Reduced Plasma Concentration of the Neuroinflammation Biomarker Chitinase-3-Like Protein (CHI3L1/YKL-40) in the CENTAUR Trial

Poster #33

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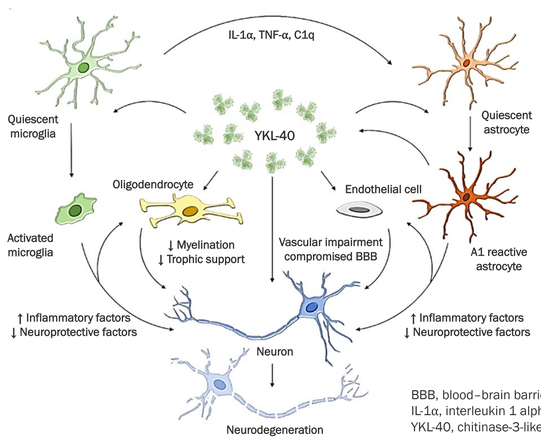
BACKGROUND

- The safety and efficacy of an oral, fixed-dose combination of sodium phenylbutyrate and taurursodiol (PB and TURSO), also known as AMX0035, in amyotrophic lateral sclerosis (ALS) were evaluated in a multicenter phase 2 trial encompassing a 24-week randomized placebo-controlled phase and an open-label extension long-term follow-up phase (CENTAUR)[1,2]
- Change in plasma phosphorylated neurofilament heavy chain and neurofilament light chain concentrations were evaluated in the randomized phase of CENTAUR and showed no differences between groups.[1,3] As biomarker development in ALS was less evolved at the time of trial design, efforts were made to collect and store plasma samples from CENTAUR for future analyses as the field of ALS biomarkers advanced
- Recently, chitinases, a class of hydrolases that are expressed by activated microglia and astrocytes within the central nervous system, have emerged as potential prognostic biomarkers in ALS and other neurodegenerative diseases including Alzheimer's disease (AD)[4]
  - Release of chitinase-3-like protein 1 (CHI3L1, also known as YKL-40) is associated with inflammation, a driver in the multistep process of ALS pathogenesis (**Figure 1**)[5]
  - YKL-40 concentration has been shown to correlate with disease severity,[6-8] speed of disease progression,[4,9,10] and survival[11] in ALS
- PB and TURSO was shown to significantly reduce cerebrospinal fluid (CSF) YKL-40 concentration compared with placebo in adults with mild cognitive impairment and mild to moderate AD dementia in a 24-week phase 2 multicenter, randomized trial (PEGASUS)
  - The change in CSF YKL-40 concentration from baseline to week 24 was −14.6 ng/mL in the PB and TURSO group compared with +1.5 ng/mL in the placebo group (difference, −16.1 ng/mL [95% CI, −27.0, −5.3]; *P*=.004)[3]

Figure 1. Proposed Role of YKL-40 in Neuroinflammation and Neurodegeneration[5]



BBB, blood–brain barrier; C1q, complement component 1q; IL-1α, interleukin 1 alpha; TNF-α, tumor necrosis factor alpha; YKL-40, chitinase-3-like protein 1.

OBJECTIVE

- To examine whether administration of PB and TURSO reduced plasma YKL-40 levels in an exploratory post-hoc analysis of plasma samples obtained during the CENTAUR trial
  - Chitinase 1 (CHIT1) and C-reactive protein (CRP) levels were also assessed as part of an inflammatory biomarkers panel

PB and TURSO is an investigational drug not approved for use pending regulatory review in the European Medicines Agency for the treatment of ALS.

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METHODS

- YKL-40, CHIT1, and CRP immunoassays were developed by the Bowser Laboratory at the Barrow Neurological Institute and nVector (previously Iron Horse Diagnostics, Inc.) on the Meso Scale Discovery (MSD) platform within nVector; all MSD assays were qualified within the nVector Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory
- Assays were conducted in a blinded manner using 0.5-mL plasma samples from CENTAUR
- As for the prespecified efficacy outcomes in CENTAUR, the participant population for these analyses was the modified intent-to-treat (mITT) population, consisting of all participants who received ≥1 dose of study medication and had ≥1 postbaseline Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) assessment
- Log10-transformed plasma biomarker measurements[4] were analyzed using a random-slope, shared-baseline, and linear mixed effects model, with calculation of geometric least squares (LS) mean biomarker concentrations for each treatment group at prespecified time points corresponding with sample collection
- Change-from-baseline analyses that did not assume a shared baseline between treatment groups were also performed; the ratios of geometric LS mean biomarker concentrations relative to baseline concentration at each time point are presented

RESULTS

- Of 135 total participants in the mITT population (PB and TURSO, n=87; placebo, n=48), 126 (PB and TURSO, n=81; placebo, n=45) had plasma samples available for these post hoc analyses
- Summary of baseline plasma biomarker concentrations are shown in **Table 1**

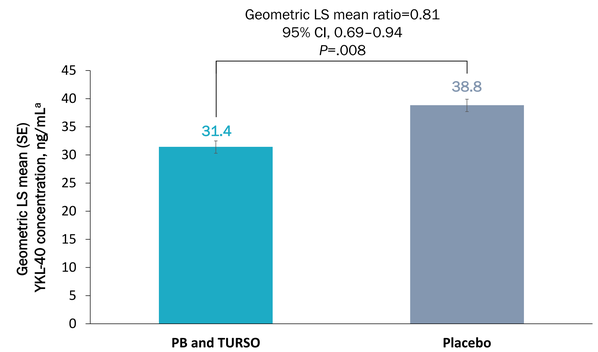
Table 1. Baseline Plasma Biomarker Concentrations

Biomarker, ng/mL	Statistic	PB and TURSO (n=81)	Placebo (n=45)
YKL-40	Mean (SD)	43.9 (47.6)	36.6 (24.1)
	Median	29.5	28.2
	Range	10.0–268.6	11.4–126.1
CHIT1	Mean (SD)	58.5 (59.0)	52.7 (40.1)
	Median	40.5	43.4
	Range	0.0–260.9	1.8–188.7
CRP	Mean (SD)	3115.0 (3915.6)	6460.5 (12,160.8)
	Median	1526.1	2228.0
	Range	130.3–20,928.9	163.9–51,801.2

CHIT1, chitinase 1; CRP, C-reactive protein; PB and TURSO, sodium phenylbutyrate and taurursodiol; YKL-40, chitinase-3-like protein 1.

- At week 24, geometric LS mean YKL-40 plasma concentrations were reduced by approximately 20% in the PB and TURSO group compared with the placebo group (*P*=.008; **Figure 2**)
  - YKL-40 concentration correlated with ALSFRS-R total score (r of −0.21; *P*=.0001) and prebaseline ALSFRS-R slope (ie, the rate of change in ALSFRS-R total score from symptom onset to baseline[12]; r of 0.11; *P*=.034) in CENTAUR

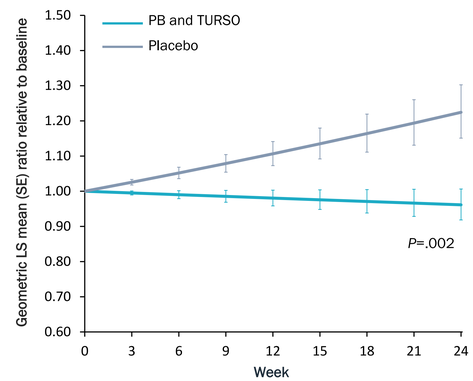
Figure 2. YKL-40 Concentration at Week 24



LS, least squares; PB and TURSO, sodium phenylbutyrate and taurursodiol; SE, standard error; YKL-40, chitinase-3-like protein 1. [a]Log10-transformed, as previously described.[4]

- Change-from-baseline analyses similarly showed a significant reduction in plasma YKL-40 concentration in the PB and TURSO versus placebo group (*P*=.002; **Figure 3**)

Figure 3. Ratio of Change from Baseline in YKL-40 Concentration Relative to Baseline Concentration Over 24 Weeks



LS, least squares; PB and TURSO, sodium phenylbutyrate and taurursodiol; SE, standard error; YKL-40, chitinase-3-like protein 1.

- Geometric LS mean CHIT1 plasma levels were not significantly different between treatment arms at week 24 (ratio, 0.88; 95% CI, 0.75–1.02; *P*=.094)
- Geometric LS mean CRP concentration was approximately 30% lower in the PB and TURSO group (1833.6 ng/mL) compared with the placebo group (2650.2 ng/mL) at week 24 (ratio, 0.69; 95% CI, 0.48–1.00; *P*=.048)

CONCLUSIONS

- CENTAUR is the first interventional study in ALS to show a reduction of plasma YKL-40 levels over 24 weeks, which correlated with retention of function as measured by ALSFRS-R
- The findings of these analyses confirm the results from a separate study in AD, in which PB and TURSO significantly reduced YKL-40 levels compared with placebo in CSF samples
- Additional analyses of YKL-40 and other inflammatory biomarkers in the ongoing phase 3 clinical trial of PB and TURSO in ALS (PHOENIX) are warranted to confirm these results

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Disclosures

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