A Phase 2, Double-Blind, Randomized, Dose-Ranging Trial Of *Reldesemtiv* In Patients With ALS

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A Phase 2, Double-Blind, Randomized, Dose-Ranging Trial Of Reldesemtiv In Patients With ALS

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Abstract

Objective: To evaluate safety, dose response, and preliminary efficacy of reldesemtiv over 12 weeks in patients with amyotrophic lateral sclerosis (ALS). Methods: Patients (≤2 years since diagnosis) with slow upright vital capacity (SVC) of ≥60% were randomized 1:1:1:1 to reldesemtiv 150, 300, or 450 mg twice daily (bid) or placebo; active treatment was 12 weeks with 4-week follow-up. Primary endpoint was change in percent predicted SVC at 12 weeks; secondary measures included ALS Functional Rating Scale-Revised (ALSFRS-R) and muscle strength mega-score. Results: Patients (N = 458) were enrolled; 85% completed 12-week treatment. The primary analysis failed to reach statistical significance (p = 0.11); secondary endpoints showed no statistically significant effects (ALSFRS-R, p = 0.09; muscle strength mega-score, p = 0.31). Post hoc analyses pooling all active reldesemtiv-treated patients compared against placebo showed trends toward benefit in all endpoints (progression rate for SVC, ALSFRS-R, and muscle strength mega-score (nominal p values of 0.10, 0.01 and 0.20 respectively)). 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 approximately 5% of patients. Both hepatic and renal abnormalities trended toward resolution after study drug discontinuation. Conclusions: Although the primary efficacy analysis did not demonstrate statistical significance, there were trends favoring reldesemtiv for all three endpoints, with effect sizes generally regarded as clinically important. Tolerability was good; modest hepatic and renal abnormalities were reversible. The impact of reldesemtiv on patients with ALS should be assessed in a pivotal Phase 3 trial. (ClinicalTrials.gov Identifier: NCT03160898)

Keywords: Randomized clinical trial, amyotrophic lateral sclerosis, reldesemtiv

Introduction

Fast skeletal muscle troponin activators (FSTAs) sensitize the sarcomere to calcium and increase muscle force. This mechanism is of potential relevance in amyotrophic lateral sclerosis (ALS) and other neuromuscular disorders that cause weakness and muscle fatigue. A first-generation FSTA, tirasemtiv, showed promise in phase 2a studies in ALS (1–3) and myasthenia gravis (4). Additionally, a large phase 2b study of tirasemtiv in ALS suggested efficacy by slowing the rates of decline of slow vital capacity (SVC) and isometric muscle strength (5). Dizziness was the most common adverse event (AE) of tirasemtiv, which often resulted in dropout from the study. A subsequent phase 3 trial was designed to reduce the incidence of early termination. The trial failed to show a statistically significant effect on any endpoint; however, large numbers of dose-dependent, early terminations due to poor tolerability still occurred and confounded the interpretation of the trial results (6).

Reledesemtiv is a second generation FSTA derived from a different chemical scaffold than tirasemtiv, with limited penetration of the blood-brain barrier to minimize off-target effects. A single-dose study in healthy participants showed that reledesemtiv had a greater pharmacodynamic effect on muscle force generation with submaximal nerve stimulation frequencies than tirasemtiv, and central nervous system side effects were not noted (7, 8). Based on these data, the phase 2b trial, FORTITUDE-ALS (Functional Outcomes in a Randomized Trial of Investigational Treatment with CK-2127107 to Understand Decline in Endpoints – in ALS), was designed to study the safety, tolerability, and preliminary efficacy of three doses of reldesemtiv versus placebo in patients with ALS.

Methods

Patients

This randomized, double-blind, multicentre, dose-ranging, placebo-controlled, phase 2b trial recruited patients from 65 clinical trial sites in the United States, Canada, Ireland, Spain, the Netherlands, and Australia. Patients were between 18 and 80 years of age, and diagnosed within 24 months with possible, laboratory-supported probable, probable, or definite ALS according to the revised El Escorial criteria (9). An upright SVC ≥60% predicted for age, height, sex, and ethnic group at screening was required for inclusion. Patients on riluzole must have taken it for ≥30 days prior to screening. Following protocol amendment 2 (August 10, 2017), patients on edaravone were eligible to enroll in the trial and must have completed ≥2 cycles prior to screening. Exclusion criteria included prior use of reldesemtiv or tirasemtiv or receipt of stem cell or gene therapy for ALS.

Standard protocol approvals, registrations, and patient consents

All patients provided written informed consent, and all sites received institutional review board
approvals prior to enrollment. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. FORTITUDE-ALS was registered with ClinicalTrials.gov (NCT03160898) and was conducted between August 2017 and March 2019.

**Trial design and assessments**

After a screening period of up to 14 days, eligible patients were randomized via an interactive web response system 1:1:1:1 to placebo or reldesemtiv (CK-2127107) oral tablets 150, 300, or 450 mg twice daily (bid) stratified by use and nonuse of riluzole and edaravone. All site clinical staff (investigators, pharmacists, support staff) involved with the study, patients, and the sponsor were blinded to treatment assignment. Study medication was to be taken twice daily, approximately 12 ± 2 hours apart and within 2 h following a meal. The active treatment period was 12 weeks with assessments at day 1 and weeks 2, 4, 8, and 12 and at a follow-up visit 4 weeks after the last dose.

The primary endpoint was the change in percent predicted SVC, from baseline to week 12. To qualify for the study, at screening in addition to having a minimum SVC of 60% of predicted based upon the global lung initiative values (10), patients also had to demonstrate less than 10% variability of the two highest values in five or fewer attempts. All flow volume loops were reviewed by blinded pulmonologists. Secondary endpoints included changes in the ALS Functional Rating Scale-Revised (ALSFRS-R) Total Score and the slope of muscle strength mega-score from baseline to week 12 measured by hand-held dynamometer and by hand grip dynamometry. The following muscle groups were tested bilaterally: elbow flexion, wrist extension, first dorsal interosseous, hip flexion, knee extension, and ankle dorsiflexion. Plasma concentrations for each dose level of reldesemtiv were assessed at day 1 and weeks 2, 4, 8, and 12. Safety assessments included the incidence and severity of treatment-emergent AEs (TEAEs) as recorded using the Medical Dictionary for Regulatory Activities version 20.0 as well as vital signs, clinical laboratory tests, electrocardiograms, Beck Depression Inventory-Fast Screen, Ashworth Score, and physical and neurological examinations.

**Statistical analysis**

The full analysis set (FAS) consisted of all randomized patients who received any study drug and had a baseline and at least one post-baseline efficacy assessment during the double-blind period. The safety analysis set included all randomized patients who received any study drug. The pharmacokinetics analysis consisted of all randomized patients with at least one evaluable plasma concentration of reldesemtiv.

The primary efficacy analysis hypothesis was that reldesemtiv had a beneficial and dose-dependent effect on function as measured by the change from baseline to week 12 in the percent predicted SVC. To test this hypothesis, a mixed model for repeated measures (MRRM) with a contrast (−5, −1, 3, 3) for the placebo and reldesemtiv 150 mg bid, 300 mg bid, and 450 mg bid dose groups was used (SAS® version 9.4 or greater). The response variable in the model was the change in the percent predicted SVC from baseline to each post-baseline visit. The model also included the terms of treatment, baseline value, pooled site, visit, and randomization stratification factors of baseline riluzole and/or edaravone use/nonuse, as well as treatment-by-visit and baseline-by-visit interactions. An unstructured variance-covariance structure was used in the model. The model included all observed data points from baseline to week 12 for all patients in the FAS with missing values maintained as missing and imputed missing data under the missing at random paradigm and provided the estimates at week 12 from the observed data. For the secondary efficacy outcomes, change from baseline in the ALSFRS-R was analyzed using the same model as above.

The global null hypothesis for the primary and secondary efficacy endpoints were tested in a prespecified order (as listed above) using a closed testing procedure, and maintained the family-wise error rate at two-sided significance level of 0.05 for all hypotheses tested. No adjustment for multiplicity was made for analyses of all reldesemtiv groups pooled versus placebo, and subgroups defined by patient characteristics that were post hoc exploratory; all p values of statistical significance are nominal. An estimated 445 patients had to be randomized to provide 90% power to detect a 2.75, 5.5, and 5.5 percentage point advantage over placebo for the 150 mg bid, 300 mg bid, and 450 mg bid reldesemtiv dose groups, respectively, in change from baseline of percent predicted SVC, at the end of the double-blind period (week 12). This calculation was based on a two-sided test with \( \alpha \) set at 0.05 and an assumed common standard deviation of 14%.

**Results**

Of the 605 patients screened, 458 were randomized to placebo \((n = 115)\) or reldesemtiv 150 mg bid \((n = 112)\), 300 mg bid \((n = 113)\), or 450 mg bid \((n = 117)\) (one patient was randomized but withdrew before treatment; Figure 1); 84.7% completed planned dosing. While early termination from active treatment occurred at similar frequencies in all groups, there was a tendency for increased numbers of patients to withdraw from
active treatment due to AEs as a function of increased dose. However, early terminations due to perceived disease progression were more common in the placebo group.

Patient characteristics in the reldesemtiv and placebo groups are detailed in Table 1. Patients were from the United States (n = 284), Canada (n = 101), Spain (n = 38), Australia (n = 20), the Netherlands (n = 11), and Ireland (n = 4). Baseline demographics were well balanced, with no meaningful differences among the 4 groups. The characteristics resemble those of most previous and current ALS trials, with the exception that time from first symptom to screening was 22.8 ± 19.1 months, which is longer than in many recent trials.(6, 11–14) For some trials, symptom onset and not time since diagnosis was the basis of the inclusion criteria, which may contribute to at least some of the differences related to this patient characteristic.(11–14) In addition, 113/457 (24.7%) of patients were on edaravone, either alone or in combination with riluzole. Edaravone was used only by patients in the United States and Canada.

**Efficacy**

The primary efficacy analysis of change from baseline to week 12 in percent predicted SVC using MMRM did not show a statistically significant weighted dose-response relationship. Placebo-treated patients showed a decline in vital capacity of 6.46 percentage points at week 12, while the patients treated with 150 mg bid, 300 mg bid, and 450 mg bid reldesemtiv showed declines of 4.97 percentage points, 4.62 percentage points, and 4.58 percentage points, respectively (p = 0.11; Figure 2(A)). Analyses of changes from baseline in the ALSFRS-R Total Score (Figure 2(C)) and the muscle strength mega-score (Figure 2(E)) using a similar mixed model also did not reach statistical significance (p = 0.09 for change from baseline to week 12 in ALSFRS-R Total Score; p = 0.31 for muscle strength mega-score slope from baseline through week 12), although both measures showed trends toward benefit at all doses. A post hoc comparison of all reldesemtiv-treated patients pooled together versus placebo showed reductions in decline by 27%, 25% and 21% for change from baseline to week 12 in SVC, change from baseline to week 12 in ALSFRS-R Total Score, and muscle strength mega-score from baseline through 12 weeks (nominal p = 0.10, 0.01, and 0.20, respectively; Figure 2(B,D,F)). As seen in Figure 2, at the week 16 visit, which was 4 weeks after the study drug was stopped, there was a tendency for beneficial effects for those assigned reldesemtiv to still be...
present for all three outcome measures, most notably for SVC and ALSFRS-R.

Post hoc comparisons of all reldesemtiv groups pooled versus placebo in subgroups defined by various patient characteristics at baseline showed that trends toward efficacy were seen with virtually all subgroups across all three outcome measures, and no subgroup appeared to be deleteriously affected by reldesemtiv, suggesting that a potentially beneficial effect of reldesemtiv was not driven by a single patient group (Figure 3(A–C)). Overall, patients appeared to benefit from reldesemtiv regardless of edaravone orriluzole treatment during the trial. There were no statistical differences between patients receiving reldesemtiv (all doses pooled) compared to the placebo group, irrespective of whether or not they were taking edaravone or riluzole ($p = 0.055$ to 0.57); patients taking riluzole and receiving reldesemtiv (all doses combined) seemed to have a nominal statistical significant reduction in the change in ALSFRS-R Total Score at 12 weeks compared to placebo ($p = 0.029$). A statistically significant reduction in the change in ALSFRS-R at 12 weeks on reldesemtiv (all dose levels pooled) versus placebo was observed among patients who had ALS symptom onset less than 2 years prior to baseline (least squares [LS] mean difference ± standard error [SE] $1.4 ± 0.5$ for all patients treated with reldesemtiv [$n = 199$] versus placebo [$n = 56$]; $p = 0.0025$) (Figure 3(B)).

In post hoc analyses, outcomes were also evaluated by estimated rate of disease progression using the date of symptom onset and the ALSFRS-R Total Score at baseline. Patients were sorted into tertiles: slowest (pretrial reduction of ALSFRS-R Total Score ≤0.37 per month), middle (0.37–0.67 per month), and fastest (>0.67 per month). In the fastest progressing tertile, there was a statistically significant difference between all reldesemtiv dose levels combined and placebo that favored reldesemtiv in the change from baseline in the ALSFRS-R (LS mean difference ± SE $1.7 ± 0.72$ for all reldesemtiv-treated patients in that tertile [$n = 96$] versus the placebo-treated patients in that tertile [$n = 30$]; $p = 0.018$) (Figure 3(B)). In the combined middle and fastest tertiles, change from baseline in ALSFRS-R Total Score at week 12 was significantly smaller in patients who received any dose of reldesemtiv versus placebo (LS mean treatment difference 1.15, $p = 0.011$); no significant difference between reldesemtiv and placebo was observed in the slowest tertile (Figure 4(A)). Changes from baseline in the ALSFRS-R Fine and Gross Motor Domain scores showed a similar pattern (Figure 4(B,C)); in the middle and fastest tertiles, a significantly smaller change from baseline in the ALSFRS-R Gross Motor Domain score at week 12 was observed in patients treated with reldesemtiv versus placebo (LS mean treatment difference 0.69, $p = 0.0002$).

Safety

Overall, reldesemtiv was well tolerated (Table 2). Serious TEAEs were infrequent; a total of 34 serious TEAEs were equally distributed across all treatment groups and organ systems. The most common serious TEAEs (occurring in >1 patient) regardless of attribution of relationship to study drug are listed in Table 2. There was one death in the placebo group during the 12 weeks of active treatment, and two deaths in the 4-week follow-up period (one in the placebo group, one in the reldesemtiv 450 mg bid group). There were six serious TEAEs as defined by the principal investigator that were attributed to study drug; the event terms were hepatoxicity (two patients), alanine transaminase increased (one patient), urinary retention (one patient), transient ischemic attack (one1 patient) and one patient with increased aspartate
aminotransferase (AST), increased alanine aminotransferase (ALT), increased creatinine kinase, and decreased estimated glomerular filtration rate (eGFR, which was based on cystatin C). Clinical TEAEs were common, occurring in 403/457 (88%) patients. Except for fatigue and nausea, which showed a dose-dependent pattern, events were equally distributed across groups (Table 2). There was no difference between active treatment and the placebo arms regarding the Beck Depression Inventory results or the Ashworth spasticity scores (data not shown). No clinically relevant abnormalities were observed in ECG measurements during the 12-week active treatment and 4-week follow-up periods.

There was a significant dose-dependent relationship noted in both increases in cystatin C and decreases in eGFR determined by cystatin C, with patients showing average reductions in eGFR from baseline to week 12 of 9.2%, 11.2%, and 14.0% in the reldesemtiv 150, 300, and 450 mg bid dose groups, respectively, compared with a small reduction of 2.1% on placebo. Mean eGFR declined to an essentially stable level by 2 weeks of active treatment and tended to recover after 4 weeks off drug (Figure 5). Manifestations of renal toxicity such as renal tubular casts or elevated urine protein were not seen. Decline in eGFR was the most common reason for early termination of study drug due to AEs, occurring in 7/457 (1.5%) patients. Elevated ALT and AST of at least five times the upper limit of normal were noted in a dose-dependent manner, occurring in six patients, four of whom were on 450 mg bid of reldesemtiv and one each on 150 mg bid and 300 mg bid. Four of the six patients were also on riluzole. For these six patients, when the drug was stopped, values returned to normal for five patients and were...
Figure 3. Forest plots from post hoc analyses of LS mean differences between treatment with reldesemtiv and placebo by subgroups for (A) percent predicted SVC, (B) ALSFRS-R, and (C) muscle strength mega-score. *Pretreatment reduction of ALSFRS-R total score per month. ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale- Revised; CI: confidence interval; LSM: least squares mean; pbo: placebo; SVC: slow vital capacity.

improving at the time of last follow-up for one patient. Elevations in ALT and AST were reported as TEAEs in 20/457 (4.4%) and 16/457 (3.5%) patients, respectively (Table 2).

**Pharmacokinetics**

Plasma concentrations of reldesemtiv increased with administration of higher dose levels. The highest levels were observed at the 3 h (± 30 min) post-
dose time point at week 2 for all doses with geometric mean ± SE values of 1.05 ± 1.07 μg/mL, 2.4 ± 1.06 μg/mL, and 3.79 ± 1.07 μg/mL for relde- semtiv 150, 300, and 450 mg bid, respectively.

Compared to a pharmacodynamic translational study in which the common fibular nerve was stimulated at varying frequencies in healthy participants and ankle dorsiflexion force was measured, all three dose levels reached concentrations active in that pharmacodynamic study (7).

Discussion

This phase 2b trial of relde- semtiv in patients with ALS did not meet its pre-specified primary efficacy analysis, despite trends toward efficacy in all functional outcome measures at all dose levels. There are several possible reasons unrelated to the intrinsic effect of relde- semtiv that might explain why the primary endpoint was not reached. First, the primary outcome measure (SVC) in the placebo group in this trial declined more slowly than in most other ALS studies, due to inclusion criteria enriching for slow progressors. Most ALS clinical trials instead try to enrich rapid progressors and have observed a decline in percent predicted SVC of approximately 3 percentage points per month (15–17). In this trial, the decline in SVC in the placebo arm over 12 weeks was 6.46 percentage points, or 2.15 percentage points per 4-week
interval. This slower than expected rate of decline in percent predicted SVC reduced the ability to demonstrate a statistically significant effect of reldesemtiv on SVC. Second, the mixed model with multiple contrasts employed in the primary analysis assumed a negligible effect of the lowest dose (150 mg bid) compared with the two higher doses. As the lowest dose appeared to be active in all three key efficacy measures, this multiple contrast approach may not have been the best analysis to demonstrate a treatment effect of reldesemtiv versus placebo. Finally, this trial enrolled more slowly progressing patients than several recent trials (6, 11–14), which may have somewhat diluted an efficacy signal by some patients not progressing appreciably during the relatively short 12-week duration of active treatment. Indeed, there appeared to be clear evidence of benefit of reldesemtiv among those patients progressing more rapidly prior to randomization and during the course of the trial.

Results of this trial are consistent across the three key outcome measures, all demonstrating reductions in the rates of decline of 20% or more. When a group of ALS experts was surveyed, slowing of the rate of decline of the ALSFRS-R Total Score by 20% was felt to be at least somewhat clinically meaningful by 93% of respondents, and slowing the decline by 25% or more was felt to be at least somewhat clinically meaningful by 100% of responding clinicians (18). It is unknown whether the magnitude of effect of reldesemtiv will continue to grow with time, but the curves for both SVC and ALSFRS-R seem to be diverging at 12 weeks, so a maximum effect may not have been reached.

With respect to ALSFRS-R, patients manifesting more aggressive disease progression showed a stronger treatment effect than those with more slowly progressing disease. Nominally statistically significant effects of treatment with reldesemtiv were seen in the middle and fastest tertiles of progressors (based on the estimated pretrial rate of disease progression) in both the ALSFRS-R Total Score and ALSFRS-R Gross Motor Domain score at week 12; numerically smaller decreases from baseline were also observed following treatment with reldesemtiv in the middle and fastest progressors in ALSFRS-R Fine Motor Domain, percent predicted SVC, and muscle strength mega-score at week 12. Similarly, patients with symptoms of ALS for less than 2 years or diagnosed for less than 1 year showed a stronger treatment effect, likely because this group includes fewer patients

| Preferred MedDRA Term, n (%) | Placebo (n = 115) | 150 mg bid (n = 112) | 300 mg bid (n = 113) | 450 mg bid (n = 117) | Overall (N = 457) |
|-----------------------------|------------------|----------------------|----------------------|----------------------|------------------|
| **At Least One TEAE**       |                  |                      |                      |                      |                  |
| Fatigue                     | 12 (10.4)        | 14 (12.5)            | 19 (16.8)            | 20 (17.1)            | 65 (14.2)        |
| Nausea                      | 14 (12.2)        | 10 (8.9)             | 13 (11.5)            | 22 (18.8)            | 59 (12.9)        |
| Headache                    | 15 (13.0)        | 16 (14.3)            | 16 (14.2)            | 11 (9.4)             | 58 (12.7)        |
| Constipation                | 15 (13.0)        | 8 (7.1)              | 14 (12.4)            | 17 (14.5)            | 54 (11.8)        |
| Dizziness                   | 11 (9.6)         | 8 (7.1)              | 12 (10.6)            | 7 (6.0)              | 38 (8.3)         |
| Constipation                | 5 (4.3)          | 7 (6.3)              | 13 (11.5)            | 10 (8.5)             | 35 (7.7)         |
| Viral upper respiratory tract infection | 9 (7.8) | 6 (5.4) | 10 (8.8) | 9 (7.7) | 34 (7.4) |
| Diarrhoea                   | 8 (7.0)          | 12 (10.7)            | 7 (6.2)              | 4 (3.4)              | 31 (6.8)         |
| **Laboratory Adverse Events** |                  |                      |                      |                      |                  |
| Cystatin C increased        | 2 (1.7)          | 8 (7.1)              | 9 (8.0)              | 20 (17.1)            | 39 (8.5)        |
| eGFR decreased              | 1 (0.9)          | 6 (5.4)              | 6 (5.3)              | 11 (9.4)             | 24 (5.3)        |
| ALT increased               | 1 (0.9)          | 2 (1.8)              | 5 (4.4)              | 12 (10.3)            | 20 (4.4)        |
| AST increased               | 1 (0.9)          | 2 (1.8)              | 3 (2.7)              | 10 (8.5)             | 16 (3.5)        |
| **At Least One Serious TEAE** |                  |                      |                      |                      |                  |
| Dyspnoea                    | 0                | 1 (0.9)              | 1 (0.9)              | 1 (0.9)              | 3 (0.7)         |
| Urinary tract infection     | 1 (0.9)          | 1 (0.9)              | 1 (0.9)              | 0                    | 3 (0.7)         |
| ALT increased               | 0                | 0                    | 0                    | 2 (1.7)              | 2 (0.4)         |
| Dysphagia                   | 0                | 2 (1.8)              | 0                    | 0                    | 2 (0.4)         |
| Hepatotoxicity              | 0                | 0                    | 0                    | 1 (0.9)              | 0 (0.9)         |
| Pneumonia aspiration        | 2 (1.7)          | 0                    | 0                    | 0                    | 2 (0.4)         |
| Pulmonary embolism          | 2 (1.7)          | 0                    | 0                    | 0                    | 2 (0.4)         |
| Weight decreased            | 1 (0.9)          | 1 (0.9)              | 0                    | 0                    | 2 (0.4)         |
| **Deaths**                  |                  |                      |                      |                      |                  |
| ALS progression             | 1 (0.9)          | 0                    | 0                    | 1 (0.9)              | 2 (0.4)         |
| Pulmonary embolism          | 1 (0.9)          | 0                    | 0                    | 0                    | 1 (0.2)         |

*Occurred during follow-up period.
ALS: amyotrophic lateral sclerosis; ALT: alanine aminotransferase; AST: aspartate aminotransaminase; bid: twice daily; eGFR: estimated glomerular filtration rate; MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event.
with more indolent disease. In contrast, the change in percent predicted SVC in reldesemtiv-treated patients (all doses pooled) compared to placebo showed benefit favoring reldesemtiv in patients with symptoms for at least 2 years and with diagnosis of ALS for at least one year. This disparity may be related to how these measures change over time; ALSFRS-R decline generally follows a somewhat curvilinear pattern but with decline occurring throughout the disease (19), while SVC may be relatively stable early in the disease (particularly given the mean baseline SVC was 84.7 ± 15.3%) and start to decline later in the disease course (20). Altogether, it appears more likely to demonstrate an effect of reldesemtiv versus placebo in patients who are more rapidly progressing on any measure than in those who are not changing or are worsening slowly. In fact, this reasoning formed the basis for the stringent inclusion/exclusion criteria adopted for the phase 3 edaravone trial aimed at enriching for rapid progressors (21).

Importantly, the estimated effect size of reldesemtiv was not different between patients taking or not taking either riluzole or edaravone, medications approved for ALS, as shown by the non-statistically significant \( p \) values for the treatment-by-existing therapy interaction. At week 12, the impact of reldesemtiv compared with placebo was similar regardless of the use/no-use of riluzole or edaravone on percent predicted change in SVC (treatment-by-riluzole use interaction \( p = 0.90 \) and treatment-by-edaravone use interaction \( p = 0.43 \)), change in ALSFRS-R Total Score (treatment-by-riluzole use interaction \( p = 0.56 \) and treatment-by-edaravone use interaction \( p = 0.63 \)), and muscle strength mega-score (treatment-by-riluzole use interaction \( p = 0.87 \) and treatment-by-edaravone use interaction \( p = 0.27 \), respectively). As ALS is heterogeneous from the pathogenesis standpoint, it is likely that effective ALS treatment will require multiple medications in combination, with any given medication exerting less benefit than the combination. Our data suggest that, should the efficacy of reldesemtiv be confirmed by a pivotal phase 3 trial, it can be effectively combined with existing approved therapies to provide ALS patients with additional benefit.

Also of interest is the observation that 4 weeks after active treatment was stopped, there was still a trend toward benefit in all outcome measures. A similar pattern was noted in the phase 2 BENEFIT-ALS trial of tirasemtiv in ALS, in which the reduction in rate of decline in SVC was also maintained 4 weeks after active treatment was discontinued. A similar persistence of effect 4 weeks after the last dose of reldesemtiv was observed on the 6 min walk test in older children and adults with spinal muscular atrophy (22). This effect cannot be explained by the half-life of the drug or any of its metabolites, so it may represent a disease-modifying effect on either nerve or muscle. It is possible that increasing muscle force and endurance results in a muscle conditioning effect that persists after stopping the study drug. Alternatively, if peripheral nerves do not need to fire as rapidly to achieve a given muscle force, one can hypothesize that motor neuron function may be preserved longer.

The safety and tolerability of reldesemtiv also appear supportive of further development. While clinical AEs were frequent, they were primarily mild and, for the most part, balanced across treatment groups. Nausea and fatigue occurred slightly more frequently in active treatment arms but did not limit continued use of the drug. The reduction in eGFR (based on cystatin C) was clearly related to dose. However, it was not progressive over time, and tended toward resolution by 4 weeks after stopping the study drug. The lack of indicators of renal toxicity such as urinary casts or elevated protein suggests that the eGFR change may be a pharmacodynamic effect rather than true nephrotoxicity. Similarly, elevations of transaminases more than five times the upper limit of normal were rare and normalized after the drug was withdrawn. Overall, the safety findings do not appear limiting to further development of reldesemtiv.
In summary, *reldesemtiv* is well tolerated and appeared to have a consistent trend toward reducing rates of decline across multiple measures of ALS disease progression. Statistically significant differences were not observed for the pre-specified primary dose-response analyses of primary and secondary endpoints, thus additional studies are warranted to fully evaluate the effect and benefit of *reldesemtiv* in patients with ALS. Its distinct mechanism of action makes it possible to use in combination with existing and future ALS therapeutics, and further development in a phase 3 trial is planned.

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**Declaration of interest**

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Data availability statement

Data reported herein are part of a sponsor-led clinical development program that is ongoing, and thus complete datasets for the trial will not be made available with this report.

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