle volume: Percent change from baseline in muscle volume of injected muscle by MRI.
- Strength: Percent change from baseline in strength of injected muscle by quantitative muscle testing (fixed system and hand-held dynamometer).
- Function: TA: 10 meter walk/run, 4-stair climb, 6 minute walk test, gait analysis.
- BB: Performance of Upper Limb (PUL), FSHD-Health Index upper extremity sub-scores.
- Health-related quality of life: FSHD-Health Index (FSHD-HI) questionnaire overall score.

Summary/Conclusions

- ACE-083 is a locally-acting agent for the growth and regeneration of muscle.
- Its mode of administration is well-suited for FSHD due to the focal involvement of specific muscles, often asymmetrical.
- Results of the Phase 1 study in healthy volunteers demonstrated marked, dose-dependent increases in muscle volume by MRI after 1 or 2 doses.
- These results support the evaluation of ACE-083 in a phase 2 study in patients with FSHD, targeting both upper arm and lower leg (foot drop) weakness (NCT02927080).

Related Adverse Events in ≥10% of Any Pooled-Active Group in Study A083-01

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>RF (Cohorts 1-5)</th>
<th>TA (Cohorts 6-7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term [%]</td>
<td>Placebo (N=10)</td>
<td>ACE-083 (N=80)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>5.0</td>
</tr>
<tr>
<td>Injection site pain</td>
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<td>Injection site reaction</td>
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<tr>
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<td>0.0</td>
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<td>Injection site bruising</td>
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<td>Injection site edema</td>
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<td>0.0</td>
</tr>
<tr>
<td>Injection site erythema</td>
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<td>0.0</td>
</tr>
<tr>
<td>Injection site reaction</td>
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<td>0.0</td>
</tr>
</tbody>
</table>

Phase 2 FSHD Clinical Study Design

- Part 1: open-label, sequential, dose-escalation cohorts in either the tibialis anterior (TA) or biceps brachii (BB), with objective to identify dose to be used in Part 2.
- Part 2: randomized, double-blind, placebo-controlled in one or both muscles, tibialis anterior (TA) and biceps brachii (BB) at the dose identified in Part 1.

Safety and Tolerability

- Part 1: open-label, sequential, dose-escalation cohorts.

- Part 2: randomized, double-blind, placebo-controlled in one or both muscles, tibialis anterior (TA) and biceps brachii (BB) at the dose identified in Part 1.

References

- Mullivor et al. World Muscle Society, 2014
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