INTRODUCTION

• Despite decades of preclinical and clinical research, highly effective therapies that significantly improve symptomatology and survival in amyotrophic lateral sclerosis (ALS) have not advanced with limited success. Biomarkers that may identify people with ALS who are more likely to respond to investigational therapeutics or predict a meaningful treatment response are needed.

• Neurofilaments (NFs) are a class of intermediate filaments in neurons of both the central and peripheral nervous systems. They are major constituents of the cytoskeletal structure of neurons, particularly in axons.

• NF light chain (NfL) and phosphorylated NF heavy chain (pNfH) have gained attention as potential biomarkers of disease in several neurologic disorders, including ALS. It is hypothesized that NfL and pNfH are released from the cytoplasm of injured or dying neurons, which can then be measured in either cerebrospinal fluid or plasma to serve as biomarkers of disease progression.

• VITALITY-ALS (NCT02496767) was a 48-week, randomized, double-blind, placebo-controlled Phase 3 study of tisagenlecleucel, a fast skeletal muscle troponin activator, in people with ALS. Results have been previously described. VITALITY-ALS enrolled 566 people with ALS, and NF plasma samples were collected every 8 weeks for 48 weeks.

OBJECTIVES

• Using data from VITALITY-ALS:
  – Compare baseline NfL and pNfH values according to demographics and clinical features.
  – Correlate baseline NfL and pNfH values with pretrial and in-study rate of disease progression (psRDP and isRDP).
  – Evaluate the change in NfL and pNfH values over 48 weeks and investigate the relationship of the change to psRDP.

METHODS

• VITALITY-ALS enrolled 566 people with ALS. 188 were randomized to placebo and 377 to one of 3 dose levels of tisagenlecleucel. Outcomes were assessed and plasma samples collected from participants at baseline and every 8 weeks for 48 weeks.

• NfL was measured using the Luminex® xMAP® technology (Luminex Corporation, Austin, TX, USA).

• In these post hoc analyses, plasma NfL and pNfH were compared by treatment, clinical characteristics, and time using a mixed model for repeated measures with baseline value adjustment.

• Pearson correlation coefficients (r) were calculated to evaluate the degree of correlation of baseline NfL and pNfH with psRDP and isRDP for the overall population, as well as psRDP and isRDP tertiles representing fast (FP), intermediate, and slow progressors.

• psRDP was calculated as change from baseline in ALSFRS-R score per month over the 48 weeks. isRDP was calculated as change from baseline in ALSFRS-R score divided by symptom duration in months.

• psRDP was calculated as change from baseline in ALSFRS-R score per month over the 48 weeks.

RESULTS

• NfL and pNfH measurements were available for 101 participants in the placebo group and 161 in the tisagenlecleucel group.

• Baseline and disease characteristics were similar across treatment arms.

• There were no significant differences in NfL or pNfH between placebo and tisagenlecleucel groups at any time point; therefore, further analysis grouped all samples.

• At baseline, NfL and pNfH did not differ by site of onset, EI Escorial criteria, or symptom duration (Table 1).

• While mean NfL values did not differ meaningfully among tertiles, baseline NfL showed a fair correlation with the psRDP (r=0.50, P<0.001) driven primarily by FP (r=0.43, P<0.001) (Figure 1A).

• Baseline NfL showed a fair correlation with 12-month isRDP (r=0.51, P<0.001), which was primarily driven by FP (r=0.41, P<0.001) (Figure 1C).

• pNfH showed similar, but less robust, patterns. Over 48 weeks, pNfH levels continuously decreased, reaching statistical significance at Week 16 (P<0.05), and declined with each 8-week interval (P<0.001 from Week 24 onward), whereas NfL did not change meaningfully over time (Figure 2).

CONCLUSIONS

• VITALITY-ALS provided a large longitudinal collection of Nf in an ALS clinical trial cohort.

• Baseline NfL values did not differ by site of onset, ALS diagnostic certainty, or symptom duration.

• Baseline NfL and pNfH correlated with both psRDP and isRDP for NfL; this was primarily driven by the FP tertile.

• pNfH decreased over time in this cohort of people with ALS – NfL appeared to decrease over time, however, the reduction was not statistically significant.

• These findings suggest NF may have utility in identifying people with ALS with higher risk of faster disease progression, although the results should be interpreted with caution given that the degree of correlation was somewhat modest.

Figure 1A. Correlation between baseline NfL or pNfH and psRDP and isRDP tertiles

Figure 2A. NfL and pNfH change from baseline (LSM), for overall group and by psRDP tertiles

Table 1. Baseline NfL and pNfH levels according to clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NfL median (IQR)</th>
<th>pNfH median (IQR)</th>
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<tbody>
<tr>
<td>Site of onset</td>
<td></td>
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<tr>
<td>Bulbar (n=96)</td>
<td>336.8 ± 173.7</td>
<td>404.9 ± 296.7</td>
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<tr>
<td>Limb (n=262)</td>
<td>269.0 ± 188.8</td>
<td>356.0 ± 406.8</td>
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<tr>
<td>El Escorial criteria</td>
<td></td>
<td></td>
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<tr>
<td>Definite (n=73)</td>
<td>317.4 ± 222.2</td>
<td>405.5 ± 452.3</td>
</tr>
<tr>
<td>Possible/probable (n=189)</td>
<td>263.0 ± 170.0</td>
<td>344.4 ± 384.4</td>
</tr>
<tr>
<td>Symptom duration, mo</td>
<td>0–12 (n=92)</td>
<td>358.5 ± 215.5</td>
</tr>
<tr>
<td>12–24 (n=118)</td>
<td>267.8 ± 194.1</td>
<td>379.1 ± 465.8</td>
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<tr>
<td>25–36 (n=50)</td>
<td>207.7 ± 115.5</td>
<td>263.0 ± 263.1</td>
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There were no statistically-significant differences between categories of clinical disease characteristics (p>0.05).

Abbreviations

- ALS: amyotrophic lateral sclerosis
- NfL: neurofilament light chain
- pNfH: phosphorylated neurofilament heavy chain
- psRDP: rate of disease progression defined as annual change in ALSFRS-R score
- isRDP: rate of disease progression defined as ALSFRS-R score divided by symptom duration
- NCT: National Clinical Trial number
- NCS: National Clinical Study number
- CTR: Clinical Trial Registry

References


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Acknowledgments and Disclosures

VITALITY-ALS was supported by Cytokinetics, Inc. Post-hoc analyses for the poster were performed by the ALS Association through a grant to support the collection of clinical data and plasma samples collected by the VITALITY-ALS registry. The ALSFRS-R was used to assess symptom impairment and progression.

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The VITALITY-ALS registry is registered with the National Institutes of Health (NCT02496767). The VITALITY-ALS registry is sponsored by Cytokinetics, Inc., South San Francisco, CA, USA. The ALSFRS-R score was calculated by assigning a score of 0 to patients with ALS without symptoms (N=47) and a score of 100 to normal healthy controls (N=52).

As with all clinical trials, data must be interpreted with caution and must always be applied in the context of the original study results and conclusions. All data were obtained under an Investigational New Drug application (#20160-004) in the United States and other countries, and under an Expanded Access Program in the United States.