CLT-20

Hospitalizations in COURAGE-ALS and Their Relationship to ALS

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BACKGROUND

- Time to hospitalization has been investigated in amyotrophic lateral sclerosis (ALS) trials and was a planned exploratory endpoint in COURAGE-ALS (NCT04944784), a Phase 3 trial of *reldesemtiv* in people living with ALS (pALS) with symptoms for ≤24 months.
- For the first 24 weeks, pALS were randomized 2:1 to *reldesemtiv* or placebo, respectively; in the following 24 weeks, all pALS knowingly took *reldesemtiv*, although blinding was maintained for all involved.
- The primary endpoint was change in ALS Functional Rating Scale-Revised total score from baseline to Week 24. Number of hospitalizations for serious adverse events (SAEs) and their relationship to ALS were additional exploratory endpoints.
- COURAGE-ALS enrolled its first pALS in August 2021 and was terminated due to futility following the second interim analysis in March 2023, with 482 pALS enrolled and included in the full analysis set.
- However, characterization of hospitalizations may be of value for future clinical trials.

OBJECTIVES

- Describe hospitalizations and related SAEs in COURAGE-ALS.
- Report the hospitalization categorization as determined by the principal investigator:
  - Related to ALS (HR-ALS)
  - Unrelated to ALS (HU-ALS)
  - Indeterminate (HI-ALS).
- Investigate hospitalization rates for those assigned to *reldesemtiv* compared with placebo.
- Explore timing of hospitalizations and their relationship to ALS.

METHODS

- Hospitalizations through Week 48 were categorized according to methods previously described.[1]
  - HR-ALS included hospitalizations ascribed to disease progression, addressed an ongoing ALS symptom, were preventative, or were due to complications of ALS treatment.
  - HU-ALS included any hospitalization that would have occurred even in the absence of ALS.
  - HI-ALS was used if the relationship could not be established.
- Hospitalizations associated with multiple SAEs were considered HR-ALS if ≥1 SAE was deemed HR-ALS.
  - When multiple SAEs were part of the same hospitalization, only the SAE(s) deemed HR-ALS were included in the listing.
- Emergency room–only events, even if reported as serious, and hospitalizations for social reasons were excluded.
- Details of how to categorize the hospitalizations were described in the study manual, and a form was provided to assist with the process.
- Categorization was reviewed by the sponsor's medical monitors and queried if needed; however, the monitors could not overrule the response.
- Proportions of each hospitalization category between the placebo and *reldesemtiv* groups were compared using a chi-square test. Time to first hospitalization was analyzed using the Kaplan–Meier method.

RESULTS

Table 1. First-time hospitalizations and their relationship to ALS

	Total first-time hospitalizations	Placebo (n=159)	*Reldesemtiv* (n=323)	*P* value*
All-cause	86	28 (17.6%)	58 (18.0%)	0.9256
HR-ALS	62	18 (11.3%)	44 (13.6%)	0.4779
HU-ALS	15	5 (3.1%)	10 (3.1%)	0.9769
HI-ALS	5	3 (1.9%)	2 (0.6%)	0.1966
Not classified	4	2 (1.3%)	2 (0.6%)	n/a

Although the study was terminated early, the total duration of exposure of both treatment arms was similar.
* *P* values are from chi-square tests comparing proportions of hospitalization between placebo and *reldesemtiv* groups.
n/a, not applicable.

Table 2. Total hospitalizations and their relationship to ALS

	Total hospitalizations	Placebo (n=159)	*Reldesemtiv* (n=323)
All-cause	110	33 (20.8%)	77 (23.8%)
HR-ALS	77	21 (13.2%)	56 (17.3%)
HU-ALS	22	7 (4.4%)	15 (4.6%)
HI-ALS	7	3 (1.9%)	4 (1.2%)
Not classified	4	2 (1.3%)	2 (0.6%)

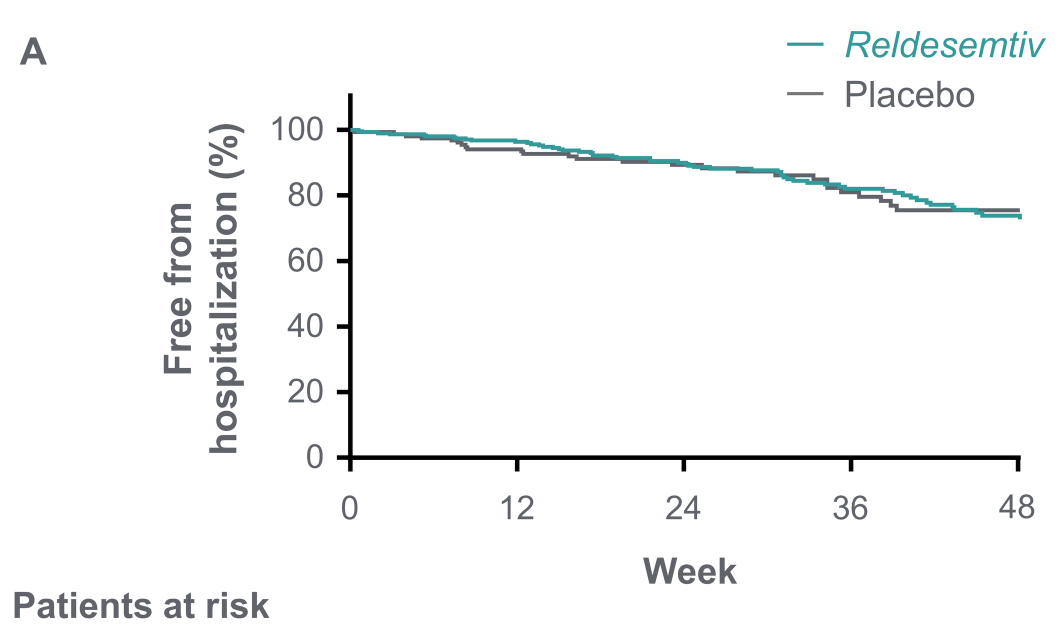
Table 3. Reasons for hospitalizations and their relationship to ALS

	Total	HR-ALS	HU-ALS	HI-ALS	Not classified
Respiratory (non-infectious)	**31**	**30**	**0**	**0**	**1**
RF with NIV initiation	11	10	0	0	1
PE	5	5	0	0	0
PE with pneumonia	2	2	0	0	0
RF	4	4	0	0	0
Aspiration pneumonia	2	2	0	0	0
Mucous plugging/retention	2	2	0	0	0
Other	5	5	0	0	0
Infections	**26**	**11**	**11**	**4**	**0**
Pneumonia (bacterial and viral)	7	6	0	1	0
COVID-19	5	1	4	0	0
UTI/Urosepsis	5	2	2	1	0
Other	9	2	5	2	0
Dysphagia	**22**	**21**	**0**	**0**	**1**
Dysphagia with PEG placed	19	18	0	0	1
Other	3	3	0	0	0
Weight loss with PEG placed	**2**	**2**	**0**	**0**	**0**
PEG tube malfunction	**3**	**2**	**1**	**0**	**0**
Traumatic injury	**8**	**7**	**1**	**0**	**0**
Head injury	3	3	0	0	0
Fracture	5	4	1	0	0
Constipation/Impaction/ Pseudo-obstruction	**4**	**1**	**0**	**2**	**1**
Kidney stones	**3**	**0**	**3**	**0**	**0**
Disease progression	**2**	**2**	**0**	**0**	**0**
Other	**6**	**0**	**4**	**1**	**1**

NIV, non-invasive ventilation; PE, pulmonary embolism; PEG, percutaneous endoscopic gastrostomy; RF, respiratory failure; UTI, urinary tract infection.

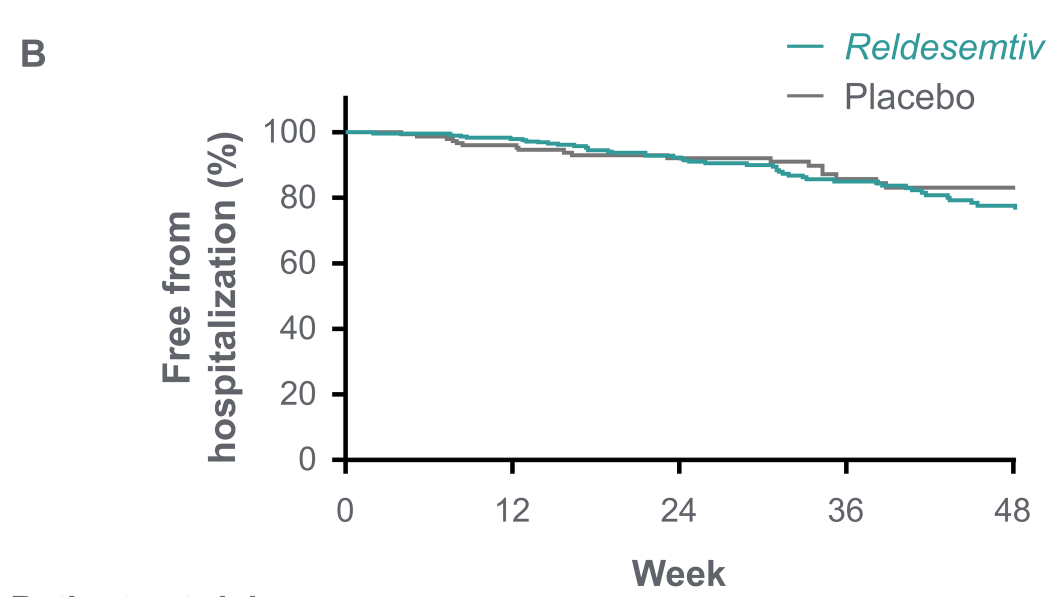
Figure 1. Hospitalizations: A) total hospitalizations; B) HR-ALS hospitalizations

A



Patients at risk					
Reldesemtiv	323	277	200	132	75
Placebo	159	136	96	61	37

B



Patients at risk					
Reldesemtiv	323	282	205	137	79
Placebo	159	138	99	64	39

pALS with Multiple Hospitalizations

- 17 pALS had 2 hospitalizations.
  - 3 pALS had 2 hospitalizations within a month of each other for linked events.
  - 1 pALS had 2 hospitalizations within a month of each other for distinct events.
- 4 pALS had 3 hospitalizations.
  - None were repeat hospitalizations for the same event.
  - Clustering was seen:
    - 2 pALS had all 3 within the course of 2 months.
    - 1 pALS had 2 within 1 month and 1 pALS had 2 within 32 days.

DISCUSSION

- The data presented here describe general findings and summary statistics.
- Although hospitalization events are common endpoints in trials of other chronic diseases, these have rarely been systematically evaluated in ALS trials.
- Given that hospitalizations unrelated to ALS are not rare in this patient population, this study suggests that determining the relationship is worthwhile. However, even with detailed information provided to the site regarding how to categorize the events, some inconsistencies in how they were assigned were seen.
- If time to hospitalization is included as an endpoint in future clinical ALS trials, employing a formal adjudication committee with a rigorous charter and process may be needed to ensure consistency.

CONCLUSIONS

- There was no difference in first hospitalization rates between pALS receiving placebo and those taking *reldesemtiv*; the duration of follow-up was similar between the 2 treatment groups.
- Dysphagia and respiratory failure were the most common SAEs that led to hospitalizations during the trial.
- The total follow-up was comparable between the 2 treatment groups; there was no difference in first hospitalization rates between pALS receiving placebo and those taking *reldesemtiv*.

Reference

1. Simmons Z, et al. European Network to Cure ALS (ENCALS), Edinburgh, UK, 2022. #h149.

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Abbreviations

ALS, amyotrophic lateral sclerosis;
HI-ALS, hospitalization indeterminate-ALS;
HR-ALS, hospitalization related-ALS;
HU-ALS, hospitalization unrelated-ALS;
pALS, people living with ALS; SAE, serious adverse event.

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