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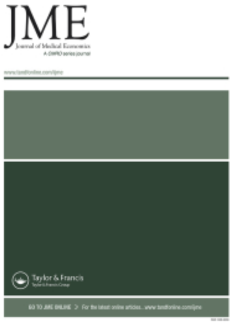

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ORIGINAL RESEARCH

Health utilities and quality-adjusted life years for patients with amyotrophic lateral sclerosis receiving *reldesemtiv* or placebo in FORTITUDE-ALS

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ABSTRACT

Aims: To estimate the health utilities and quality-adjusted life years (QALYs) in patients with amyotrophic lateral sclerosis (ALS) receiving *reldesemtiv* versus placebo in FORTITUDE-ALS.

Materials and methods: We performed a post hoc analysis of clinical trial data from FORTITUDE-ALS (NCT03160898). This Phase IIb, double-blind, randomized, dose-ranging, placebo-controlled, parallel-group, 12-week trial evaluated *reldesemtiv* in patients with ALS. Health utilities from the five-level version of the EuroQol five-dimensional questionnaire (EQ-5D-5L) were estimated using ALS Functional Rating Scale-Revised (ALSFRS-R) scores collected during the trial. QALYs were estimated using the area under the curve method.

Results: The full analysis set consisted of 456 patients (*reldesemtiv* $n = 342$, placebo $n = 114$), who received at least one dose of the double-blind study drug, and had ALSFRS-R assessed at baseline and at least one post-baseline assessment. The difference in EQ-5D-5L utility least-squares (LS) mean change from baseline to week 12 for *reldesemtiv* versus placebo, adjusted for baseline values, was statistically significant (0.03, 95% confidence interval [CI]: 0.01, 0.05; $p = .0008$). The incremental QALY of *reldesemtiv* versus placebo adjusted for baseline utility values showed a modest, but statistically significant, difference (0.004, 95% CI: 0.001, 0.007; $p = .0058$).

Conclusions: This post hoc analysis of FORTITUDE-ALS suggests that *reldesemtiv* showed a modest but significant benefit in health utilities and QALYs compared with placebo. Future long-term studies that include direct collection of EQ-5D-5L data will be needed to confirm our findings.

ClinicalTrials.gov identifier: NCT03160898

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Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that affects both upper and lower motor neurons[1–4]. ALS is clinically heterogeneous with variability in site of onset, age of onset, upper motor neuron or lower motor neuron signs and symptoms, the rate of disease progression, and survival[1,3]. Typically, death occurs within three to five years from disease onset, most often due to respiratory paralysis[5].

The ALS Functional Rating Scale-Revised (ALSFRS-R) is considered the standard for assessment of disease progression in both clinical practice and randomized clinical trials in ALS[3,6]. The ALSFRS-R is a multidimensional scale that includes 12 items covering four domains (bulbar, lower limb, upper limb, and respiratory), with each item scored 0 (no function) through 4 (no deficit)[7].

Reldesemtiv is a fast skeletal muscle troponin activator, which acts by increasing muscle force generation[8]. It is currently being investigated in a Phase III clinical trial for the treatment of ALS.

FORTITUDE-ALS was a Phase IIb, double-blind, randomized, dose-ranging, placebo-controlled, parallel-group, 12-week trial of *reldesemtiv* in patients with ALS[8]. The trial was designed to assess the safety, tolerability, and potential

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efficacy of three dose levels of *reldesemtiv* versus placebo. Slow vital capacity (SVC) was the primary outcome measure and ALSFRS-R total score was a key secondary measure. When the three dose groups were assessed separately versus placebo, the primary efficacy analysis of change from baseline to week 12 in SVC was not statistically significant. However, in post hoc analyses comparing all doses of *reldesemtiv* combined versus placebo, *reldesemtiv* appeared to slow the decline in the ALSFRS-R total score by 25%, with nominal statistical significance ($p = .01$)[8]. The main purpose of the current study was to estimate the effect of *reldesemtiv* on health utilities and quality-adjusted life years (QALYs) compared with placebo during the trial period.

Materials and methods

Clinical trial overview

The FORTITUDE-ALS (ClinicalTrials.gov identifier: NCT03160898) study design, including eligibility criteria, patient characteristics, and results, has been published previously[8]. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Briefly, eligible patients with ALS were randomized 1:1:1:1 to receive either *reldesemtiv* oral tablets 150, 300, or 450 mg or placebo, dosed twice daily for 12 weeks. ALSFRS-R total score was assessed during screening, at day 1, and weeks 2, 4, 8, 12, and follow-up.

Data collection

For this analysis, data from all three *reldesemtiv* doses (150, 300, or 450 mg, twice daily) were pooled. Analyses were conducted on data from the full analysis set from FORTITUDE-ALS, which included all patients who received at least one dose of the double-blind study drug, had an efficacy assessment at baseline, and at least one post-baseline assessment. We also reported separate analyses of the three doses of *reldesemtiv* versus placebo to determine if the results were consistent with the pooled analysis.

Analysis

Health utilities from EQ-5D-5L were calculated for baseline and weeks 2, 4, 8, and 12. As EQ-5D-5L was not administered in FORTITUDE-ALS, EQ-5D-5L utility was estimated from the ALSFRS-R using a published mapping algorithm[9]. The algorithm uses a linear regression model with five of the 12 items of the ALSFRS-R to estimate the EQ-5D-5L utilities (EQ-5D-5L utility $= 0.086203 + 0.057486 \times$ item 6 [dressing and hygiene] $+ 0.046674 \times$ item 7 [turning in bed and adjusting bed clothes] $+ 0.058688 \times$ item 8 [walking] $+ 0.035927 \times$ item 9 [climbing stairs] $+ 0.021126 \times$ item 10 [dyspnea])[9], based on a published value set for England[10]. Changes in EQ-5D-5L utility index scores from baseline to each post-baseline visit up to week 12 were analyzed using a mixed model for repeated measures (MMRM) with the treatment, baseline utility values, baseline riluzole use, baseline edaravone use, pooled sites, visit, interaction of visit-by-treatment, and interaction of visit-by-baseline-utility-value as covariates[11,12]. Analyses were based on available data, with no imputation for missing values. As previously reported[8], one patient (in the placebo group) died during the 12-week treatment period; subsequent values for that patient were set to missing and were not included in the analyses. Subsequently, QALYs were calculated using the area under the curve, using the baseline, week 2, 4, 8, and 12 EQ-5D-5L utilities[13,14]. Where a utility value was missing, QALYs were estimated with available data; for example, if a week 8 utility value was missing, the QALY was estimated using linear interpolation between weeks 4 and 12. Incremental QALY adjusted for baseline utility values was estimated using a multiple linear regression model[14,15]. We report the difference in EQ-5D-5L utility least-squares (LS) mean change from baseline to week 12 and incremental QALY between *reldesemtiv* and placebo along with the 95% confidence interval (CI). Analyses were conducted using SAS version 9.4 or greater (SAS Institute, Cary, NC, USA).

Results

Patient demographics and clinical characteristics

A total of 456 patients who were randomized to receive either *reldesemtiv* ($n = 342$) or placebo ($n = 114$) were included in the analyses. Patient characteristics for the two treatment arms were well balanced between the *reldesemtiv* and placebo groups (Table 1), including the baseline ALSFRS-R total score (mean total score of 37.5 vs. 37.0, respectively).

EQ-5D-5L health utilities and QALYs

The majority of patients completed the 12-week treatment period; the number of patients with data available for analysis at each time point is shown in Table 2. At baseline, the mean EQ-5D-5L utilities for patients in the *reldesemtiv* and placebo groups were similar (0.67 vs. 0.64, respectively) (Table 2). The mean health utilities in both groups declined during the trial, but the decrement was smaller in the *reldesemtiv* group compared with placebo (Table 2). By the end of the trial, the decrement in EQ-5D-5L utility score was

Table 1. Baseline characteristics of patients with ALS in FORTITUDE-ALS.

Characteristic	*Reldesemtiv* ($n = 342$)	Placebo ($n = 114$)
Age, years, mean (SD)	58.3 (10.8)	59.7 (10.6)
Male, *n* (%)	209 (61.1)	67 (58.8)
White, *n* (%)	316 (92.4)	106 (93.0)
BMI, kg/m^2, mean (SD)	26.7 (4.7)	26.1 (4.4)
ALSFRS-R total score, mean (SD)	37.5 (5.5)	37.0 (5.6)
SVC, % predicted, mean (SD)	84.6 (15.5)	84.9 (14.8)
Time since diagnosis, months, mean (SD)	8.5 (6.0)	8.8 (6.4)
Time since 1st symptom, months, mean (SD)	23.0 (20.9)	22.2 (12.4)
ALS site of onset: bulbar, *n* (%)	65 (19.0)	22 (19.3)
On riluzole alone, *n* (%)	194 (56.7)	63 (55.3)
On edaravone alone, *n* (%)	14 (4.1)	5 (4.4)
On riluzole plus edaravone, *n* (%)	70 (20.5)	24 (21.1)

Abbreviations. ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; BMI, body mass index; SD, standard deviation; SVC, slow vital capacity.

Table 2. EQ-5D-5L utility scores and QALY for *reldesemtiv* and placebo in FORTITUDE-ALS.

Time point	*Reldesemtiv*			Placebo			Difference between *reldesemtiv* and placebo, mean (95% CI)	*p* Value
	N	Mean (SD)	Change from baseline, mean (SD)	*N*	Mean (SD)	Change from baseline, mean (SD)		
Baseline	342	0.67 (0.177)	NA	114	0.64 (0.188)	NA	0.04 (−0.002, 0.074)	
Week 2	339	0.66 (0.182)	−0.010 (0.0527)	113	0.62 (0.187)	−0.018 (0.0541)	0.04 (0.002, 0.081)	
Week 4	331	0.66 (0.186)	−0.016 (0.0573)	107	0.60 (0.192)	−0.033 (0.0597)	0.05 (0.012, 0.093)	
Week 8	314	0.64 (0.191)	−0.037 (0.0649)	104	0.59 (0.201)	−0.054 (0.0787)	0.05 (0.010, 0.096)	
Week 12	305	0.63 (0.190)	−0.050 (0.0761)	100	0.57 (0.210)	−0.081 (0.0879)	0.07 (0.021, 0.110)	
QALY		0.1639 (0.045)			0.1513 (0.048)		0.004 (0.001, 0.007)	.0058

Abbreviations. EQ-5D-5L, EuroQol-5D-5L five-dimensional-5-level questionnaire; NA, not applicable; QALY, quality-adjusted life year; SD, standard deviation.

Table 3. Change from baseline in EQ-5D-5L at all visits.

	Reldesemtiv		Placebo		Difference between *reldesemtiv* and placebo		
	LS mean (SE)	95% CI	LS mean (SE)	95% CI	LS mean difference (SE)	95% CI	*p* Value
Change from baseline to week:							
2	−0.01 (0.004)	(−0.02, −0.01)	−0.02 (0.006)	(−0.03, −0.01)	0.01 (0.006)	(−0.00, 0.02)	.1665
4	−0.02 (0.004)	(−0.03, −0.01)	−0.04 (0.006)	(−0.05, −0.02)	0.02 (0.006)	(0.00, 0.03)	.0122
8	−0.04 (0.005)	(−0.05, −0.03)	−0.06 (0.007)	(−0.07, −0.04)	0.01 (0.008)	(−0.00, 0.03)	.0680
12	−0.06 (0.005)	(−0.07, −0.05)	−0.09 (0.008)	(−0.10, −0.07)	0.03 (0.009)	(0.01, 0.05)	.0008

Note: Based on a MMRM with the treatment, baseline utility values, baseline riluzole use, baseline edaravone use, pooled sites, visit, interaction of visit-by-treatment, and interaction of visit-by-baseline-utility-value as covariates.
Abbreviations. CI, confidence interval; EQ-5D-5L, EuroQol-5D-5L five-dimensional-5-level questionnaire; LS, least-squares; MMRM, mixed model for repeated measures; SE, standard error.

Table 4. Change from baseline in EQ-5D-5L at all visits for *reldesemtiv* 150 mg BID and placebo in FORTITUDE-ALS.

	Reldesemtiv 150 mg BID		Placebo		Difference between *reldesemtiv* and placebo		
	LS mean (SE)	95% CI	LS mean (SE)	95% CI	LS mean difference (SE)	95% CI	*p* Value
Change from baseline to week:							
2	−0.01 (0.006)	(−0.02, −0.00)	−0.02 (0.006)	(−0.03, −0.01)	0.01 (0.007)	(−0.00, 0.02)	.2009
4	−0.02 (0.006)	(−0.03, −0.01)	−0.04 (0.006)	(−0.05, −0.02)	0.02 (0.008)	(0.00, 0.03)	.0241
8	−0.04 (0.007)	(−0.05, −0.02)	−0.06 (0.007)	(−0.07, −0.04)	0.02 (0.009)	(0.00, 0.04)	.0322
12	−0.05 (0.008)	(−0.07, −0.03)	−0.09 (0.008)	(−0.10, −0.07)	0.04 (0.011)	(0.01, 0.06)	.0013

Note: Based on a MMRM with the treatment, baseline utility values, baseline riluzole use, baseline edaravone use, pooled sites, visit, interaction of visit-by-treatment, and interaction of visit-by-baseline-utility-value as covariates.
Abbreviations. CI, confidence interval; EQ-5D-5L, EuroQol-5D-5L five-dimensional-5-level questionnaire; LS, least-squares; MMRM, mixed model for repeated measures; SE, standard error.

Table 5. Change from baseline in EQ-5D-5L at all visits for *reldesemtiv* 300 mg BID and placebo in FORTITUDE-ALS.

	Reldesemtiv 300 mg BID		Placebo		Difference between *reldesemtiv* and placebo		
	LS mean (SE)	95% CI	LS mean (SE)	95% CI	LS mean difference (SE)	95% CI	*p* Value
Change from baseline to week:							
2	−0.01 (0.006)	(−0.02, −0.00)	−0.02 (0.006)	(−0.03, −0.01)	0.01 (0.007)	(−0.00, 0.02)	.1418
4	−0.02 (0.006)	(−0.03, −0.01)	−0.04 (0.006)	(−0.05, −0.02)	0.02 (0.008)	(−0.00, 0.03)	.0536
8	−0.05 (0.007)	(−0.06, −0.04)	−0.06 (0.007)	(−0.07, −0.04)	0.01 (0.009)	(−0.01, 0.02)	.5257
12	−0.06 (0.008)	(−0.07, −0.04)	−0.09 (0.008)	(−0.10, −0.07)	0.03 (0.011)	(0.01, 0.05)	.0124

Note: Based on a MMRM with the treatment, baseline utility values, baseline riluzole use, baseline edaravone use, pooled sites, visit, interaction of visit-by-treatment, and interaction of visit-by-baseline-utility-value as covariates.
Abbreviations. CI, confidence interval; EQ-5D-5L, EuroQol-5D-5L five-dimensional-5-level questionnaire; LS, least-squares; MMRM, mixed model for repeated measures; SE, standard error.

smaller in the *reldesemtiv* group compared with the placebo group (–0.06 vs. −0.09, respectively) after baseline adjustment. The difference in EQ-5D-5L utility LS mean change from baseline to week 12 for *reldesemtiv* versus placebo, adjusted for baseline values, was statistically significant (0.03, 95% CI: 0.01, 0.05; $p = .0008$) (Table 3). For each dose of *reldesemtiv* versus placebo, trends were consistent with those of the pooled analysis (Tables 4, 5, and 6).

The QALYs for *reldesemtiv* and placebo were 0.1639 and 0.1513, respectively (Table 2). The incremental QALY of *reldesemtiv* versus placebo, adjusted for baseline utility values, showed a modest, but statistically significant, difference (0.004, 95% CI: 0.001, 0.007; $p = .0058$) (Table 2). The incremental QALYs for each dose of *reldesemtiv* versus placebo were consistent with the results of the pooled analysis (Tables 7, 8, and 9).

Discussion

The main objective of this study was to assess the effect of *reldesemtiv* on health utilities and QALYs compared with placebo during the trial period. Our results showed that at

Table 6. Change from baseline in EQ-5D-5L at all visits for *reldesemtiv* 450 mg BID and placebo in FORTITUDE-ALS.

	Reldesemtiv 450 mg BID		Placebo		Difference between *reldesemtiv* and placebo		
	LS mean (SE)	95% CI	LS mean (SE)	95% CI	LS mean difference (SE)	95% CI	*p* Value
Change from baseline to week:							
2	−0.02 (0.005)	(−0.03, −0.01)	−0.02 (0.006)	(−0.03, −0.01)	0.00 (0.007)	(−0.01, 0.02)	.5128
4	−0.02 (0.006)	(−0.03, −0.01)	−0.04 (0.006)	(−0.05, −0.02)	0.02 (0.008)	(0.00, 0.03)	.0479
8	−0.04 (0.007)	(−0.05, −0.03)	−0.06 (0.007)	(−0.07, −0.04)	0.02 (0.009)	(−0.00, 0.03)	.0932
12	−0.06 (0.008)	(−0.07, −0.04)	−0.09 (0.008)	(−0.10, −0.07)	0.03 (0.011)	(0.01, 0.05)	.0109

Note: Based on a MMRM with the treatment, baseline utility values, baseline riluzole use, baseline edaravone use, pooled sites, visit, interaction of visit-by-treatment, and interaction of visit-by-baseline-utility-value as covariates.
Abbreviations. CI, confidence interval; EQ-5D-5L, EuroQol-5D-5L five-dimensional-5-level questionnaire; LS, least-squares; MMRM, mixed model for repeated measures; SE, standard error.

Table 7. EQ-5D-5L utility scores and QALY for *reldesemtiv* 150 mg BID and placebo in FORTITUDE-ALS.

Time point	*Reldesemtiv* 150 mg BID			Placebo			Difference between *reldesemtiv* and placebo, mean (95% CI)	*p* Value
	N	Mean (SD)	Change from baseline, mean (SD)	N	Mean (SD)	Change from baseline, mean (SD)		
Baseline	112	0.65 (0.167)	NA	114	0.64 (0.188)	NA	0.02 (−0.027, 0.066)	
Week 2	112	0.65 (0.171)	−0.009 (0.0546)	113	0.62 (0.187)	−0.018 (0.0541)	0.03 (−0.022, 0.073)	
Week 4	110	0.64 (0.177)	−0.014 (0.0541)	107	0.60 (0.192)	−0.033 (0.0597)	0.04 (−0.013, 0.086)	
Week 8	103	0.63 (0.183)	−0.033 (0.0585)	104	0.59 (0.201)	−0.054 (0.0787)	0.04 (−0.013, 0.092)	
Week 12	104	0.61 (0.186)	−0.048 (0.0721)	100	0.57 (0.210)	−0.081 (0.0879)	0.05 (−0.007, 0.103)	
QALY		0.1593 (0.044)			0.1513 (0.048)		0.004 (0.001, 0.008)	.0187

Abbreviations. EQ-5D-5L, EuroQol-5D-5L five-dimensional-5-level questionnaire; NA, not applicable; QALY, quality-adjusted life year; SD, standard deviation.

Table 8. EQ-5D-5L utility scores and QALY for *reldesemtiv* 300 mg BID and placebo in FORTITUDE-ALS.

Time point	*Reldesemtiv* 300 mg BID			Placebo			Difference between *reldesemtiv* and placebo, mean (95% CI)	*p* Value
	N	Mean (SD)	Change from baseline, mean (SD)	N	Mean (SD)	Change from baseline, mean (SD)		
Baseline	113	0.66 (0.180)	NA	114	0.64 (0.188)	NA	0.03 (−0.019, 0.077)	
Week 2	111	0.66 (0.192)	−0.008 (0.0547)	113	0.62 (0.187)	−0.018 (0.0541)	0.04 (−0.014, 0.085)	
Week 4	107	0.65 (0.197)	−0.016 (0.0597)	107	0.60 (0.192)	−0.033 (0.0597)	0.04 (−0.009, 0.096)	
Week 8	101	0.63 (0.200)	−0.044 (0.0725)	104	0.59 (0.201)	−0.054 (0.0787)	0.04 (−0.017, 0.093)	
Week 12	98	0.62 (0.194)	−0.050 (0.0815)	100	0.57 (0.210)	−0.081 (0.0879)	0.06 (−0.001, 0.113)	
QALY		0.1615 (0.047)			0.1513 (0.048)		0.004 (0.000, 0.007)	.0415

Abbreviations. EQ-5D-5L, EuroQol-5D-5L five-dimensional-5-level questionnaire; NA, not applicable; QALY, quality-adjusted life year; SD, standard deviation.

Table 9. EQ-5D-5L utility scores and QALY for *reldesemtiv* 450 mg BID and placebo in FORTITUDE-ALS.

Time point	*Reldesemtiv* 450 mg BID			Placebo			Difference between *reldesemtiv* and placebo, mean (95% CI)	*p* Value
	N	Mean (SD)	Change from baseline, mean (SD)	N	Mean (SD)	Change from baseline, mean (SD)		
Baseline	117	0.69 (0.183)	NA	114	0.64 (0.188)	NA	0.06 (0.010, 0.106)	
Week 2	116	0.68 (0.182)	−0.014 (0.0489)	113	0.62 (0.187)	−0.018 (0.0541)	0.06 (0.015, 0.111)	
Week 4	114	0.68 (0.182)	−0.017 (0.0583)	107	0.60 (0.192)	−0.033 (0.0597)	0.08 (0.027, 0.126)	
Week 8	110	0.67 (0.188)	−0.035 (0.0631)	104	0.59 (0.201)	−0.054 (0.0787)	0.08 (0.028, 0.132)	
Week 12	103	0.66 (0.189)	−0.051 (0.0753)	100	0.57 (0.210)	−0.081 (0.0879)	0.09 (0.036, 0.147)	
QALY		0.1707 (0.044)			0.1513 (0.048)		0.004 (0.001, 0.008)	.0244

Abbreviations. EQ-5D-5L, EuroQol-5D-5L five-dimensional-5-level questionnaire; NA, not applicable; QALY, quality-adjusted life year; SD, standard deviation.

baseline the mean EQ-5D-5L utilities mapped from the ALSFRS-R for patients in the *reldesemtiv* and placebo groups were similar. While mean health utilities in both treatment arms declined over time, the decrement was smaller in the *reldesemtiv* group. Furthermore, the incremental QALY of *reldesemtiv* versus placebo showed a modest but significant difference. This analysis suggests that *reldesemtiv* may provide benefit in EQ-5D health utilities and QALYs compared with placebo, although this requires further confirmatory research.

ALS is a devastating disease that can lead to a significant decline in patients' health-related quality of life (HRQoL) as the disease progresses. The EQ-5D is a preferred measure of HRQoL by the National Institute for Health and Care Excellence (NICE) in the United Kingdom and the Institute for Clinical and Economic Review (ICER) in the United States[16,17]. There are several published studies that reported the minimum important difference (MID) for EQ-5D, albeit based on the EQ-5D-3L, and difference index values[18]. Overall, these previous studies found the MID for EQ-5D ranges from 0.03 to 0.52, with the wide range resulting from the use of EQ-5D in a variety of diseases with different levels of severity[18]. MID represents the smallest amount of benefit that patients

consider valuable. In our analyses of clinical trial data from FORTITUDE-ALS, we found patients with ALS who received *reldesemtiv* had a greater health utility, as assessed by the EQ-5D-5L, compared with those in the placebo group, with a significant difference of 0.03. This incremental health benefit of *reldesemtiv* falls within the reported ranges of the MID for EQ-5D-3L using the UK scoring algorithm.

We also assessed the impact of *reldesemtiv* versus placebo on QALYs in FORTITUDE-ALS. *Reldesemtiv* provides a modest and statistically significant difference of 0.004 QALY over placebo, equivalent to 1.5 days in perfect health when it is expressed in quality-adjusted life days (=QALY × 365 days) over the 12-week period[19]. Clearly, the shorter the trial period (or time horizon within an economic model), the smaller the QALY gain[20]. Unfortunately, there is very little published information available for comparison in ALS. Recently, ICER reported a lifetime incremental QALY of 0.04 and 0.14 for two other ALS interventions, oral edaravone, and AMX0035, respectively[21]. However, our analysis of QALY for *reldesemtiv* was based on data collected during 12 weeks and was not extrapolated over lifetime. Therefore, direct comparison of those QALYs is not appropriate.

Limitations

There are several limitations in our analysis. EQ-5D-5L utility values were estimated through mapping from the ALSFRS-R because EQ-5D-5L was not administered in the clinical trial. Thus, the quality of our results and conclusions may have been affected by the robustness of the mapping algorithm used to estimate the EQ-5D-5L utility values. The authors stated that the mapping results of the study fell within the reported mean squared errors ranges of other published mapping studies and asserted it is possible to derive EQ-5D-5L from ALSFRS-R with reasonable accuracy[9]. In addition, none of the items of the ALSFRS-R are related to pain/discomfort or anxiety/depression, which are included in the EQ-5D-5L. It has been suggested that these items are usually reported in less severe terms by patients with ALS[9], but this can only be confirmed by the inclusion of EQ-5D-5L into a future placebo-controlled randomized trial. Another limitation is that the EQ-5D-5L value set for England is not recommended by NICE. However, there is an ongoing study to generate the EQ-5D-5L value set for the UK funded by EuroQol with advice from NICE[22]. Lastly, while this analysis has estimated QALYs over 12 weeks, within an economic analysis framework, the correct time horizon specification is lifetime, meaning that there is time horizon bias in the QALY estimates.

To the best of our knowledge, this is the first time that data from a randomized controlled trial have been applied to the published mapping algorithm developed by Moore et al.[9] to estimate utilities from the EQ-5D-5L from the ALSFRS-R. Our results suggest this mapping method[9] (ALSFRS-R mapped to EQ-5D-5L) may be useful to show the treatment effect in terms of health utilities in clinical trials of ALS. The modest effect of *reldesemtiv* on QALYs is likely due to the three-month short-term trial period.

A strength of our analysis is the use of data from a randomized, placebo-controlled clinical trial, in which ALSFRS-R data were collected prospectively. Future long-term studies that include direct collection of EQ-5D-5L data will be needed to confirm our findings.

Conclusions

This post hoc analysis of FORTITUDE-ALS suggests that *reldesemtiv* showed a modest but significant benefit in health utilities and QALY compared with placebo in patients with ALS.

Transparency

Declaration of funding

FORTITUDE-ALS was conducted by Cytokinetics, Incorporated in collaboration with Astellas Pharma Inc.

Declaration of financial/other relationships

PG, LM, SAR, JW, AAW, and MB own stock and are employees of Cytokinetics, Incorporated. PS was an employee at the time of the FORTITUDE-ALS trial. AC serves on the advisory board for Biogen, Cytokinetics, Incorporated, D enali Pharma, Amylyx, and Mitsubishi Tanabe Pharma. JAA has received research funding to their institution from Alexion, AZTherapies, Amylyx, Biogen, Cytokinetics, Orion, Novartis, MGH Foundation, Ra Pharma, Biohaven, Clene, and Prilenia and consulting fees from AL-S. Affinia, Amylyx, Apellis, Biogen, Cytokinetics, Denali, Orphazyme, NeuroSense, Novartis, UCB, and Wave Life Sciences. AG has served as a consultant for AB Science, AL-S Pharma, AveXis, Biogen, Cytokinetics, Incorporated, Mitsubishi Tanabe Pharma America, and Roche. DAH has no conflicts of interest to declare. CEJ has served as a member of data safety monitoring boards for Anelixis Therapeutics, Inc. and Mitsubishi Tanabe Pharma America. NL has served as a consultant/advisor for Cytokinetics, Incorporated, Hill-Rom Services, Inc., and Vertex Pharmaceuticals Incorporated; and has received research support from AstraZeneca and Vertex Pharmaceuticals Incorporated. TMM has served as a consultant/advisor for Biogen, Ionis Pharmaceuticals, Disarm Therapeutics, and Cytokinetics, Incorporated; has received research support from Biogen and Ionis Pharmaceuticals; and receives licensing fees from Ionis Pharmaceuticals and C2N. JMS reports compensation received as a consultant from Amylyx, Apic Biosciences, NeuroSense Therapeutics, Cytokinetics, Incorporated, Denali Therapeutics, GSK, Mitsubishi Tanabe Pharma America, Orphazyme, Orthogonal, Pinteon Therapeutics, RRD, SwanBio, Helixmith, Novartis, Sanofi, PTC, and EMD Serono; and reports research support from Amylyx, Biogen, Biotie Therapies (now Acorda Therapeutics), Cytokinetics, Incorporated, Mitsubishi Tanabe Pharma America, Alexion, MediciNova Inc, Ionis, Alector, and Orphazyme. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

PG provided support with concept and design. PG, LM, and JW provided statistical analysis. PG and PS provided support with interpretation of data. PG drafted the manuscript. All authors provided critical revision/review of the paper, final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Data availability statement

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

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