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RESEARCH ARTICLE

Prescription and acceptance of durable medical equipment in FORTITUDE-ALS, a study of *reldesemtiv* in ALS: post hoc analyses of a randomized, double-blind, placebo-controlled clinical trial

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Abstract


Objective: To evaluate the possible effect of *reldesemtiv*, a fast skeletal muscle troponin activator, on prescription and acceptance of durable medical equipment (DME) in the FORTITUDE-ALS trial. **Methods:** Health economic outcome information was collected in FORTITUDE-ALS (NCT03160898); sites recorded if and when DME, specifically manual or power wheelchairs, gastrostomy tubes, noninvasive ventilators, or augmentative language devices, was prescribed by a physician and accepted by the patient (DME-PAP) during the trial. Acceptance was defined as the patient agreeing the item was needed. Cox regression analysis compared time to DME-PAP for each *reldesemtiv* dose with placebo. Post hoc analyses evaluated all *reldesemtiv* doses compared with placebo. **Results:** At least one DME item was prescribed and accepted by 33/114 (28.9%) of placebo patients, 19/112 (17.0%) of patients receiving *reldesemtiv* 150 mg bid, 24/113 (21.2%) receiving 300 mg bid, and 29/117 (24.8%) receiving 450 mg bid. The proportion of new DME-PAP was significantly lower in patients receiving *reldesemtiv* 150 mg bid vs placebo (17.0% vs 28.9%, $p = 0.032$). The hazard ratio versus placebo for accepting at least one DME item for all *reldesemtiv* doses combined was 0.61 (confidence interval: 0.39, 0.96, $p = 0.032$). 25% of placebo patients were prescribed and agreed to obtain a DME item by 84 days; this threshold was met for *reldesemtiv*-treated patients at 120 days. **Conclusions:** Results suggest ALS patients receiving *reldesemtiv* may have lower risk of and delayed need for DME related to impaired mobility, breathing, swallowing, or speaking; this delay is consistent with other measures indicating delay in disease progression.

Keywords: Disease burden, clinical trial, *reldesemtiv*, FORTITUDE-ALS, health outcomes research

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease associated with significant social and economic burden on both the patients and their caregivers. Without a cure, treatment is primarily supportive, and medical and

assistive needs invariably increase over the course of the disease progression (1,2). Effective therapies for patients with ALS may preserve quality of life and reduce costs for these patients. These potential benefits of treatment may also delay the time to reach disease-related functional milestones, such

 Supplemental data for this article can be accessed [here](#).

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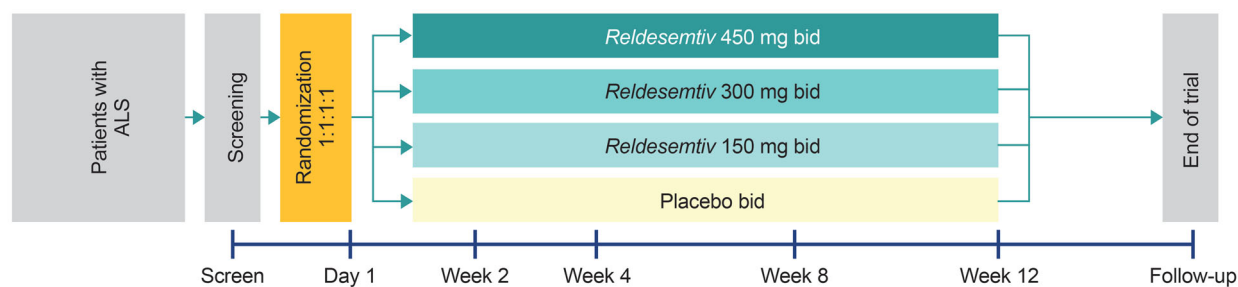


Figure 1.. FORTITUDE-ALS trial design. ALS: amyotrophic lateral sclerosis; bid: twice daily.

as requiring durable medical equipment (DME). Previous reports suggest that 46–96% of patients with ALS will require a variety of DME depending on the site of onset, with 55% of patients with ALS requiring five or more assistive technology devices (2,3). Delaying the time to need items of DME would permit the patient to be more independent for a longer period of time.

Reeldesemtiv is a second-generation fast skeletal muscle troponin activator (FSTA) that sensitizes the sarcomere to calcium leading to increased muscle force, particularly at low- to mid-range stimulation frequencies, intended to improve physical functions such as walking, breathing, and swallowing. A single-dose study in healthy participants showed that *reeldesemtiv* had a greater pharmacodynamic effect on muscle force generation with submaximal nerve stimulation frequencies than was observed in an earlier study with *tirasemtiv* (a first-generation FSTA) without central nervous system side effects (4,5). This led to the design of FORTITUDE-ALS (Functional Outcomes in a Randomized Trial of Investigational Treatment with CK-2127107 to Understand Decline in Endpoints in ALS; NCT03160898), a phase 2b clinical trial evaluating the safety, tolerability, and efficacy of three doses of *reeldesemtiv* compared with placebo in patients with ALS (6). This randomized, double-blind, placebo-controlled clinical trial did not demonstrate a statistically significant difference between *reeldesemtiv* and placebo for the dose–response analyses of the primary endpoint (change from baseline in slow vital capacity [SVC] at 12 weeks), key secondary endpoints (change from baseline in the ALS Functional Rating Scale-Revised [ALSFRS-R] and slope of the muscle mega-score from baseline to 12 weeks). However, a pre-specified analysis of the two highest doses of *reeldesemtiv* combined, and a post hoc analysis of all doses of *reeldesemtiv* combined compared with placebo, revealed statistically significant differences favoring *reeldesemtiv* in the change from baseline to Week 12 of the ALSFRS-R Total Score.

We wished to evaluate the potential health economic impact of *reeldesemtiv* by investigating the time to prescription and acceptance of DME items and the number of patients who were prescribed and agreed to obtain at least one DME item while

participating in FORTITUDE-ALS. The DME items specifically recorded were manual wheelchair, power wheelchair, gastrostomy tube, noninvasive ventilator (NIV), or augmentative language device. The endpoint was the time to have the DME prescribed by the physician and accepted by the patient as needed (DME-PAP). This endpoint was selected (rather than the actual receipt of, or first use of the DME) given the relatively short trial duration and the variability across insurance coverages and countries in the time to receive the DME once prescribed.

Materials and methods

Trial design

FORTITUDE-ALS (NCT03160898) was a phase 2b, randomized, double-blind, placebo-controlled, dose-ranging trial conducted at 65 sites in the United States ($n = 283$), Canada ($n = 100$), Ireland ($n = 4$), Spain ($n = 38$), the Netherlands ($n = 11$), and Australia ($n = 20$) (6). The trial evaluated the safety, tolerability, and efficacy of three doses of *reeldesemtiv* compared with placebo in patients with ALS (6). All sites received institutional review board approvals before enrollment, and all patients provided written informed consent. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

The methodology of FORTITUDE-ALS has been reported (6). Briefly, patients were eligible if they were between 18 and 80 years of age and had a diagnosis of ALS established within the past 24 months. Patients were required to have an upright SVC $\geq 60\%$ predicted for age, height, sex, and ethnicity at screening, and to be either not taking or on stable doses of riluzole (for ≥ 30 days before screening) and/or edaravone (completed two or more cycles before screening). Patients were excluded from the trial if at screening they used NIV, could not swallow a whole tablet, had prior use of *reeldesemtiv* or *tirasemtiv*, or had received stem cell or gene therapy for ALS. The trial had an active treatment period of 12 weeks and a 4-week follow-up period after the last dose of double-blind study drug. Patients ($N = 457$) were randomized (1:1:1:1) and treated with *reeldesemtiv*

Table 1.. Baseline ALSFRS-R scores for items 1, 3, 5, and 8 for patients in the placebo and *reldesemtiv* groups.

Response at baseline, <i>n</i> (%)	Reldesemtiv (<i>n</i> = 342)	Placebo (<i>n</i> = 114)
Item 1: Speech		
4: Normal speech processes	164 (48.0)	57 (50.0)
3: Detectable speech disturbance	103 (30.1)	38 (33.3)
2: Intelligible with repeating	56 (16.4)	14 (12.3)
1: Speech combined with non-vocal communication	18 (5.3)	4 (3.5)
0: Loss of useful speech	1 (0.3)	1 (0.9)
Either 0 or 1	19 (5.6)	5 (4.4)
Item 3: Swallowing		
4: Normal eating habits	212 (62.0)	80 (70.2)
3: Early eating problems, occasional choking	93 (27.2)	19 (16.7)
2: Dietary consistency changes	36 (10.5)	15 (13.2)
1: Needs supplemental tube feedings	1 (0.3)	0 (0)
Either 0 or 1	1 (0.3)	0 (0)
Item 5: Cutting food/handling utensils		
Patients who used 5A to answer question (without gastrostomy)	341 (99.7)	114 (100)
Patients who used 5B to answer question (with gastrostomy)	1 (0.3)	0 (0)
Item 8: Walking		
4: Normal	98 (28.7)	22 (19.3)
3: Early ambulation difficulties	76 (22.2)	22 (19.3)
2: Walks with assistance	150 (43.9)	55 (48.3)
1: Non-ambulatory functional movement only	14 (4.1)	13 (11.4)
0: No purposeful leg movement	4 (1.2)	2 (1.8)
Either 0 or 1	18 (5.3)	15 (13.2)

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised.

150, 300, or 450 mg twice daily (bid), or placebo (Figure 1).

DME-PAP assessment and post hoc analysis

Information on health economic outcomes was collected for all patients in FORTITUDE-ALS, recording if and when at least one of the following pieces of DME was prescribed and accepted by the patient during the course of the trial: manual wheelchair, power wheelchair, gastrostomy tube, noninvasive ventilator, or augmentative communication device. Augmentative communication devices were not pre-defined; therefore, they may have included devices ranging from an off-the-shelf tablet with text-to-voice capability to a sophisticated built-for-purpose speech-generating device activated through eye gaze. A pre-specified Cox regression analysis was used to compare time to first prescription and acceptance of any new DME in each *reldesemtiv* dose group with placebo, stratifying for riluzole or edaravone use in the full analysis set (FAS). The 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. Post hoc analyses compared the use of DME for all *reldesemtiv* doses combined compared with placebo. In the Cox regression analysis, treatment groups were fixed terms with baseline scores of ALSFRS-R items 1, 3, 5, and 8 as covariates,

stratifying for the following factors: pooled sites, riluzole use at baseline, and edaravone use at baseline. If a patient terminated early and without the event of DME-PAP, the patient was censored at the date of last contact. If a patient terminated early and had DME-PAP before early termination, the patient was counted as having DME-PAP at the time of DME-PAP before early termination. *p* values were generated from a Chi-square test.

Results

Patient disposition and baseline characteristics

As reported in Shefner et al. (6), the mean age of patients was 58.7 years, the mean number of months since diagnosis was 8.6 months, and 60.5% of patients were male. The overall mean ALSFRS-R Total Score was 37.4, and mean SVC was 84.7% of predicted (6). The site of onset of ALS was similar across patients treated with placebo compared with all *reldesemtiv* doses combined (upper limb onset: 42.1%, 44.4%; lower limb onset: 38.6%, 36.5%; bulbar onset: 19.3%, 19.0%, respectively).

In order to determine if there was imbalance between the placebo and *reldesemtiv* groups regarding their use of specific DME items at baseline, we reviewed responses to ALSFRS-R item 1 (speech), item 3 (swallowing), item 5B (used when a patient has a feeding tube), and item 8 (walking) (Table

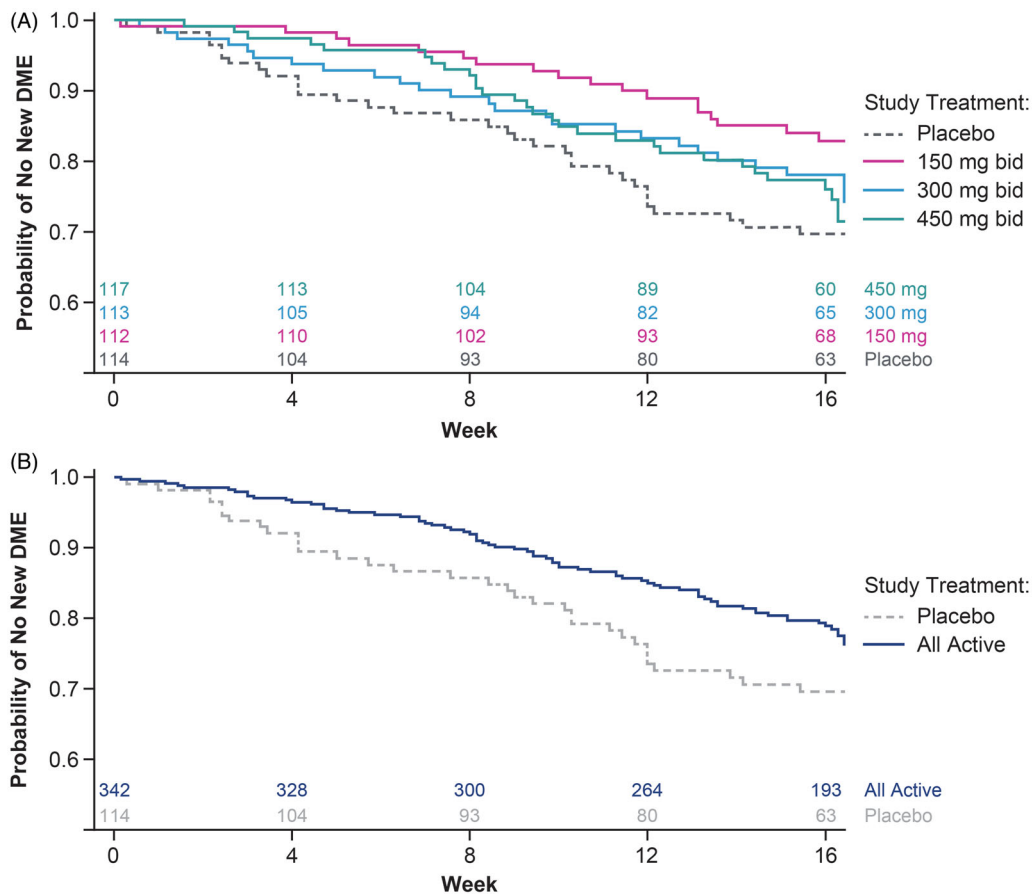


Figure 2.. Probability of no new DME-PAP over time with *reldesemtiv* treatment compared with placebo. (A) Each dose of *reldesemtiv*, and (B) for all doses of *reldesemtiv* combined. Numbers of patients per group are indicated on top of the x-axis. bid: twice daily; DME-PAP: durable medical equipment prescribed and accepted by the patient.

1). Patients who scored 0 or 1 on item 1 may have sufficiently impaired speech to necessitate an augmentative language device; these scores were recorded in similar percentages of patients on *reldesemtiv* (5.6%) and placebo (4.4%). A score of 0 or 1 on item 3 would indicate the patient had a gastrostomy tube, as would using item 5B instead of item 5A to answer questions about using eating utensils. Only one patient, who was in the *reldesemtiv* group, had a gastrostomy tube. Patients who were non-ambulatory and therefore required a wheelchair would score 0 or 1 on item 8. Being non-ambulatory was more common in patients on placebo (13.2%) than on *reldesemtiv* (5.3%).

Overall, 105/456 (23.0%) patients were prescribed and accepted at least one DME; of these, 33/114 (28.9%) patients were randomized to placebo, 19/112 (17.0%) patients were receiving *reldesemtiv* 150 mg bid, 24/113 (21.2%) were receiving 300 mg bid, and 29/117 (24.8%) were receiving 450 mg bid.

DME-PAP

The probability of new DME-PAP was delayed for all doses of *reldesemtiv* compared with placebo, with the highest probability of no new DME over time for patients randomized to *reldesemtiv* 150 mg

bid (Figure 2(A)). For all *reldesemtiv* doses combined, the probability of new DME-PAP was significantly reduced compared with placebo ($p=0.032$; Figure 2(B)). Twenty-five percent of patients given placebo had been prescribed and accepted a DME item by 84 days while 25% of patients treated with *reldesemtiv* had not been prescribed and accepted a DME item until 120 days. The calculated value of 120 days for all *reldesemtiv* doses combined was longer than the planned 112-day duration of the study (i.e. from the first dose of double-blind study drug to the end of the follow-up period), because the final follow-up study visits were sometimes scheduled more than 4 weeks after the last dose of double-blind study drug.

Compared with placebo, the hazard ratio (HR) for the time to first DME-PAP was significantly reduced for patients randomized to *reldesemtiv* 150 mg bid (HR = 0.43 [95% confidence interval: 0.23, 0.79, $p=0.006$]) (6), and was numerically reduced for patients randomized to *reldesemtiv* 300 mg bid and 450 mg bid (Table 2). The HR for the time to first DME-PAP was significantly lower for all *reldesemtiv* doses combined (HR = 0.61 [CI: 0.39, 0.96], $p=0.032$) compared with placebo. Thus, for patients taking *reldesemtiv*, there was a

Table 2.. Hazard ratios^a for *reldesemtiv* compared with placebo for at least one DME-PAP over the course of the trial.

Reldesemtiv group	Hazard ratio vs placebo	95% CI	<i>p</i> Value ^b
150 mg bid	0.43	0.23, 0.79	0.006
300 mg bid	0.81	0.46, 1.43	0.473
450 mg bid	0.66	0.38, 1.14	0.137
All doses combined	0.61	0.39, 0.96	0.032

bid: twice daily; CI: confidence interval; DME-PAP: durable medical equipment prescribed and accepted by the patient.

^aHazard ratio for the time to patients prescribed and agreeing to receive at least one DME of noninvasive ventilation, gastrostomy tube, manual wheelchair, power wheelchair, or augmentative and alternative communication.

^bThe *p* value was obtained from a Cox regression model stratified by pooled site, riluzole use, and edaravone use, with treatment and scores of ALSFRS-R items 1, 3, 5, and 8 as covariates. Patients who did not have an event were censored at the last date of study visit.

39% lower chance of being prescribed and accepting new DME over the course of the trial.

The proportion of new DME-PAP was significantly lower in the *reldesemtiv* 150 mg bid group (19/112 [17.0%], *p* = 0.032) and was numerically reduced in patients randomized to *reldesemtiv* 300 mg bid (24/113 [21.2%], *p* = 0.18), *reldesemtiv* 450 mg bid (29/117 [24.8%], *p* = 0.48), and all *reldesemtiv*-treated groups combined (72/342 [21.1%], *p* = 0.083) compared with placebo (33/114 [28.9%]; Figure 3, Supplemental Table 1). No one type of DME appeared to drive this result; with the exception of the augmentative communication device (which was prescribed and agreed to by the smallest numbers of patients for all doses), the percentage of each new DME for patients receiving placebo was numerically higher than for all *reldesemtiv* doses combined.

Discussion

Progression of ALS is often accompanied by difficulties with ambulation, breathing, speech, and swallowing. DME such as wheelchairs, noninvasive ventilators, augmentative communication devices, and gastrostomy tubes are frequently required as the disease progresses, and dependency on these items may be viewed as a disability milestone. Therapies that slow disease progression may delay the burden of DME for patients. It would be logical to presume that treatments that can improve patients' level of physical function and extend the time to the need for DME would at least maintain, if not improve, the quality of life in patients with ALS. In this post hoc analysis of data from a randomized double-blind trial, compared with placebo, the probability of new DME-PAP was significantly reduced for all doses of *reldesemtiv* combined, and *reldesemtiv* treatment delayed the 25th percentile time to patients being prescribed

and accepting DME by 36 days. Patients receiving *reldesemtiv* had a significantly (39%) lower chance of being prescribed and accepting DME related to impaired mobility, breathing, swallowing, or speaking compared with placebo. The results of this post hoc analysis indicate that there is a longer time to DME being prescribed and accepted by patients receiving *reldesemtiv* relative to placebo.

We believe this is the first ALS clinical trial to analyze the time to have a physician prescribe and the patient agree to use an item of DME. We chose to utilize this novel outcome measure given the rising emphasis on health economics outcome research as well as the focus on outcome measurements that are clinically meaningful to the patient. For patients, delaying the time to requiring wheelchairs, augmentative communication devices, feeding tubes, or noninvasive ventilation are endpoints that are easily understood since independence and the resultant impact on caregiver burden are issues with which all patients with ALS struggle.

We recognize that there are multiple factors that influence procurement and use of DME. It is well known that the timing of NIV is quite variable both by country and by treating physician, and healthcare systems vary regarding how easy or difficult it may be to qualify for insurance coverage for NIV. Previous reports show that about half of patients with ALS experience difficulties procuring DME, most often because of long delivery times and waiting lists (7). There is a high failure rate in the procurement of assistive technology devices crucial for the management of ALS, including powered wheelchairs (52%) and communication devices (39%). Some of the most common causes for this failed procurement of essential equipment include having coverage declined by health insurance providers (50.9%), the DME refused by the patient (29.5%), or death of the patient before equipment delivery (19.6%) (3). Patient reasons for refusing DME include worries about increased reliance on caregivers; DME use may also reinforce perceptions of deterioration in their own physical condition (2,3,8). In addition, the willingness of patients to accept the need for DME may also be influenced by out-of-pocket expenses and personal circumstances (such as the availability of a van to transport a power wheelchair). However, there is no reason to expect that these issues would differentially impact the patients in the various treatment arms.

This analysis has a few limitations. Given the short trial duration, a limited number of patients were prescribed and agreed to obtain DME items. This short trial duration may also have contributed to the non-significant but numerical differences between the placebo and *reldesemtiv* 300 mg bid and 450 mg bid groups; perhaps a longer follow-up would have revealed significant differences over

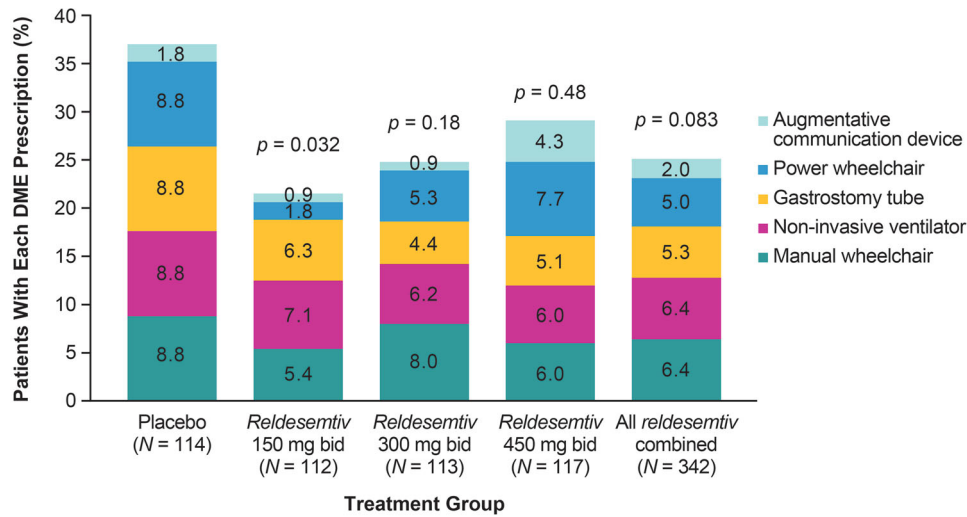


Figure 3.. Proportion of DME-PAP by treatment group over the course of the trial. bid: twice daily; DME-PAP: durable medical equipment prescribed and accepted by the patient. p Values for *reldesemtiv* versus placebo were obtained from a Chi-square test.

time for all doses. The small portion of patients with DME data also made it difficult to explore possible trends related to the site of ALS onset. Another limitation in interpretation of these data is that baseline DME items was not definitively established. Patients were not using NIV at baseline, as per inclusion/exclusion criteria, but whether patients already had a gastrostomy tube but were still able to swallow a tablet whole, or had a wheelchair or augmentative communication device (which also could be highly heterogeneous) was not recorded. Comparison of the groups showed that similar percentages of patients in the *reldesemtiv* and placebo groups were likely to be using an augmentative communication device (i.e. scored 0 or 1 on item 1), and that one patient had a gastrostomy tube at baseline. We could not distinguish between manual or power wheelchair use at baseline, nor could we distinguish patients who had a wheelchair but were still ambulatory. However, being non-ambulatory was about 8% more common in patients on placebo than those on *reldesemtiv*, meaning that there were more patients on *reldesemtiv* at risk for losing ambulation. In order to address the possible imbalance in DME use at baseline between the placebo and *reldesemtiv* groups, we included baseline ALSFRS-R items 1, 3, 5, 8 as covariates in the Cox model. This technique reasonably estimates baseline DME use for augmentative communication devices and wheelchairs and is a direct way to determine baseline gastrostomy use without the basis of randomization.

Our data suggest that DME prescription and use may be a useful novel outcome measure in ALS trials. Future research may include collecting data for when different DME items are first prescribed, obtained, and used, as this may highlight the challenges and delays experienced by patients with ALS obtaining DME. Longer trials would

also permit collection of how extent of use may change over time, and further investigate onset site as it relates to which DME items are used early compared to later in the disease course. Recording reasons for obtaining DME may also help to better understand the variability that may be seen in DME utilization. Given that there is a wide range of different types of augmentative and assistive communication devices that may be used by a patient with a similarly broad range of cost, collecting more detailed information on the specific device would be useful for a cost analysis. Additional studies are also warranted to investigate the cost-benefit relationship of a reduced risk of DME use, and the effect of delayed requirement for DME on the quality of life for patients with ALS.

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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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