CLT-24

Update on FORTITUDE-ALS: a Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of *Reldesemtiv* in Patients With Amyotrophic Lateral Sclerosis

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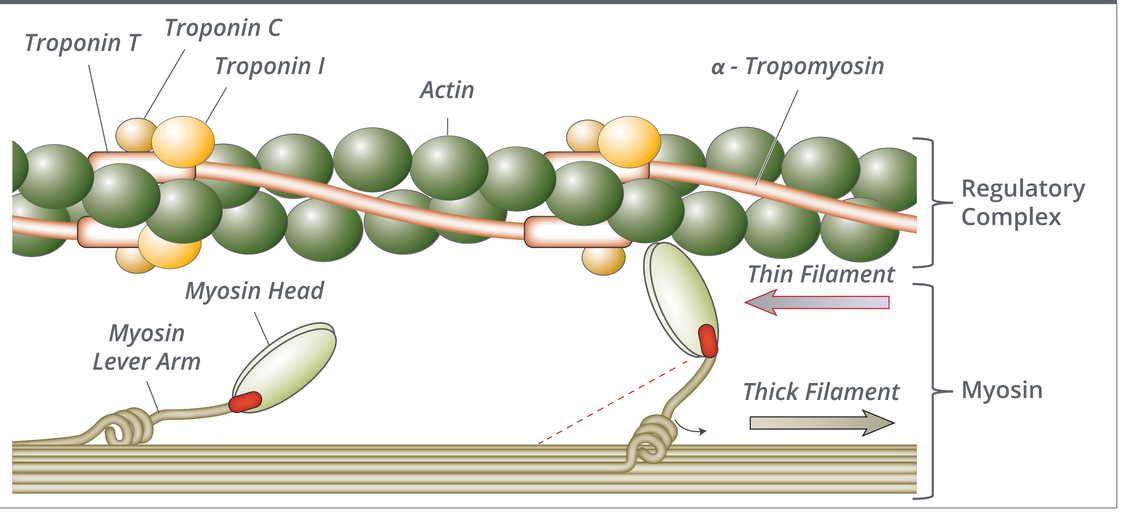
BACKGROUND

- *Reldesemtiv*, also known as CK-2127107 or CK-107, is a selective, small-molecule fast skeletal muscle troponin activator (FSTA) that sensitizes the sarcomere to Ca2+ by slowing the rate of Ca2+ release from troponin **(Figure 1)**
  - FSTAs have the potential to slow the decline of skeletal muscle function in diseases and conditions associated with muscle weakness or fatigue including amyotrophic lateral sclerosis (ALS)

Figure 1. FSTAs selectively activate the fast skeletal muscle troponin complex



FSTA, fast skeletal muscle troponin activator

- A phase 3 clinical trial (VITALITY-ALS) of *tirasemtiv* (a first-generation FSTA of unrelated structure) in patients with ALS was impacted by dose-related tolerability issues[1]
  - However, trends were noted suggesting a benefit of *tirasemtiv* in patients tolerating their assigned dose. *Reldesemtiv* is optimized to limit crossing the blood-brain barrier
- In preclinical studies, *reldesemtiv* showed greater pharmacodynamic effects at lower plasma concentrations than *tirasemtiv*[2,3]
- A phase 1 trial of *reldesemtiv* in healthy volunteers demonstrated increased tibialis anterior muscle power with sub-tetanic stimulation rates of the common fibular nerve[4] most marked with rates of 7.5–12.5 hz
- Repeated doses of *reldesemtiv* at doses up to 500 mg twice daily (BID) for up to 17 days were well tolerated[4]

OBJECTIVE

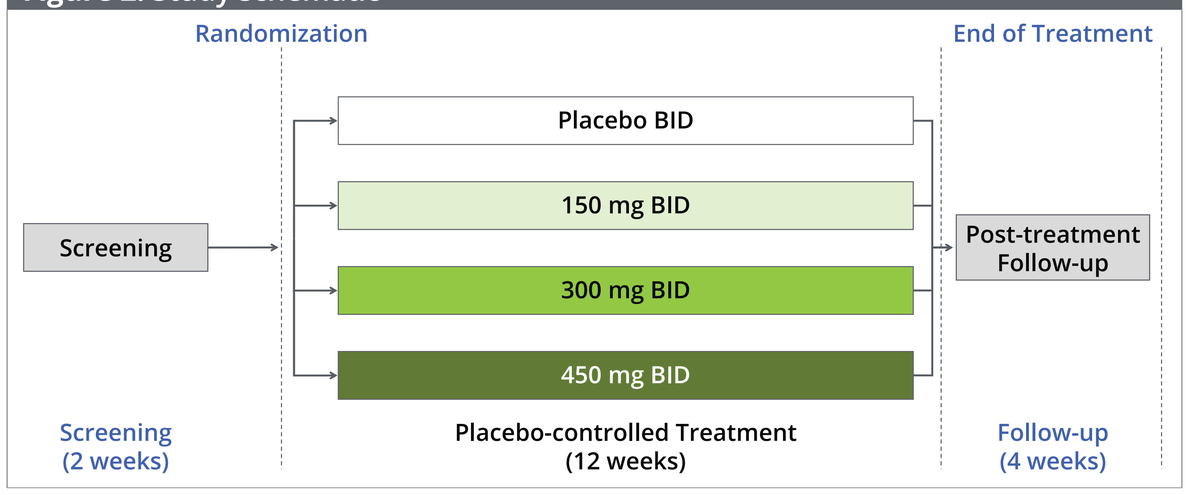
- To evaluate the tolerability and preliminary efficacy of *reldesemtiv* versus placebo in patients with ALS

METHODS

FORTITUDE-ALS

- Phase 2, double-blind, randomized, placebo-controlled, multiple-dose study of *reldesemtiv* in patients with ALS
- Patients are randomized 1:1:1:1 to placebo or *reldesemtiv* 150, 300, or 450 mg BID for 12 weeks **(Figure 2)**

Figure 2. Study schematic



BID, twice daily

Key Design Elements

Population:

- Diagnosis of ALS for ≤24 months
- Upright slow vital capacity (SVC) ≥60% of predicted for age, height, and sex at screening
- Patients were stratified by riluzole and edaravone use

Primary Endpoint:

- Change from baseline to week 12 in percent predicted SVC

Secondary Endpoints:

- Slope of the change from baseline in the mega-score of muscle strength measured by handheld dynamometry and handgrip dynamometry from baseline to week 12 in patients on *reldesemtiv* compared with placebo
- Change from baseline to week 12 in the ALS Functional Rating Scale – Revised (ALSFRS-R)

Safety Endpoints:

- Incidence and severity of treatment-emergent adverse events

Pharmacokinetic Measurements:

- Plasma concentrations of *reldesemtiv* at the sampled time points during the study

Unique Study Design Features

Exploratory and Other Endpoints:

- Fine motor skills assessed on iPad app at clinic visits
- Voice recording assessed on app on a patient device weekly at home and on iPad at clinic visits
- Weekly home SVC testing
- Health economics outcome measures: when a patient is prescribed and agrees to use
  - Manual or power wheelchair
  - Augmentative/alternative communication
  - Feeding tube
  - Noninvasive ventilation
- Central review of flow volume loop by pulmonologist

RESULTS

- Overall, 458 patients were randomized **(Table 1)**

Table 1. Patient disposition stratified by riluzole or edaravone use

	Use Neither	Use Riluzole Only	Use Edaravone Only	Use Both	Overall
Number of patients randomized	86	259	19	94	458

- Demographics/baseline characteristics were similar between patients who received riluzole or edaravone alone, both, or neither **(Table 2)**

Table 2. Demographics and baseline disease characteristics of randomized patients

	Use Neither (n = 86)	Use Riluzole Only (n = 259)	Use Edaravone Only (n = 19)	Use Both (n = 94)	Overall (N = 458)
Age, y, mean ± SD	60.9 ± 11.8	58.0 ± 10.7	56.6 ± 11.0	58.9 ± 9.4	58.7 ± 10.7
Sex, n (%)					
Male	47 (54.7)	158 (61.0)	16 (84.2)	57 (60.6)	278 (60.7)
Female	39 (45.3)	101 (39.0)	3 (15.8)	37 (39.4)	180 (39.3)
Race, n (%)					
Black or African American	0	8 (3.1)	0	2 (2.1)	10 (2.2)
Asian	2 (2.3)	5 (1.9)	0	7 (7.4)	14 (3.1)
White	82 (95.3)	241 (93.1)	19 (100)	82 (87.2)	424 (92.6)
Native Hawaiian or Other Pacific Islander	0	1 (0.4)	0	0	1 (0.2)
Other	2 (2.3)	4 (1.5)	0	3 (3.2)	9 (2.0)
BMI, kg/m^2, mean ± SD	(n = 78) 26.2 ± 5.5	(n = 232) 26.6 ± 4.4	(n = 17) 26.7 ± 4.0	(n = 84) 26.6 ± 4.6	(n = 411) 26.5 ± 4.7
Months since	(n = 79)	(n = 235)	(n = 17)	(n = 84)	(n = 415)
Symptom onset, mean ± SD	26.9 ± 35.3	22.1 ± 16.2	20.5 ± 9.1	21.7 ± 9.6	22.9 ± 20.2
Diagnosis, mean ± SD	7.6 ± 5.9	8.0 ± 8.2	11.5 ± 6.3	9.9 ± 6.4	8.4 ± 7.5
Site of onset, n (%)					
Upper limb	36 (41.9)	112 (43.2)	15 (78.9)	36 (38.3)	199 (43.4)
Lower limb	34 (39.5)	89 (34.4)	3 (15.8)	43 (45.7)	169 (36.9)
Bulbar	16 (18.6)	58 (22.4)	1 (5.3)	13 (13.8)	88 (19.2)
Unknown	0	0	0	2 (2.1)	2 (0.4)
Percent predicted slow vital capacity, mean ± SD	(n = 78) 84.5 ± 16.3	(n = 232) 87.7 ± 14.5	(n = 17) 91.1 ± 16.5	(n = 84) 85.8 ± 12.7	(n = 411) 86.8 ± 14.6
ALSFRS-R	(n = 78)	(n = 232)	(n = 17)	(n = 84)	(n = 411)
Total score, mean ± SD	37.4 ± 5.8	37.4 ± 5.9	36.9 ± 3.7	37.2 ± 5.4	37.3 ± 5.7
Respiratory domain score, mean ± SD	11.3 ± 1.1	11.6 ± 0.9	11.8 ± 0.4	11.5 ± 0.8	11.5 ± 0.9
ALS family history, n (%)					
Yes	11 (12.8)	25 (9.7)	2 (10.5)	12 (12.8)	50 (10.9)
No	69 (80.2)	225 (86.9)	16 (84.2)	76 (80.9)	386 (84.3)
Unknown	6 (7.0)	9 (3.5)	1 (5.3)	6 (6.4)	22 (4.8)
El Escorial criteria for ALS, n (%)					
Possible	4 (4.7)	35 (13.5)	1 (5.3)	11 (11.7)	51 (11.1)
Probable	31 (36.0)	102 (39.4)	6 (31.6)	30 (31.9)	169 (36.9)
Probable laboratory supported	14 (16.3)	38 (14.7)	3 (15.8)	19 (20.2)	74 (16.2)
Definite	37 (43.0)	84 (32.4)	9 (47.4)	32 (34.0)	162 (35.4)
Unknown	0	0	0	2 (2.1)	2 (0.4)

ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS Functional Rating Scale; BMI, body mass index; SD, standard deviation

CONCLUSIONS

- **This phase 2 study will evaluate tolerability and preliminary efficacy of *reldesemtiv* in patients with ALS**
- **FORTITUDE-ALS is fully enrolled and completion of the trial is anticipated in the first half of 2019**
- **Demographics of the participants enrolled in FORTITUDE-ALS are similar to those of other recent, large ALS clinical trials**

References

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Disclosures

Shefner has consulted for Biogen, Biohaven, Cytokinetics, Inc., Mitsubishi Tanabe Pharma, and Neurosense and has received research support from ALS Association, ALS Finding a Cure, Biogen, Biohaven, Cytokinetics, Inc., Neuraltus, and NIH. **Andrews** has consulted for and is a former employee of Cytokinetics, Inc., has consulted for Biohaven, and received research support from Neuraltus Pharmaceuticals, Inc. and Roche. **Genge** has been an investigator for AB Sciences, Alexion, AL-S Pharma, Baxter, Bioblast, Biogen, CSL Behring, Cytokinetics, Genzyme, Grifols, Ionis, Novartis, Roche, Sanofi, and UCB. **Jackson** has served as a consultant/advisor for Cytokinetics, MT Pharma, and OneWorld Meds; has participated in scientific studies/trials for Brainstorm, Cytokinetics, Mallinckrodt, and Neuraltis; and is a board member/officer/trustee on the American Academy of Neurology Board of Directors. **Lechtzin** has served as a consultant/advisor for Cytokinetics, Inc., Hill-Rom, PMD Healthcare, and Vertex and lectured and participated at meetings on behalf of Cytokinetics, Inc. and Hill-Rom. **Miller** is a former employee of Cytokinetics, Inc., and is currently an employee of the Sanofi organization with no conflicts of interest to report. **Cockroft, Malik, Wolff,** and **Rudnicki** are employees of and own stock in Cytokinetics, Inc.

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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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