Impact of Patient Characteristics on Effect Size in FORTITUDE-ALS

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INTRODUCTION

- **FORTITUDE-ALS** (NCT03160898) was a 12-week, Phase 2, double-blind study of *reldesemtiv* in 458 patients with amyotrophic lateral sclerosis (ALS) randomized to 1 of 3 *reldesemtiv* doses or placebo. Outcome measures included slow vital capacity (SVC), ALS Functional Rating Scale-Revised (ALSFRS-R), and quantitative muscle strength
- Although the primary analysis of the weighted dose-response in the change in SVC from baseline to Week 12 did not reach statistical significance ($p = 0.11$), each outcome measure demonstrated a trend toward reduced progression rates with *reldesemtiv*

OBJECTIVE

- To determine whether baseline patient characteristics are associated with the magnitude of effect of *reldesemtiv* versus placebo in FORTITUDE-ALS

METHODS

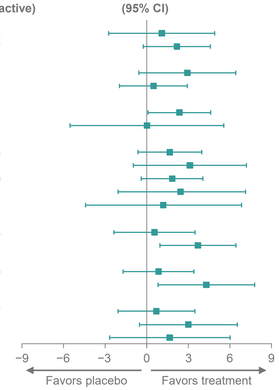
- Study inclusion required diagnosis ≤ 24 months; symptom duration was recorded at screening. Subgroup analyses were performed to identify whether baseline characteristics predicted differential treatment effects on both SVC and ALSFRS-R
- We evaluated baseline characteristics such as SVC, ALSFRS-R, treatment with riluzole and edaravone, and anatomical site of symptom onset
- Characteristics that influenced underlying rate of progression were also analyzed

RESULTS

- **Figures 1** and **2** show how dividing patients according to certain demographic and disease progression variables influenced the extent to which *reldesemtiv* impacted disease progression as assessed by SVC and ALSFRS-R
- In general, static measures of disease state (such as baseline SVC and medications at baseline, and bulbar vs spinal onset) did not predict impact of *reldesemtiv*. However, estimates of pre-study rate of disease progression and related parameters were closely linked to the effect of *reldesemtiv*
- Patients with faster pre-study ALSFRS-R progression rates showed larger treatment effects. In the combined middle and fastest progressing tertiles, there was a 27% difference in ALSFRS-R scores (1.15 points, $p = 0.011$) at 12 weeks between placebo versus *reldesemtiv*-treated patients, whereas the difference in the slowest progressing tertile of patients was 18% (0.4 points, $p = 0.43$) (**Figure 3**)
- As shorter symptom duration tended to predict faster progression, such patients also had a more favorable effect of treatment than those with longer symptom duration. In addition, patients minimally affected at baseline (ALSFRS-R ≥ 45) were mostly slow progressors (41/43 in the slowest tertile) and tended to show a smaller treatment effect
- **Table 1** demonstrates that patients who had both a shorter duration of symptoms and an ALSFRS-R score of no more than 44 (indicating some degree of disease burden) showed larger treatment effects compared with the original patient population

Figure 1. Subgroup analysis of percentage predicted SVC

	No. of patients (placebo/all active)	Estimate	*p*-value
Percentage predicted SVC at baseline			
< 80%	38/102	1.037	0.5935
≥ 80%	52/187	2.135	0.0834
ALSFRS-R total score at baseline			
< Median	43/118	2.886	0.1041
≥ Median	47/171	0.451	0.7146
Anatomic site of disease onset			
Limb	73/234	2.309	0.0448
Bulbar	17/55	−0.027	0.9923
Riluzole and/or edaravone use at baseline			
Use riluzole	72/226	1.642	0.1605
Use edaravone	25/75	3.075	0.1367
Use edaravone or riluzole	77/239	1.798	0.1128
Use edaravone and riluzole	20/62	2.745	0.2384
Use neither edaravone nor riluzole	13/50	1.172	0.6779
Time since ALS symptom onset			
< 2 years	50/188	0.530	0.7211
≥ 2 years	40/101	3.640	0.0094
Time since ALS diagnosis			
< 1 year	65/210	0.819	0.5263
≥ 1 year	25/79	4.237	0.0172
Pre-study rate of disease progression*			
1st tertile ≤ (0.3667)	29/107	0.663	0.6361
2nd tertile > (0.3667) – (0.6673)	35/94	2.960	0.0976
3rd tertile > (0.6673)	26/88	1.620	0.4597



*Pre-study disease progression: 48 (max score) minus ALSFRS-R score at baseline divided by symptom duration
CI, confidence interval; LSM, least square means

Figure 2. Subgroup analyses of ALSFRS-R total scores

What are the clinical features that may increase the ability to detect a treatment effect?

	No. of patients (placebo/all active)	Estimate	*p*-value
Percentage predicted SVC at baseline			
< 80%	43/109	1.588	0.0089
≥ 80%	57/196	0.264	0.5296
ALSFRS-R total score at baseline			
< Median	48/129	1.107	0.0585
≥ Median	52/176	0.685	0.0987
Anatomic site of disease onset			
Limb	80/245	0.872	0.0279
Bulbar	20/60	0.861	0.2194
Riluzole and/or edaravone use at baseline			
Use riluzole	79/238	0.861	0.0285
Use edaravone	27/77	1.249	0.0549
Use edaravone or riluzole	84/251	0.798	0.0350
Use edaravone and riluzole	22/64	1.632	0.0269
Use neither edaravone nor riluzole	16/54	1.092	0.2360
Time since ALS symptom onset			
< 2 years	56/199	1.422	0.0025
≥ 2 years	44/106	0.475	0.3439
Pre-study rate of disease progression*			
1st tertile ≤ (0.3667)	32/110	0.389	0.4298
2nd tertile > (0.3667 – 0.6673)	38/99	0.987	0.0665
3rd tertile > (0.6673)	30/96	1.733	0.0177

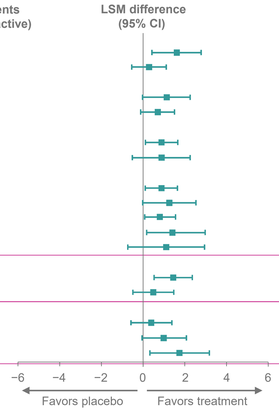


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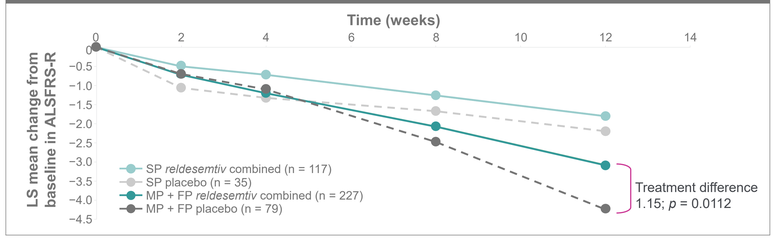
Figure 3. Change from baseline in ALSFRS-R score by progressor tertiles



FP, fast progressing; LS, least square; MP, medium progressing; SP, slow progressing

Table 1. ALSFRS-R total score change from baseline to Week 12

	Placebo		*Reldesemtiv* (BID)							
			150 mg		300 mg		450 mg		All active	
	A N = 100	B N = 51	A N = 104	B N = 62	A N = 98	B N = 55	A N = 103	B N = 65	A N = 305	B N = 182
LSM (SE)	−3.53 (0.31)	−4.87 (0.45)	−2.40 (0.31)	−3.05 (0.42)	−2.62 (0.32)	−2.77 (0.43)	−2.94 (0.31)	−3.23 (0.40)	−2.66 (0.191)	−3.03 (0.254)
Diff. of LSM vs placebo (SE)			1.13 (0.43)	1.82 (0.60)	0.91 (0.43)	2.10 (0.61)	0.59 (0.43)	1.64 (0.58)	0.87 (0.35)	1.84 (0.494)
***p*-value (*reldesemtiv* vs placebo)**			0.0087	0.0025	0.035	0.0006	0.16	0.0052	0.013	0.0002

A. Original FORTITUDE-ALS trial population. B. Patients with symptom onset ≤ 24 months and baseline ALSFRS-R total score ≤ 44 (post hoc analysis); In patients with symptom onset > 24 months or baseline ALSFRS-R total score > 44, change from baseline in the ALSFRS-R total score at Week 12 was −2.18 on placebo with a LSM difference between all *reldesemtiv*-treated patients and placebo of 0.18 ($p = 0.69$) at Week 12.
LSM, least square means; SE, standard error

CONCLUSIONS

- The treatment effect of *reldesemtiv* was more apparent in patients with faster pre-study rates of progression
- Short symptom duration and lower baseline ALSFRS-R scores are both correlates of faster progression rate; this is consistent with recent clinical trials in which stringent inclusion requirements limited study populations to early onset, faster progressing patients as slowly progressing patients may contribute little to detecting a treatment effect
- Future studies of *reldesemtiv* in ALS will consider strategies to minimize but not exclude patients with slower pre-study disease progression to increase trial efficiency and sensitivity

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