CLT-22

Quality of Life and Depression Measurements in the Placebo Arm of FORTITUDE-ALS

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BACKGROUND

- Quality of life (QoL) in patients with ALS may change over time and may be influenced by depression
- FORTITUDE-ALS was a randomized, double-blind, placebo-controlled, dose-ranging trial of *reldesemtiv* treatment for 12 weeks in patients with ALS, with an additional 4-week follow-up
  - At baseline and every subsequent study visit, patients completed a QoL instrument, the ALS Assessment Questionnaire-5 (ALSAQ-5), as well as a depression assessment tool, the Beck Depression Inventory-Fast Screen (BDI-FS)

OBJECTIVES

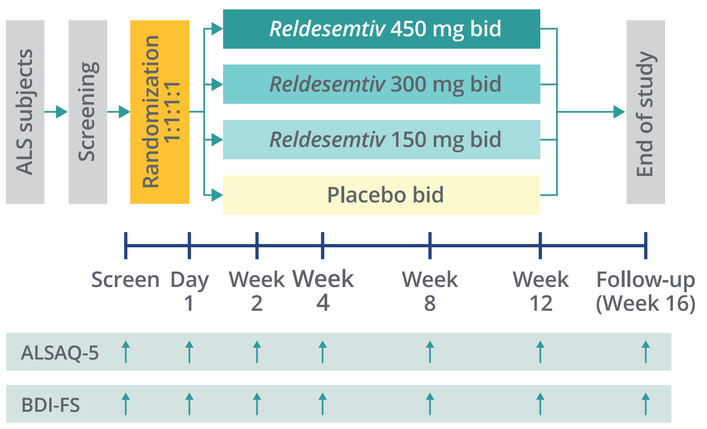
- To evaluate how QoL and depression may change over time in ALS patients who received placebo during a clinical trial, and to assess the relationship between depression and a QoL scale heavily weighted to physical function
  - Data from patients receiving placebo were used for the analysis to ensure a true correlation between QoL and depression without the influence of treatment effect

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 ≥ 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



ALSAQ-5, ALS Assessment Questionnaire-5; BDI-FS, Beck Depression Inventory-Fast Screen; bid, twice daily.

QoL and depression assessments

- The ALSAQ-5 and BDI-FS were assessed at baseline (Day 1) and Weeks 2, 4, 8, and 12, and data were analyzed from 115 patients who received placebo in FORTITUDE-ALS
- The ALSAQ-5 is a QoL instrument heavily weighted to physical function
  - Composed of 1 question each on difficulty standing, using arms, eating, and speaking, and a fifth question on feeling hopeless about the future
  - Each item is scored 0–4, then transformed to a 0–100 scale, with higher scores representing worse QoL
  - Total scores are interpreted as: 0–19, no problems; 10–39, problems rarely; 40–59, problems sometimes; 60–79 problems often; 80–100, problems always/nearly always or unable to do at all[1]
- The BDI-FS is a depression assessment scale
  - Patients choose the most accurate statement of 4 options for 7 topics, including hopelessness and suicidal thoughts
  - Higher scores represent worsening depression
  - Total scores of BDI-FS are classified as: 0–3, minimal depression; 4–6, mild depression; 7–9, moderate depression; and 10–21, severe depression[2]
- Mean ALSAQ-5 and BDI-FS scores at Weeks 2, 4, 8, and 12 were compared with baseline to determine changes over time

Statistical analysis

- Spearman correlation coefficients were used to describe correlation between ALSAQ-5 and BDI-FS scores overall and by time point
- For the BDI-FS, mixed model repeated measures were used to examine whether age, sex, site of ALS onset, or edaravone use may influence changes in depression score over time
- A Wilcoxon signed rank test was used to test whether BDI-FS scores changed significantly from baseline to Week 12

RESULTS

Table 1. ALSAQ-5 and BDI-FS total scores at baseline

Baseline score	Placebo (n = 114)	All *Reldesemtiv* Combined (n = 342)	Overall (N = 457)
ALSAQ-5, mean (SD)	29.0 (16.2)	27.7 (15.3)	28.0 (15.5)
BDI-FS, mean (SD)	2.1 (2.0)	2.0 (2.2)	2.0 (2.2)

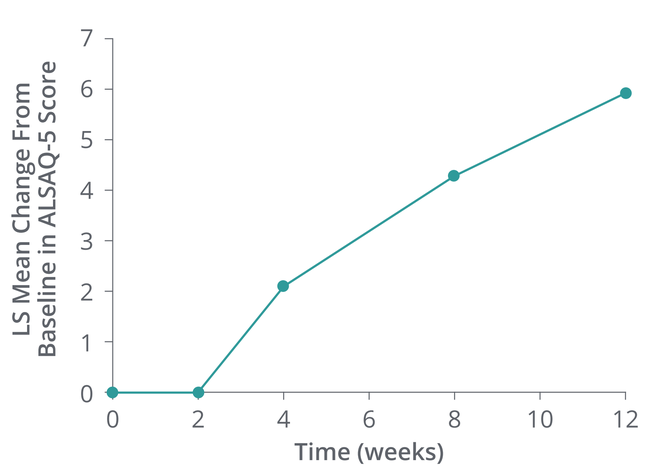
ALSAQ-5, ALS Assessment Questionnaire-5; BDI-FS, Beck Depression Inventory-Fast Screen; SD, standard deviation.

ALSAQ-5 and BDI-FS scores over time

- In the placebo group, QoL modestly worsened over the course of the study as indicated by the change in ALSAQ-5 scores; the difference was statistically significant **(Figure 2A)**
- Depression worsened minimally over the course of the study as indicated by the change in BDI-FS scores; the change did not meet statistical significance **(Figure 2B)**
- The ALSAQ-5 and BDI-FS were well correlated over time; the overall Spearman correlation coefficient was 0.54 ($p < 0.0001$) **(Figure 3)**

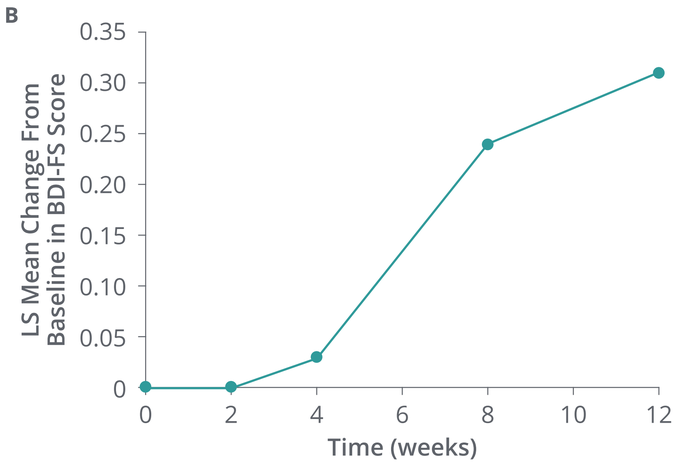
Figure 2. Change over time in (A) ALSAQ-5 and (B) BDI-FS total scores compared with baseline

A



ALSAQ-5	Baseline	Week 12	*p* Value
Mean (SD)	29.0 (16.2)	33.0 (20.9)	< 0.0001

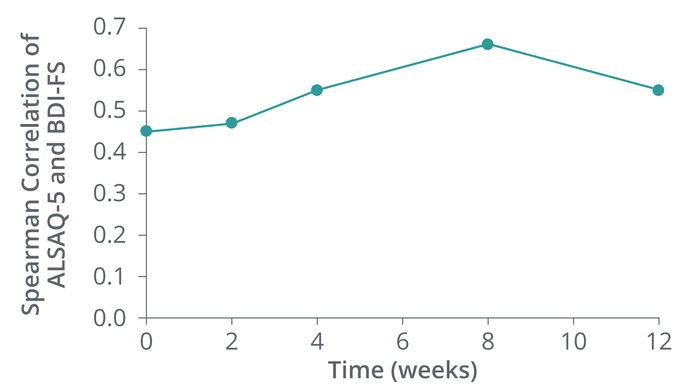
B



BDI-FS	Baseline	Week 12	*p* Value
Mean (SD)	2.1 (2.0)	2.2 (2.4)	0.082

ALSAQ-5, ALS Assessment Questionnaire-5; BDI-FS, Beck Depression Inventory-Fast Screen, LS, least squares; SD, standard deviation.
p value from mixed-effect model repeated measures.

Figure 3. Correlation of ALSAQ-5 and BDI-FS scores



ALSAQ-5, ALS Assessment Questionnaire-5; BDI-FS, Beck Depression Inventory-Fast Screen.

Relation between BDI-FS total score and patient characteristics

- Age, sex, site of onset, and riluzole use were not related to change in BDI-FS total scores as estimated by mixed model repeated measures **(Table 2)**
- Patients taking edaravone showed a lower decline of BDI-FS score by 0.48 points ($p = 0.05$)

BDI-FS classification

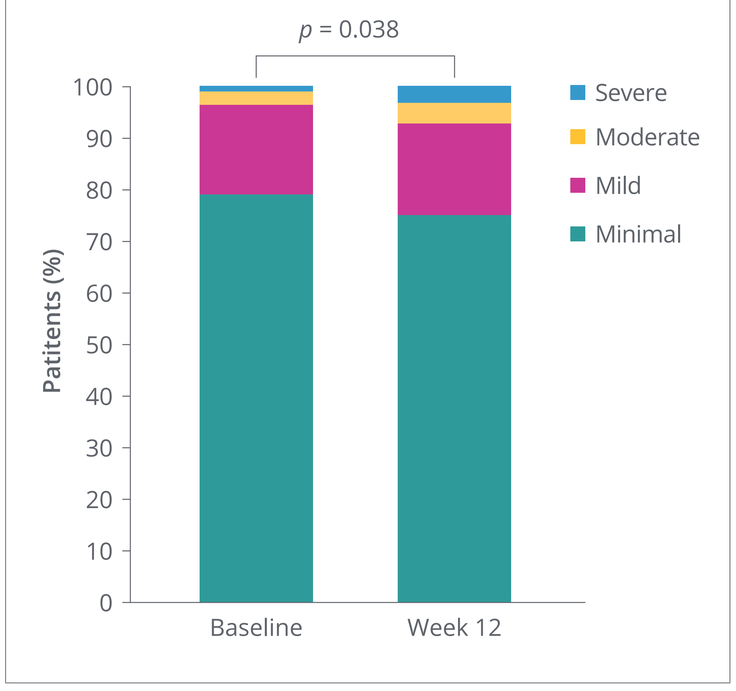
- BDI-FS depression classification significantly changed from baseline to Week 12 in that greater percentages of patients reported mild, moderate, or severe depression ($p = 0.038$) **(Figure 4)**

Table 2. Effect of patient characteristics on BDI-FS total scores

Reldesemtiv Group	Estimate	*p* Value
Sex: Male vs female	0.12	0.58
Age: ≥ 65 vs < 65 years	0.11	0.60
ALS site: upper limb vs bulbar	0.18	0.54
ALS site: lower limb vs bulbar	−0.01	0.98
ALS site: upper limb vs lower limb	0.19	0.45
Riluzole use: yes vs no	−0.19	0.43
Edaravone use: yes vs no	−0.48	0.05

BDI-FS, Beck Depression Inventory-Fast Screen.

Figure 4. Change in BDI-FS depression classification



BDI-FS, Beck Depression Inventory-Fast Screen.
p value from Wilcoxon signed rank test comparing BDI depression levels at baseline vs Week 12.

CONCLUSIONS

- Over 12 weeks, patients in the placebo arm of FORTITUDE-ALS experienced:
  - A statistically significant worsening in QoL as measured by the ALSAQ-5
  - A statistically significant shift in the classification of depression using the BDI-FS from minimal to mild, moderate, or severe depression
  - A borderline significant worsening in the total score of the BDI-FS
- A moderate association between functional QoL and depression was observed in the FORTITUDE-ALS placebo patient population
- These longitudinal data shed some light on the change in depression and in a QoL scale weighted to physical function in patients with ALS over 3 months

References

1. Jenkinson C, et al. ALSAQ User Manual: Amyotrophic Lateral Sclerosis Assessment Questionnaire. Oxford, UK: Health Services Research Unit, University of Oxford; 2001.
2. Beck AT, et al. Manual for the Beck Depression Inventory – Fast Screen for Medical Patients. San Antonio, TX: Psychological Corporation; 2000.

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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 Amylyx, 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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