BACKGROUND

• Reldesemtiv, also known as CLT-217 or CLT-107, is a selective, small molecule fast skeletal muscle troponin activator (FSTA) that sensitizes the sarcolemma to Ca2+ by slowing the rate of Ca2+ release from troponin (Figure 1).

• FSTAs have the potential to slow the decline of skeletal muscle function in diseases and conditions associated with muscle weakness or fatigue including amyotrophic lateral sclerosis (ALS).

Figure 1. FSTAs selectively activate the fast skeletal muscle troponin complex

• A phase 3 clinical trial (VITALITY-ALS) of riluzole (a first generation FSTA of unrelated structure) in patients with ALS was impacted by dose-related tolerability issues1.

• However, trends were noted suggesting a benefit of riluzole in patients tolerating their assigned dose.

• Reldesemtiv is optimized to limit crossing the blood brain barrier.

• Preclinical studies, reldesemtiv showed greater pharmacodynamic effects at lower plasma concentrations than riluzole.2

• A phase 1 trial of reldesemtiv in healthy volunteers demonstrated increased tibialis anterior muscle power with sub-tetanic stimulation rates of the common fibular nerve most marked with rates of 7.5–12.5 Hz.

• Repeated doses of reldesemtiv at doses up to 500 mg twice daily (BID) for up to 17 days were well tolerated.

OBJECTIVE

• To evaluate the tolerability and preliminary efficacy of reldesemtiv versus placebo in patients with ALS.

METHODS

FORTITUDE-ALS

• Phase 2, double-blind, randomized, placebo-controlled, multiple-dose study of reldesemtiv in patients with ALS.

• Patients are randomized 1:1:1:1 to placebo or reldesemtiv 150, 300, or 450 mg BID for 12 weeks (Figure 2).

Figure 2. Study schematic

Key Design Elements

Population:

• Diagnosis of ALS for ≤24 months.

• Uptight slow vital capacity (EVC) ≥60% of predicted for age, height, and sex at screening.

• Patients were stratified by riluzole and edaravone use.

Primary Endpoint:

• Change from baseline to week 12 in percent predicted SVC.

Secondary Endpoints:

• Slope of the change from baseline in the mega score of muscle strength measured by handheld dynamometry and hand grip dynamometry from baseline to week 12 in patients on reldesemtiv compared with placebo.

• Change from baseline to week 12 in the ALS Functional Rating Scale – Revised (ALSFRS-R).

Safety Endpoints:

• Incidence and severity of treatment-emergent adverse events.

• Pharmacokinetic Measurements:

• Plasma concentrations of reldesemtiv at the sampled time points during the study.

• Unique Study Design Features

• Exploratory and Other Endpoints

• Fine motor skills assessed on iPad app at clinic visits.

• Voice recording assessed on app on a patient device weekly at home and on iPad at clinic visits.

• Weekly home SVC testing.

• Health economics outcome measures: when a patient is prescribed and agrees to use:

– Manual or power wheelchair
– Augmentative/alternative communication
– Feeding tube
– Noninvasive ventilation
– Central review of flow volume loop by pulmonologist

RESULTS

• Overall, 458 patients were randomized (Table 1).

<table>
<thead>
<tr>
<th>Use Neither</th>
<th>Use Riluzole Only</th>
<th>Use Edaravone Only</th>
<th>Use Both</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients randomized</td>
<td>86</td>
<td>259</td>
<td>19</td>
<td>94</td>
</tr>
</tbody>
</table>

• Demographic and baseline characteristics were similar between patients who received riluzole or edaravone alone, both, or neither (Table 2).

Table 2. Demographics and baseline disease characteristics of randomized patients

• Efficacy: riluzole and edaravone use was associated with a slower decline in functional measurements compared with placebo.

• Across the study period, riluzole and edaravone were well tolerated.

CONCLUSIONS

• This phase 2 study will evaluate tolerability and preliminary efficacy of reldesemtiv in patients with ALS.

• FORTITUDE-ALS is fully enrolled and completion of the trial is anticipated in the first half of 2019.

• Demographics of the participants enrolled in FORTITUDE-ALS are similar to those of other recent, large ALS clinical trials.

References


2. Personal communication, Noah Lechtzin, MD, PhD; Senior Medical Director, Evidence-Based Medicine, Biogen, Cambridge, MA, USA; 2018.

Disclosures

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• The authors have no other financial interests or personal relationships that could have appeared to influence the work reported in this presentation.

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• Andrew JA, et al. Presentation at Motor Neurone Disease Association; 28th International Symposium on ALS/MND; 8–10 December 2017; Boston, MA.