A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled Trial to Evaluate the Efficacy and Safety of *Reldesemtiv* in Patients with Amyotrophic Lateral Sclerosis (ALS): COURAGE-ALS Trial Design

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BACKGROUND

- Fast skeletal muscle troponin activators (FSTAs) increase muscle force by sensitizing the sarcomere to calcium[1]
- *Reldesemtiv* is a second generation FSTA being investigated as a potential therapy for treating muscle fatigue and weakness in amyotrophic lateral sclerosis (ALS)
- FORTITUDE-ALS (NCT03160898) was a 12-week, Phase 2, double-blind study in patients with ALS (N = 458) randomized to 1 of 3 doses of *reldesemtiv* or placebo[2]
  - The primary analysis of change from baseline to Week 12 in slow vital capacity (SVC) did not reach statistical significance, but positive trends were seen in SVC, ALS Functional Rating Scale-Revised (ALSFRS-R), and muscle strength
  - The effect of *reldesemtiv* was more evident in patients with shorter symptom duration and faster pre-study disease progression rates
  - There was a dose-dependent decrease in estimated glomerular filtration rate (eGFR) that reversed on discontinuation

OBJECTIVE

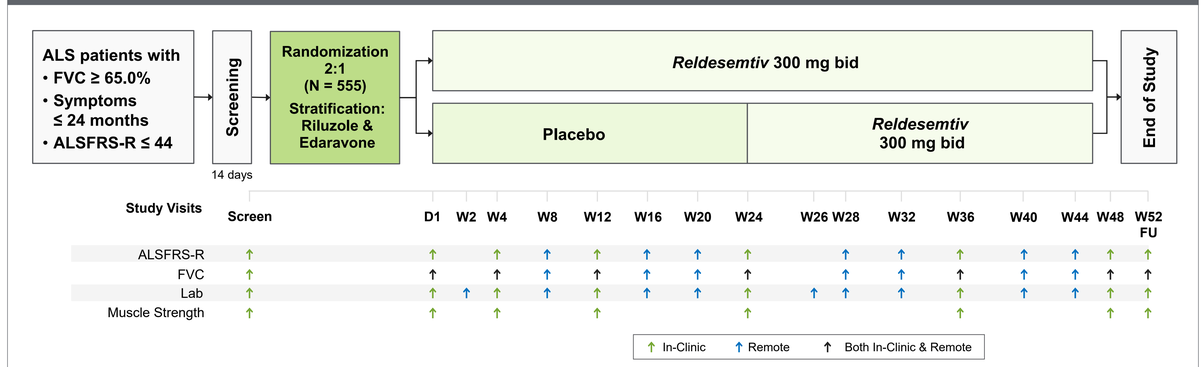
- To design a Phase 3 trial investigating the impact of treatment with *reldesemtiv* 300 mg bid up to 48 weeks in patients with ALS, building on insights gained from FORTITUDE-ALS with respect to dose level, taking into account outcomes and adverse events, as well as the appropriate patient population

METHODS

COURAGE-ALS (Clinical Outcomes Using *Reldesemtiv* on ALSFRS-R in a Global Evaluation in ALS) will be a randomized, double-blind, placebo-controlled Phase 3 trial

- Approximately 555 patients will be randomized in a 2:1 ratio to achieve at least 90% power to detect a 1.8-point treatment difference between *reldesemtiv* 300 mg bid or placebo in the change from baseline to Week 24 in ALSFRS-R total score
- The double-blind, placebo-controlled period will be followed by a 24-week, open-label period in which all patients will receive *reldesemtiv*
- *Reldesemtiv* will be taken bid, morning and afternoon (at least 8 hours apart), within a 2-hour period following food
- Study schematic and visits are shown in **Figure 1**

Figure 1. Study schematic



ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; FU, follow-up; FVC, forced vital capacity

Key inclusion criteria at screening

- Age 18–80 years
- Upright forced vital capacity (FVC) ≥ 65.0% predicted using Global Lung Function Initiative reference values
- Symptoms ≤ 24 months
- ALSFRS-R ≤ 44 (re-screening permitted)
- On riluzole for ≥ 30 days prior to screening or not been on it for ≥ 30 days prior to screening
- Completed at least 2 cycles of edaravone at the time of screening or not been on it for ≥ 30 days prior to screening
- Able to swallow whole tablets

Key exclusion criteria at screening

- Other medically significant neurological conditions that could interfere with the assessment of ALS symptoms, signs, or progression
- Presence at screening of any medically significant cardiac, pulmonary, gastrointestinal, musculoskeletal, or psychiatric illness that might interfere with the patient's ability to comply with study procedures or that might confound the interpretation of clinical safety or efficacy data
- $eGFR_{CysC}$ (estimated glomerular filtration rate calculated using cystatin C) < 45.0 mL/min/1.73 m^2 at screening
- Has received or is considering receiving during the course of the trial any form of gene therapy for the treatment of ALS
- Has received or is considering obtaining during the course of the trial a diaphragmatic pacing system
- Has a tracheostomy

Study endpoints

- Primary
  - Change from baseline to Week 24 in ALSFRS-R total score using a mixed model for repeated measures
- Secondary
  - Combined assessment of ALSFRS-R total score, time to onset of respiratory insufficiency, and survival time up to Week 24 using a joint rank test, following an algorithm that ranks each patient against the other
    - Respiratory insufficiency is defined as patients with a tracheostomy or using non-invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days
    - Patients with respiratory insufficiency are ranked lower than those with the largest drops in ALSFRS-R scores but higher than those who have died
  - Change from baseline to Week 24 in the % predicted FVC
  - Change from baseline to Week 24 in the ALS Assessment Questionnaire-40 (ALSAQ-40)
  - Change from baseline to Week 24 in handgrip strength (average of both hands)
  - Selected exploratory endpoints include time to receipt, first and substantial use of durable medical equipment; time spent in each Milano Torino Stage and number of stages moved; and hand-held dynamometry of selected intrinsic hand muscles

Planned interim analyses

- First interim analysis
  - May be conducted 12 weeks after about 1/3 of the planned sample size is randomized
  - Futility analysis: determine whether the treatment difference of the change from baseline at Week 12 in ALSFRS-R total score favors placebo vs *reldesemtiv*
- Second interim analysis
  - To be conducted 24 weeks after at least 1/3 of the planned sample size is randomized
  - Interim analysis: to determine if the study is futile or promising based on the conditional power to achieve the primary endpoint and if it requires a pre-specified fixed increase of sample size to increase the power of the trial

CONCLUSIONS

- The Phase 3 COURAGE-ALS trial will test the hypothesis that fast skeletal muscle activation using *reldesemtiv* is an important therapeutic strategy in ALS
- Given that patients in this trial will be symptomatic and progressing on their existing background therapy, those randomized to *reldesemtiv* may be afforded an opportunity to slow the decline in their function

References

1. Hwee et al. (2015). *J Pharmacol Exp Ther.* 353:159–168.
2. Shefner et al. (2020). *Amyotroph Lateral Scler Frontotemporal Degener.* Epub ahead of print.

Acknowledgments

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