Update of COURAGE-ALS: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Efficacy and Safety of *Reldesemtiv* in Patients With ALS

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BACKGROUND

Reldesemtiv

- *Reldesemtiv* is a selective, small molecule, fast skeletal muscle troponin activator that sensitizes the sarcomere to calcium by increasing the affinity of troponin for calcium

FORTITUDE-ALS

- FORTITUDE-ALS (NCT03160898) was a 12-week, Phase 2, double-blind trial in which patients with amyotrophic lateral sclerosis (ALS) were randomized to 1 of 3 *reldesemtiv* orally administered doses or placebo[1]
  - Key eligibility criteria were diagnosis of ALS ≤ 24 months before the trial and slow vital capacity (SVC) at screening ≥ 60% of predicted
  - No restrictions were placed on patients' ALS Functional Rating Scale-Revised (ALSFRS-R) scores (total or single item) or pre-study disease progression
- Trial results showed *reldesemtiv* was well tolerated; with nausea and fatigue being the most common side effects
  - A dose-dependent decrease in estimated glomerular filtration rate was noted, and transaminase elevations were seen in ~5% of patients; both hepatic and renal abnormalities trended toward resolution after study drug discontinuation
- The primary efficacy analysis (change in SVC from baseline to Week 12) did not achieve statistical significance; nevertheless, post hoc analyses pooling all active *reldesemtiv*-treated patients versus placebo showed trends toward benefit in all endpoints (progression rate for SVC, ALSFRS-R, and muscle strength)
  - Further post hoc analyses suggested that treatment effects might be more apparent in patients with shorter duration of symptoms and lower baseline ALSFRS-R scores; that is, faster rates of disease progression before the study[1]
- In clinical trials, including a higher proportion of patients with faster pre-study disease progression could increase trial efficiency and sensitivity to detect a treatment effect

COURAGE-ALS

- COURAGE-ALS (**Cl**inical **O**utcomes **U**sing ***R**eldesemtiv* on **A**LSFRS-R in a **G**lobal **E**valuation in **ALS**, also known as CY 5031 or NCT04944784) is a randomized, double-blind, placebo-controlled, Phase 3 trial
- The trial was designed to evaluate the effect of *reldesemtiv* versus placebo on functional outcomes and a joint rank test of function, respiratory insufficiency, and survival in patients with ALS
- In light of the FORTITUDE-ALS data, different eligibility criteria were applied to COURAGE-ALS, with the aim of enrolling a higher proportion of patients with moderate to fast disease progression

OBJECTIVES

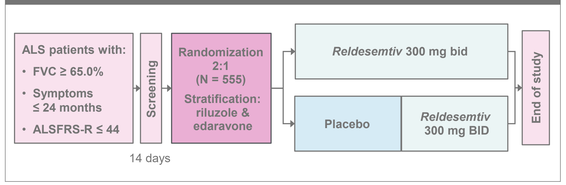
- Compare baseline characteristics of patients enrolled in FORTITUDE-ALS with patients enrolled, as of 29 October 2021, in COURAGE-ALS
- Determine if, at this early stage of the trial enrollment period, targeted inclusion criteria have achieved the intended goal to minimize (but not exclude) enrollment of patients with slower pre-study disease progression
  - Targeted criteria were symptom duration of ≤ 24 months and a maximum total score of 44 on the ALSFRS-R

TRIAL UPDATE

COURAGE-ALS Study Design Overview

- Key inclusion criteria for COURAGE-ALS (**Figure 1**) include symptom onset within 24 months, ALSFRS-R total score of ≤ 44, and upright forced vital capacity (FVC) ≥ 65% of predicted for age, height, and sex
- Stable doses of riluzole and/or edaravone are permitted, with randomization stratified accordingly
- Participants (planned enrollment = 555) are randomized 2:1 to *reldesemtiv* 300 mg orally twice daily or placebo for 24 weeks; all patients then receive open-label *reldesemtiv* for an additional 24-week period

Figure 1. COURAGE-ALS study schematic



ALSFRS-R, ALS Functional Rating Scale-Revised; BID, twice daily; FVC, forced vital capacity

Trial Status

- The first patient enrolled in COURAGE-ALS in August 2021
- At the data cut-off on 29 October 2021, 27 patients had enrolled

Patient Characteristics

- **Table 1** shows characteristics of patients enrolled to date in COURAGE-ALS alongside the FORTITUDE-ALS population

Pre-Study Disease Progression Rate (PSDPR)

- The ALS pre-study disease progression rate (PSDPR) was estimated with the formula:

$$\frac{48 - (\text{ALSFRS-R total score at baseline})}{\text{Duration of ALS symptoms in months}}$$

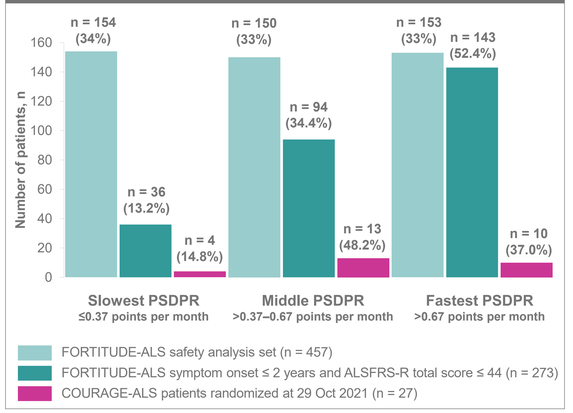
- Progression categories were defined by PSDPR tertiles of patients in FORTITUDE-ALS:
  - Slow progressors ≤0.37 points per month
  - Middle progressors >0.37–0.67 points per month
  - Fast progressors >0.67 points per month
- For patients enrolled to date in COURAGE-ALS, we determined the proportion in each of these PSDPR categories (**Figure 2**)

Table 1. Patient demographics and characteristics

	FORTITUDE-ALS (n = 457) (full study enrollment)	COURAGE-ALS (n = 27) (at 29 Oct 2021)
Age, years, mean ± SD	58.7 ± 10.7	62.7 ± 12.8
Male, n (%)	277 (60.6)	15 (55.6)
ALSFRS-R total score, mean ± SD	37.4 ± 5.5	37.1 ± 3.9
Vital capacity (% predicted), mean ± SD*	84.7 ± 15.3	87.7 ± 14.8
Months since diagnosis, mean ± SD	8.6 ± 6.1	8.0 ± 6.0
Months since 1st symptom, mean ± SD	22.8 ± 19.1	16.7 ± 6.8
ALS site of onset: bulbar, n (%)	87 (19.0)	6 (22.2)
ALS family history: yes, n (%)	53 (11.6)	1 (3.7)
ALS therapies, n (%)†		
On riluzole alone	258 (56.5)	15 (55.6)
On edaravone alone, n (%)	19 (4.2)	1 (3.7)
On riluzole & edaravone, n (%)	94 (20.6)	10 (37.0)

*Slow vital capacity in FORTITUDE-ALS; forced vital capacity in COURAGE-ALS.
†One patient in COURAGE-ALS was on neither riluzole or edaravone.
ALSFRS-R, ALS Functional Rating Scale-Revised; SD, standard deviation

Figure 2. Distribution to date of patients in COURAGE-ALS according to PSDPR tertiles defined in FORTITUDE-ALS



Descriptive statistics only. Percentages for the 3 groups, respectively, show the proportion of the FORTITUDE-ALS safety analysis set (all patients who received ≥ 1 study drug dose), the FORTITUDE-ALS subgroup who had symptom onset ≤ 2 years and ALSFRS-R total score ≤ 44, and the COURAGE-ALS population randomized as of 29 October 2021.
ALSFRS-R, ALS Functional Rating Scale-Revised; PSDPR, pre-study disease progression rate

SUMMARY

- The COURAGE-ALS trial has been undertaken to provide clear evidence as to whether a fast skeletal troponin activator can have a meaningful role in the treatment of patients with ALS
- The trial began enrolling patients in August 2021, and 27 patients had enrolled as of 29 October 2021
- Following results from the Phase 2 FORTITUDE-ALS trial, the Phase 3 COURAGE-ALS trial was designed with different entry criteria
  - The aim was to minimize (but not exclude) the proportion of participants with more slowly progressing disease (defined as a PSDPR of < 0.37 points per month) and to increase the proportion with moderate or fast pre-study disease progression (defined as ≥ 0.37 points per month)
  - Adjustments to entry criteria to achieve this included limiting ALS symptom onset to 24 months before starting the trial and setting the maximum screening ALSFRS-R total score to 44 points

CONCLUSIONS

- In this very early analysis of the limited patient population who have enrolled thus far in COURAGE-ALS, it appears that adjusting the inclusion criteria is achieving the planned goal of increasing the proportion of patients with moderate and fast pre-study disease progression rates as compared with FORTITUDE-ALS
  - Once the study is fully enrolled, we will be able to ascertain if that shift has been maintained throughout the trial

References

1. Shefner JM et al. Amyotroph Lateral Scler Frontotemporal Degener 2021;22: 287-99.

Acknowledgments

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