CLT-23

Impact of ALSFRS-R Progression Rates on Outcome Measures in FORTITUDE-ALS

Stacy A. Rudnicki,[1] Jinsy A. Andrews,[2] Angela Genge,[3] Carlayne Jackson,[4] Noah Lechtzin,[5] Timothy M. Miller,[6] Bettina M. Cockroft,[1] Fady I. Malik,[1] Lisa Meng,[1] Jenny Wei,[1] Andrew A. Wolff,[1] Jeremy M. Shefner[7]

[1]Cytokinetics, Inc., South San Francisco, CA, USA; [2]The Neurological Institute, Columbia University, New York, NY, USA; [3]Montreal Neurological Institute, Montreal, QC, Canada; [4]University of Texas Health Science Center, San Antonio, TX, USA; [5]Johns Hopkins School of Medicine, Baltimore, MD, USA; [6]Washington University School of Medicine, St. Louis, MO, USA; [7]Barrow Neurological Institute, Phoenix, AZ, USA

BACKGROUND

- Rates of progression of ALS vary among patients
- Baseline progression rates may influence the ability to detect a potential benefit from a therapeutic intervention
- FORTITUDE-ALS was a double-blind, randomized, placebo-controlled, phase 2 trial of *reldesemtiv*, a fast skeletal muscle troponin activator, in patients with ALS that suggested a clinical benefit in patients treated for 3 months

OBJECTIVE

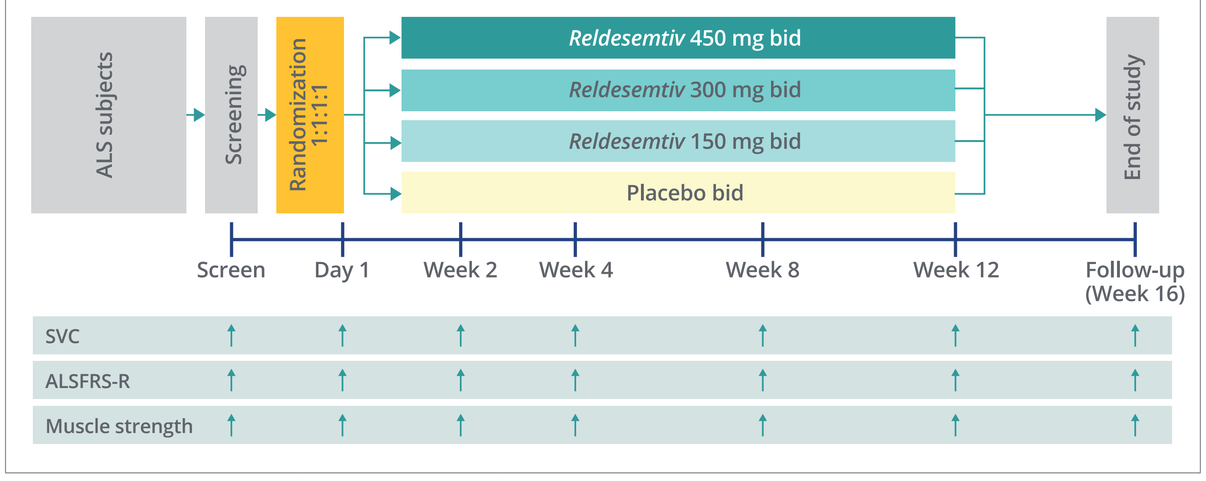
- To examine outcomes in a post hoc analysis by estimated rate of prestudy disease progression defined using ALS Functional Rating Scale-Revised (ALSFRS-R) total scores from the FORTITUDE-ALS clinical trial

METHODS

FORTITUDE-ALS study

- Key inclusion/exclusion criteria:
  - Males or females between 18 and 80 years of age
  - Diagnosis of ALS for ≤ 24 months
  - Upright slow vital capacity (SVC) ≥ 60% predicted for age, height, and sex at screening
  - Either not taking or on stable doses of riluzole and/or edaravone for ≥ 30 days
- Patients (N = 457) were randomized (1:1:1:1) and treated with *reldesemtiv* 150, 300, or 450 mg twice daily (bid) or placebo **(Figure 1)**

Figure 1. FORTITUDE-ALS study design



ALSFRS-R, ALS Functional Rating Scale-Revised; bid, twice daily; SVC, slow vital capacity.

Outcome assessment by disease progression tertiles

- Prestudy disease progression was estimated by assuming an ALSFRS-R total score of 48 at symptom onset and calculating a rate of decline using the ALSFRS-R total score at study baseline (defined as the most immediate ALSFRS-R before the first dose of study treatment)
- The study population was then divided into tertiles by prestudy reduction of ALSFRS-R total score per month:
  - Slowest progressors (SP; n = 152): ≤ 0.37
  - Middle progressors (MP; n = 152): > 0.37–0.67
  - Fastest progressors (FP; n = 153): > 0.67
- Changes from baseline over time were calculated for percent predicted SVC, ALSFRS-R total score, ALSFRS-R Fine and Gross Motor Domain scores, and muscle strength mega-score by prestudy disease progression tertiles and treatment

RESULTS

Patients

- Patient baseline characteristics are summarized in **Table 1**

Table 1. Baseline patient characteristics by prestudy rate of ALS progression

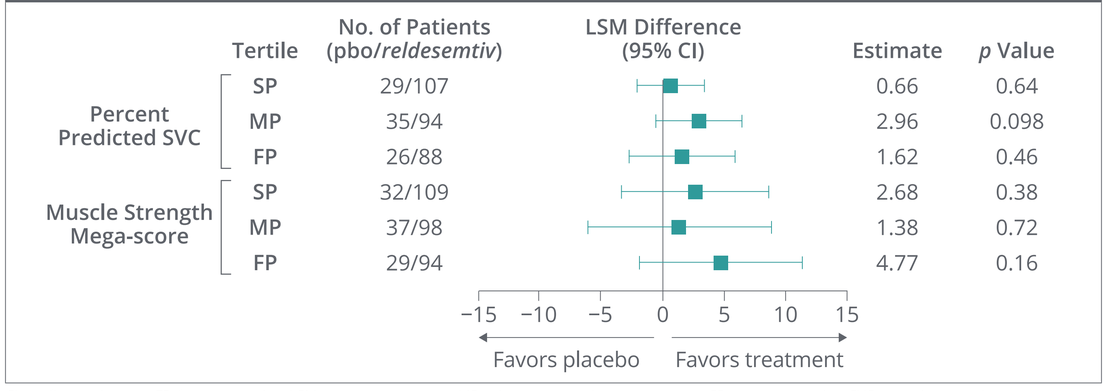
Characteristic	SP Tertile (≤ 0.37)		MP Tertile (> 0.37 ≤ 0.67)		FP Tertile (> 0.67)		Overall (N = 457)
	Placebo (n = 35)	*Reldesemtiv* (n = 117)	Placebo (n = 40)	*Reldesemtiv* (n = 112)	Placebo (n = 40)	*Reldesemtiv* (n = 113)	
Age (years), mean (SD)	60.6 (11.1)	58.4 (10.9)	58.8 (9.1)	58.2 (10.9)	59.6 (11.7)	58.4 (10.6)	58.7 (10.7)
Male, n (%)	21 (60.0)	76 (65.0)	23 (57.5)	63 (56.3)	24 (60.0)	70 (61.9)	277 (60.6)
BMI (kg/m^2), mean (SD)	25.8 (4.2)	27.2 (4.9)	26.3 (4.6)	26.9 (4.4)	26.2 (4.4)	26.1 (4.7)	26.6 (4.6)
ALSFRS-R total score, mean (SD)	41.3 (4.2)	41.8 (3.4)	36.3 (4.4)	36.9 (4.4)	33.9 (5.5)	33.7 (5.2)	37.4 (5.5)
SVC (% predicted), mean (SD)	88.2 (15.7)	89.6 (15.2)	85.4 (12.3)	85.1 (16.0)	81.7 (15.9)	79.0 (13.4)	84.7 (15.3)
Months since diagnosis, mean (SD)	9.6 (7.0)	9.7 (6.7)	10.0 (6.9)	9.6 (6.2)	6.8 (4.6)	6.2 (4.1)	8.6 (6.1)
Months since first symptom, mean (SD)	29.4 (16.3)	33.2 (31.5)	23.3 (8.0)	21.7 (8.2)	14.6 (6.6)	13.9 (5.9)	22.8 (19.1)
ALS site of onset: bulbar, n (%)	7 (20.0)	25 (21.4)	8 (20.0)	15 (13.4)	7 (17.5)	25 (22.1)	87 (19.0)
On riluzole alone, n (%)	21 (60.0)	69 (59.0)	19 (47.5)	59 (52.7)	24 (60.0)	66 (58.4)	258 (56.5)
On edaravone alone, n (%)	1 (2.9)	3 (2.6)	2 (5.0)	5 (4.5)	2 (5.0)	6 (5.3)	19 (4.2)
On riluzole and edaravone, n (%)	6 (17.1)	21 (17.9)	11 (27.5)	32 (28.6)	7 (17.5)	17 (15.0)	94 (20.6)

ALSFRS-R, ALS Functional Rating Scale-Revised; BMI, body mass index; FP, fast progressing; MP, middle progressing; SD, standard deviation; SP, slow progressing; SVC, slow vital capacity.

Change from baseline in SVC and muscle strength

- Changes from baseline in percent predicted SVC and muscle strength mega-score at Week 12 were numerically but not significantly smaller in patients who received any dose of *reldesemtiv* versus placebo in each of the 3 tertiles **(Figure 2)**

Figure 2. Change from baseline by progressor tertiles for percent predicted SVC and muscle strength mega-score

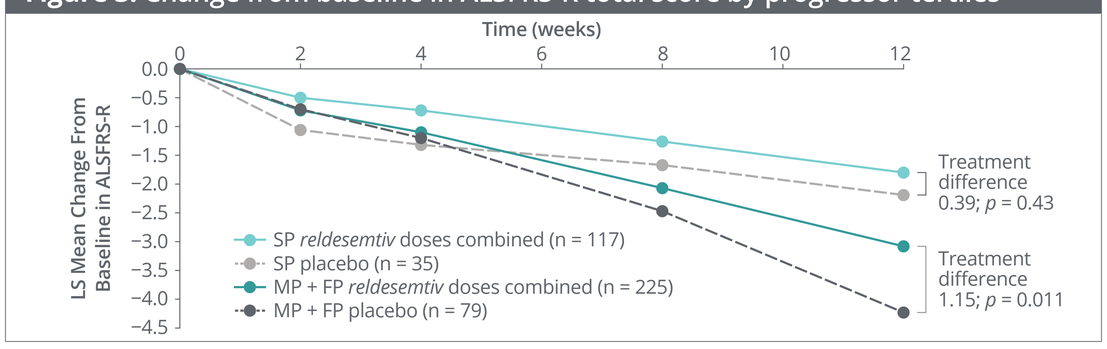


CI, confidence interval; FP, fast progressing; LSM, least squares mean; MP, middle progressing; pbo, placebo; SP, slow progressing; SVC, slow vital capacity.

Change from baseline in ALSFRS-R scores

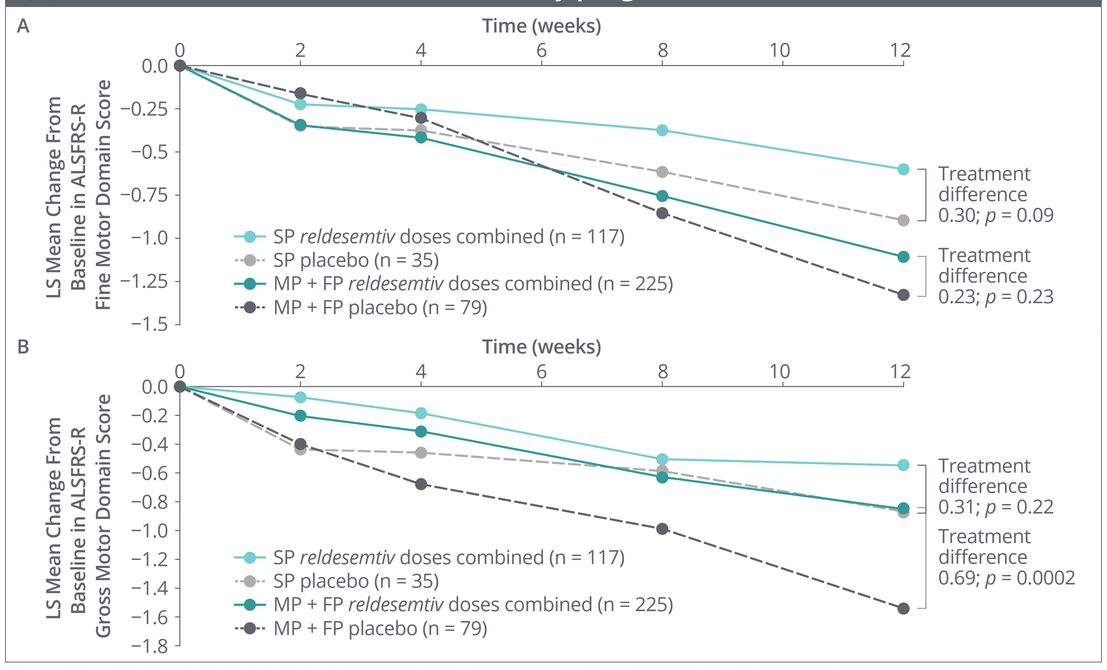
- In the combined MP and FP tertiles, change from baseline in ALSFRS-R total score at Week 12 was significantly smaller in patients who received any dose of *reldesemtiv* versus placebo **(Figure 3)**
- Change from baseline in the ALSFRS-R Gross Motor Domain score at Week 12 was also significantly smaller in patients who received any dose of *reldesemtiv* versus placebo in the middle and fastest progressor tertiles **(Figure 4)**

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



ALSFRS-R, ALS Functional Rating Scale-Revised; FP, fast progressing; LS, least squares; MP, middle progressing; SP, slow progressing.

Figure 4. Change from baseline in (A) ALSFRS-R Fine Motor Domain and (B) ALSFRS-R Gross Motor Domain score by progressor tertiles



ALSFRS-R, ALS Functional Rating Scale-Revised; FP, fast progressing; LS, least squares; MP, middle progressing; SP, slow progressing.

CONCLUSIONS

- Statistically significant effects of *reldesemtiv* treatment were seen in the middle and fastest tertiles (based on estimated prestudy disease progression rate using the ALSFRS-R total score) in both the ALSFRS-R Total and ALSFRS-R Gross Motor Domain scores at Week 12
- Numerically smaller changes from baseline were also observed with *reldesemtiv* treatment in the middle and fastest progressors in both percent predicted SVC and muscle strength mega-score at Week 12
- Patients progressing slowly at study entry will likely change little over 12 weeks and so may not be able to contribute to detecting a treatment effect
- Findings from FORTITUDE-ALS indicate that patients with more rapid prestudy disease progression may better enable detection of a treatment benefit in ALS trials of shorter duration

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Disclosures

Andrews has served as a consultant for Avexis, Biohaven, and Clene Nanomedicine; has served as a consultant for Cytokinetics and is a former employee of Cytokinetics; and has received research support from Biogen, Neuraltus, Orion, and Roche. **Genge** has served as a consultant for AB Sciences, AL-S Pharma, Avexis, Biogen, Cytokinetics, MTPA, and Roche. **Jackson** has served as a consultant for Argenex, Cytokinetics, ITF Pharma, MTPA, and Strongbridge Pharmaceuticals; served on Speaker's Bureau for Avanir, CSL Behring, MTPA, and Strongbridge Pharmaceuticals; has received research support from Amlyx, Cytokinetics, and NIH; and is currently serving as a member of a Data Safety Monitoring Board for Anelixis, Brainstorm, and Mallinckrodt. **Lechtzin** has served as a consultant/advisor for Cytokinetics, Hill-Rom, and Vertex; and has received research support from AstraZeneca and Vertex. **Miller** has served as a consultant/advisor for Biogen and Cytokinetics; has received research support from Biogen and Ionis; and receives licensing fees from C2N. **Shefner** has served as a consultant for Biogen, Biohaven, Cytokinetics, MT Pharma America, and Novartis; has received research support from Amylyx, Biogen, Biohaven, Biotie, Cytokinetics, MT Pharma America, Neuraltus, and Orphazyme; and has received compensation from UpToDate for serving as neuromuscular section editor. **Cockroft** was an employee of Cytokinetics at the time of the study and owns stock in Cytokinetics. **Rudnicki, Malik, Meng, Wei,** and **Wolff** are employees of and own stock in Cytokinetics.

In collaboration with Astellas Pharma, Inc., Cytokinetics is developing *reldesemtiv* as a potential treatment for people living with ALS and certain other debilitating diseases and conditions associated with skeletal muscle weakness and/or fatigue.

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