ENCALS Predictive Survival Model in FORTITUDE-ALS

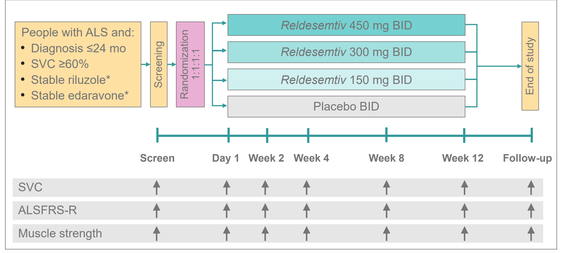
Tyrell Simkins,[1] Stuart Kupfer,[1] Fady I Malik,[1] Lisa Meng,[1] Stacy A Rudnicki,[1] Jeremy M Shefner,[2] Jenny Wei,[1] Andrew A Wolff,[1] Ruben PA van Eijk[3,4]

[1]Cytokinetics Incorporated, South San Francisco, CA, USA; [2]Barrow Neurological Institute, University of Arizona and Creighton University, Phoenix, AZ, USA; [3]UMC Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Biostatistics & Research Support, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

BACKGROUND & OBJECTIVES

- The heterogeneity of disease progression in amyotrophic lateral sclerosis (ALS) presents a particular challenge in clinical trials, leading to difficulty in demonstrating clear effects of potential therapeutics. Researchers therefore have great interest in strategies to enrich clinical trials with participants who are more likely to show a response.
- FORTITUDE-ALS was a 12-week, randomized, double-blind, placebo-controlled Phase 2 study of *reldesemtiv* in people with ALS (**Figure 1**).

Figure 1. FORTITUDE-ALS trial design



*If patients were on riluzole and/or edavarone, they were to be stable before screening.
ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale Revised; BID, twice daily; SVC, slow vital capacity

- Primary results have been previously reported.[1] In a post hoc analysis looking at disease progression, participants were grouped into tertiles according to pre-study rate of decline in the ALS Functional Rating Scale Revised (ALSFRS-R) total score (ΔFRS).
  - The largest treatment effect was observed in participants in intermediate- or fast-progressing tertiles.[1] Most participants in these tertiles had experienced symptoms for ≤24 months and had a baseline ALSFRS-R total score ≤44 (henceforth called the 24/44 criteria).
- Another method of assessing disease progression is the ENCALS survival model, which provides risk scores (RS) segmenting participants into 1 of 5 groups based on predicted survival: very short (G1), short (G2), intermediate (G3), long (G4), and very long (G5).[2] RS considers age at onset, onset site, cognition, vital capacity, El Escorial classification, diagnostic delay, *C9orf72* expansion repeat, and ΔFRS.[2]

Objectives

- Objectives of this post hoc analysis of FORTITUDE-ALS data were to:
  - Determine if survival predicted by the ENCALS model was similar for participants assigned *reldesemtiv* compared with placebo.
  - Compare survival predictions in participants who met the 24/44 criteria vs those who did not.

METHODS

- The FORTITUDE-ALS primary results and post hoc analyses by subgroups have been previously described.[1]
- In this post hoc analysis, the ENCALS predicted survival RS[2] was calculated for all participants enrolled in FORTITUDE-ALS.
- Based on their RS, participants were assigned to 1 of 5 risk groups (G1 through G5) and comparisons made between the distribution of the RS by treatment arm (placebo vs all *reldesemtiv* doses combined) and by whether the 24/44 criteria were met.

RESULTS

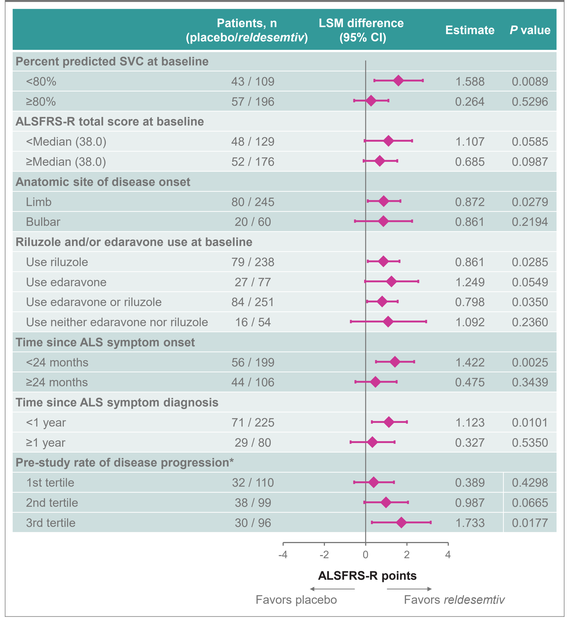
- As previously reported,[1] baseline demographics and disease characteristics of participants enrolled in FORTITUDE-ALS were well balanced across treatment arms.
- The mean ENCALS RS was similar for patients treated with placebo and *reldesemtiv* (**Table 1**).
- When participants were categorized according to their ENCALS RS, there was no statistically significant difference in the distribution of risk groups for those assigned *reldesemtiv* compared with placebo (**Table 1**).
- In a post hoc analysis evaluating treatment with *reldesemtiv* or placebo by patient subgroups, the greatest treatment effect was demonstrated in patients with SVC <80% predicted, symptom onset <24 months, and those in the fast-progressing tertile of pre-study disease progression (**Figure 2**).
- When participants who met the 24/44 criteria (n=272) and those who did not (n=184) were categorized according to ENCALS RS, those who met the criteria were primarily in G1, G2, or G3, whereas those who did not were primarily in the G4 and G5 risk groups, which are associated with longer survival (**Table 2**).

Table 1. FORTITUDE-ALS participants by category of ENCALS risk score

	All patients (n=456)	Placebo (n=114)	All *reldesemtiv* (n=342)	*P* value
ENCALS risk score (mean)	−4.77	−4.65	−4.80	0.4136
Risk group, n (%)				
G1	38 (8.3)	7 (6.1)	31 (9.1)	0.3280
G2	89 (19.5)	26 (22.8)	63 (18.4)	0.3062
G3	106 (23.3)	27 (23.7)	79 (23.1)	0.8981
G4	129 (28.3)	33 (29.0)	96 (28.1)	0.8571
G5	94 (20.6)	21 (18.4)	73 (21.4)	0.5039

P value for comparison of placebo vs *reldesemtiv*.

Figure 2. Change in ALSFRS-R total score in subgroups of FORTITUDE-ALS



Post hoc analysis between treatment with *reldesemtiv* (all doses combined) and placebo.[1]
*Pre-study reduction of ALSFRS-R total score per month (1st tertile ≤0.3667 points per month; 2nd tertile >0.3667–0.6673 points per month; 3rd tertile >0.6673 points per month).
ALS, amyotrophic lateral sclerosis; CI, confidence interval; LSM, least squares mean; SVC, slow vital capacity

Table 2. FORTITUDE-ALS participants according to 24/44 criteria

	Met 24/44 criteria (n=272)	Did not meet 24/44 criteria (n=184)	*P* value
Risk group, n (%)			
G1	38 (14.0)	0 (0)	<0.0001
G2	81 (29.8)	8 (4.3)	<0.0001
G3	80 (29.4)	26 (14.1)	0.0002
G4	61 (22.4)	68 (37.0)	0.0007
G5	12 (4.4)	82 (44.6)	<0.0001

P value for comparison of groups who met vs did not meet the 24/44 criteria.

SUMMARY

- In FORTITUDE-ALS, distribution of participants according to the ENCALS RS was well balanced across treatment arms.
- In participants meeting the 24/44 criteria, there was a shift in the ENCALS RS distribution towards those with shorter predicted survival.
- Although the ENCALS model was developed for survival prediction, there is a strong correlation with the rate of decline in the ALSFRS-R score and the ENCALS RS.
  - Therefore, patients in G1, G2, or G3 are expected to have faster decline in their ALSFRS-R than those in G4 or G5.[3]
- The ongoing COURAGE-ALS Phase 3 clinical trial (NCT04944784) of *reldesemtiv* in ALS utilizes the 24/44 criteria, chosen to enhance the ability to detect a treatment effect.
- Findings from the current analysis suggest the COURAGE-ALS inclusion criteria of symptoms ≤24 months and an ALSFRS-R ≤44 will meet the objective of maximizing enrollment of participants with more rapidly progressive disease and minimizing, but not excluding, the proportion of participants progressing more slowly.

References

1. Shefner JM, et al. *Amyotroph Lateral Scler Frontotemporal Degener* 2021;22:287-99.
2. Westeneng H-J, et al. *Lancet Neurol* 2018;17:423-33.
3. van Eijk RPA, et al. *Neurology* 2021;97:528-36.

Acknowledgments

FORTITUDE-ALS was conducted by Cytokinetics, Incorporated in collaboration with Astellas Pharma Inc. We thank the participants of FORTITUDE-ALS and their families for their contributions to the clinical trial.

Assistance with formatting this poster was provided by Engage Scientific Solutions, Horsham, UK, and was funded by Cytokinetics, Incorporated.

Disclosures

TS: employee of Cytokinetics Incorporated. **SK**, **FIM**, **LM**, **SAR**, **JW**, and **AAW**: employees of and own stock in Cytokinetics Incorporated. **RPAE**: nothing to disclose. **JMS**: compensation as a consultant from Amylyx, Apic Biosciences, Cytokinetics Incorporated, Denali, EMD Serono, GSK, Helixsmith, Mitsubishi Tanabe Pharma America, Neurosense, Novartis, Orphazyme, Orthogonal, Pinteon, PTC, RRD, Sanofi, and Swanbio; and research support from Alector, Alexion, Amylyx, Biogen, Biotie Therapies (now Acorda Therapeutics), Cytokinetics Incorporated, Ionis, Medicinova, Mitsubishi Tanabe Pharma America, and Orphazyme.

Acronyms

COURAGE-ALS: **C**linical **O**utcomes **U**sing ***R*eldesemtiv** on **A**LSFRS-R in a **G**lobal **E**valuation in **ALS**

ENCALS: the European Network for the Cure of ALS

FORTITUDE-ALS: **F**unctional **O**utcomes in a **R**andomized **T**rial of **I**nvestigational **T**reatment with CK-2127107 to **U**nderstand **D**ecline in **E**ndpoints – in **ALS**

Presented at the Motor Neurone Disease Association 33rd International Symposium on Amyotrophic Lateral Sclerosis / Motor Neurone Disease (ALS-MND) | December 6–9, 2022 | Virtual Symposium

FORTITUDE ALS

Cytokinetics