CLT-21

Responder and Subgroup Analyses for FORTITUDE-ALS, a Phase 2 Trial of *Reldesemtiv* in Patients with ALS

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

[1]Barrow Neurological Institute, Phoenix, AZ, 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]Cytokinetics, Inc., South San Francisco, CA, USA

BACKGROUND

- FORTITUDE-ALS, a randomized, double-blind, phase 2 study of the fast skeletal muscle troponin activator *reldesemtiv*, enrolled patients with ALS to placebo or 1 of 3 dose groups
- Slow vital capacity (SVC), ALS Functional Rating Scale-Revised (ALSFRS-R), and muscle strength by handheld dynamometry (HHD) were assessed during and after 12 weeks of treatment
- Although the primary efficacy analysis of change in SVC from baseline to 12 weeks was not statistically significant ($p = 0.11$), a consistent trend toward slower disease progression for all outcomes was observed

OBJECTIVES

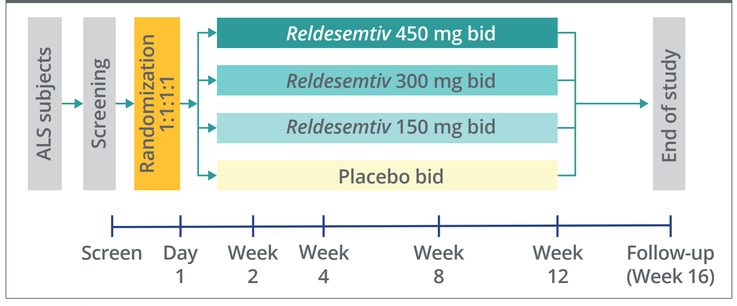
- To determine the effects of *reldesemtiv* with and without edaravone and/or riluzole, and the extent to which edaravone impacted outcomes on placebo
- To determine geographic impacts on treatment with *reldesemtiv*
- To examine whether a responder analysis adds information on utility of *reldesemtiv* in patients with ALS

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 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



bid, twice daily.

FORTITUDE-ALS secondary analyses

- All *reldesemtiv* groups were combined and change from baseline to Week 12 was compared with placebo
- The impact of edaravone use/non-use and riluzole use/non-use was evaluated
- The impact of edaravone on SVC, ALSFRS-R, and HHD was examined in the placebo group
- Outcomes were evaluated by geographic regions, which were defined as North America, Europe, and Australia
- Responders were defined as improved or no change at 12 weeks in any given outcome

RESULTS

Patients

- No significant differences were observed between the 4 treatment groups at baseline **(Table 1)**
- Over half of patients (56.5%) were taking riluzole alone, 4.2% were taking edaravone alone, and 20.6% were taking both
  - Riluzole use alone was lower in the US compared with the EU (50.8% vs 92.5%, $p < 0.0001$); combined edarovone and riluzole use was higher in the US (24.5% US vs 0% in EU, $p < 0.0001$)

Table 1. Baseline patient demographics and disease characteristics

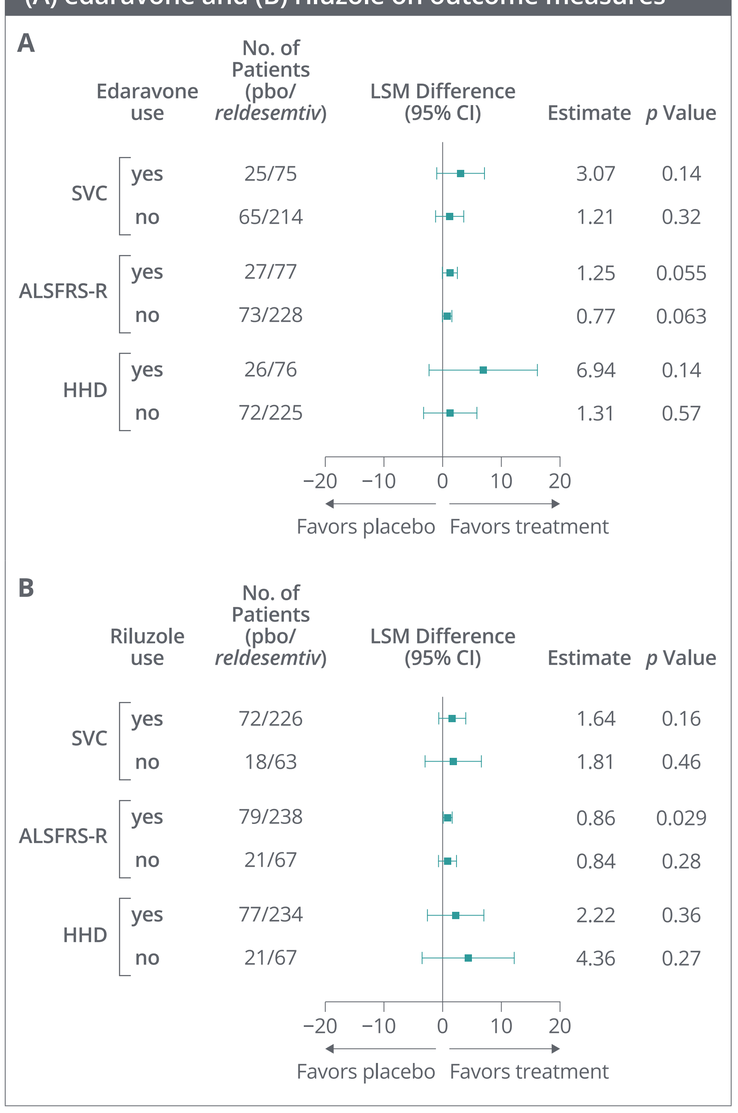
Characteristic	Placebo (n = 115)	*Reldesemtiv* 150 mg (n = 112)	*Reldesemtiv* 300 mg (n = 113)	*Reldesemtiv* 450 mg (n = 117)	Overall (N = 457)
Age (years), mean (SD)	59.6 (10.6)	57.1 (10.9)	57.8 (10.2)	60.1 (11.0)	58.7 (10.7)
Male, n (%)	68 (59.1)	71 (63.4)	71 (62.8)	67 (57.3)	277 (60.6)
BMI (kg/m^2), mean (SD)	26.1 (4.4)	26.9 (5.1)	26.2 (4.4)	27.1 (4.6)	26.6 (4.6)
ALSFRS-R total score, mean (SD)	37.0 (5.6)	37.1 (5.5)	37.6 (5.6)	37.8 (5.5)	37.4 (5.5)
SVC (% predicted), mean (SD)	85.0 (14.8)	85.7 (14.8)	83.7 (14.5)	84.5 (17.1)	84.7 (15.3)
Months since diagnosis, mean (SD)	8.8 (6.3)	8.6 (6.4)	8.7 (6.1)	8.2 (5.6)	8.6 (6.1)
Months since first symptom, mean (SD)	22.1 (12.4)	23.9 (27.5)	22.5 (14.6)	22.7 (18.7)	22.8 (19.1)
ALS site of onset: bulbar, n (%)	22 (19.1)	18 (16.1)	17 (15.0)	30 (25.6)	87 (19.0)
On riluzole alone, n (%)	64 (55.7)	64 (57.1)	64 (56.6)	66 (56.4)	258 (56.5)
On edaravone alone, n (%)	5 (4.3)	5 (4.5)	4 (3.5)	5 (4.3)	19 (4.2)
On riluzole and edaravone, n (%)	24 (20.9)	22 (19.6)	24 (21.2)	24 (20.5)	94 (20.6)

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

Effects of use or non-use of edaravone or riluzole

- The impact of *reldesemtiv* on SVC, ALSFRS-R, and HHD was similar regardless of the use of edaravone or riluzole **(Figure 2)**

Figure 2. Effect of *reldesemtiv* and the use or non-use of (A) edaravone and (B) riluzole on outcome measures



ALSFRS-R, ALS Functional Rating Scale-Revised; CI, confidence interval; HHD, handheld dynamometry; LSM, least squares mean; pbo, placebo; SVC, slow vital capacity.

- In the placebo group, the use of edaravone was not associated with improved outcomes compared with non-use **(Table 2)**

Table 2. Effect of edaravone use on outcome measures in the placebo group

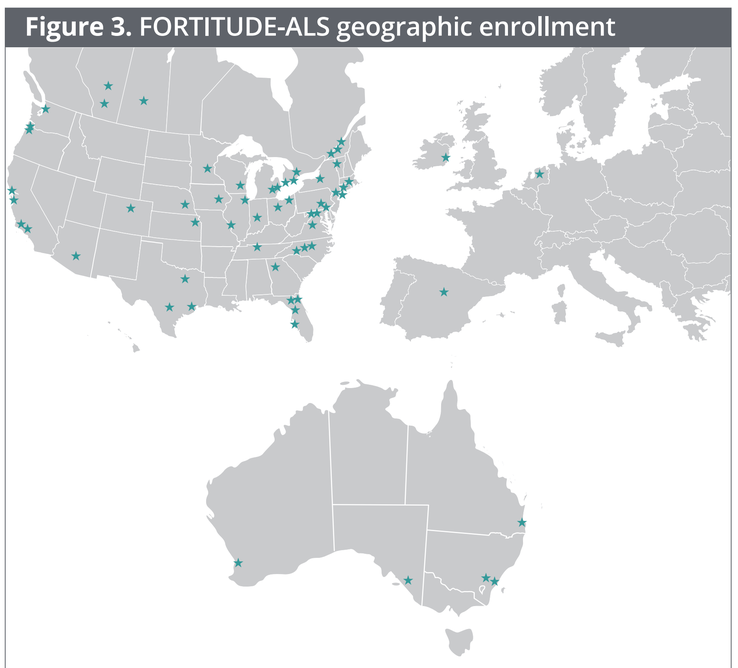
Outcome Measure	LS Mean Change From Baseline at Week 12	
	Edaravone Use	Edaravone Non-use
SVC	−7.21	−6.11
ALSFRS-R	−3.70	−3.33
HHD	−17.05	−11.17

p values for the change from baseline were not significant.
ALSFRS-R, ALS Functional Rating Scale-Revised; HHD, handheld dynamometry; LS, least squares; SVC, slow vital capacity.

Effects of geographic location on treatment with *reldesemtiv*

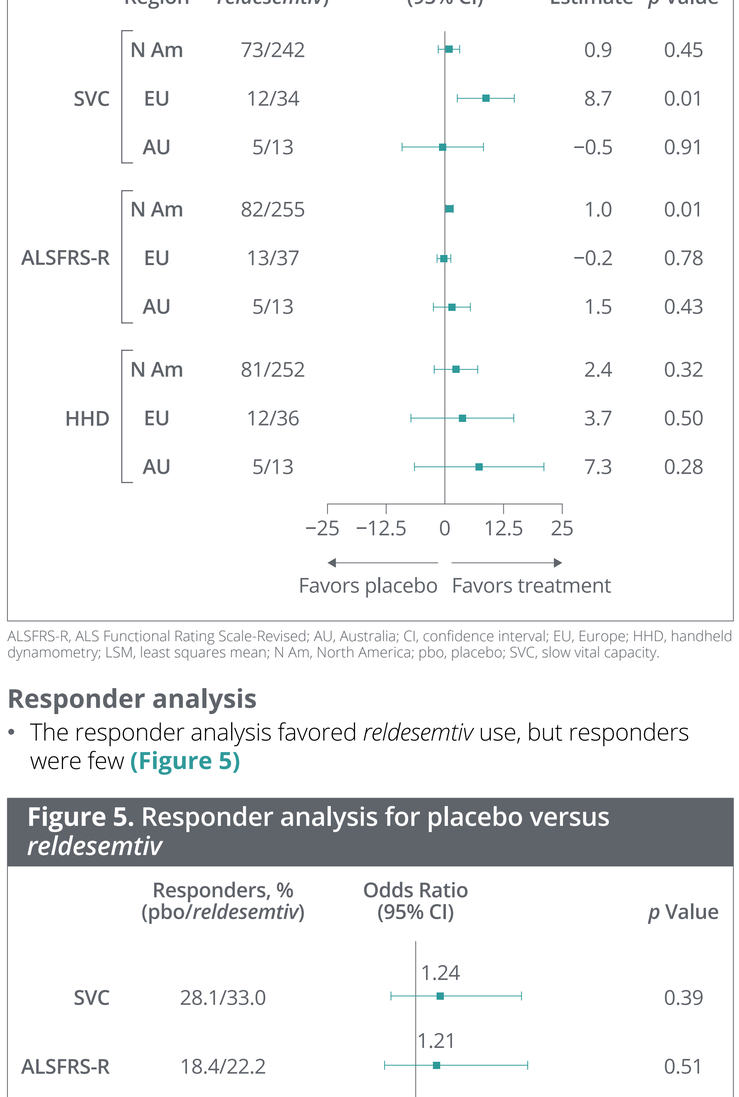
- The impact of *reldesemtiv* on SVC, ALSFRS-R, and HHD was generally similar regardless of geographic region, though the small number of patients in Europe showed significantly better SVC with *reldesemtiv* compared with placebo **(Figure 3, Figure 4)**

Figure 3. FORTITUDE-ALS geographic enrollment



Worldwide (65 Sites)	458 Patients Randomized
United States (48)	284 patients (62%)
Canada (9)	101 patients (22%)
Spain (1)	38 patients (8.3)
Australia (5)	20 patients (4.4%)
The Netherlands (1)	11 patients (2.4%)
Ireland (1)	4 patients (0.1%)

Figure 4. Effect of *reldesemtiv* on outcome measures at Week 12 by geographic location

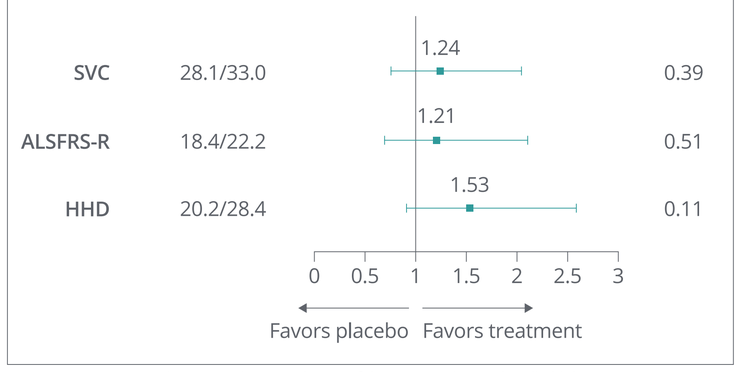


ALSFRS-R, ALS Functional Rating Scale-Revised; AU, Australia; CI, confidence interval; EU, Europe; HHD, handheld dynamometry; LSM, least squares mean; N Am, North America; pbo, placebo; SVC, slow vital capacity.

Responder analysis

- The responder analysis favored *reldesemtiv* use, but responders were few **(Figure 5)**

Figure 5. Responder analysis for placebo versus *reldesemtiv*



ALSFRS-R, ALS Functional Rating Scale-Revised; CI, confidence interval; HHD, handheld dynamometry; pbo, placebo; SVC, slow vital capacity.

CONCLUSIONS

- FORTITUDE-ALS showed an effect of *reldesemtiv* over 12 weeks in patients with ALS, whether or not patients were taking edaravone and/or riluzole
- Should these effects of *reldesemtiv* be confirmed in a phase 3 trial, *reldesemtiv* will likely be useful with other approved agents
- Geographic location did not influence outcomes with *reldesemtiv*, although in the EU, the slower decline in SVC on *reldesemtiv* versus placebo achieved nominal statistical significance ($p = 0.01$)
- A responder analysis did not improve our understanding of the impact of *reldesemtiv* in ALS

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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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