Learnings from the CENTAUR and PHOENIX Trials: Biomarker Results

Poster CL-65

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BACKGROUND

- Two placebo-controlled trials have been completed with sodium phenylbutyrate and ursodoxicoltaurine (PB&TURSO) in ALS; one positive trial in 137 US participants (CENTAUR) and one negative trial in 664 US and European participants (PHOENIX)
- Evaluating biomarker results between the trials, and specifically between the PHOENIX CENTAUR-like and CENTAUR populations, may allow for insight into these results

RESULTS

Summary of Biomarker Results from CENTAUR at Week 24

- No difference between treatment groups for NfH or NfL at Week 24[1]
- YKL-40 levels were **20% lower** at Week 24 in PB&TURSO group compared to placebo (p=0.008)[2]
  - YKL-40 concentration correlated with ALSFRS-R total score (r of –0.21; p<0.0001) and ALSFRS-R slope (r of 0.11; p=0.034)
- CRP levels were **30%** lower at Week 24 in the PB&TURSO group compared to placebo (p=0.048)[2]

Labs Performing Analyses

- YKL-40 and CRP in CENTAUR and PHOENIX: *n*Vector, USA
- All other PHOENIX Biomarkers: ICON Bioanalytical Laboratory, The Netherlands

Plasma Biomarker Results from PHOENIX at Week 48: Change from Baseline (log-transformed MMRM)

PHOENIX Overall Population

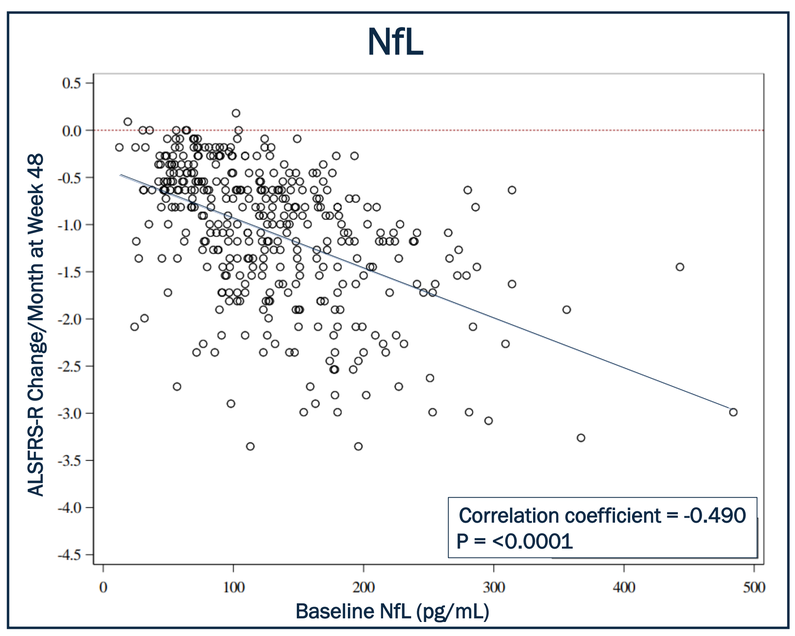
Biomarker	Geometric Mean Ratio to Baseline (95% CI) PB&TURSO N = 397	Geometric Mean Ratio to Baseline (95% CI) Placebo N = 267	Geometric Mean Ratio (95% CI)	p-value
NfL (pg/mL)	0.986 (0.951, 1.02) n = 217	0.997 (0.954, 1.04) n = 143	0.989 (0.934, 1.05)	0.691
YKL-40 (ng/mL)	1.05 (0.997, 1.11) n = 214	1.19 (1.11, 1.27) n = 142	0.884 (0.815, 0.959)	**0.003**
CRP (ng/mL)	1.13 (0.973, 1.31) n = 211	1.21 (1.01, 1.45) n = 141	0.934 (0.738, 1.18)	0.570
Total tau (fg/mL)	0.933 (0.885, 0.984) n = 216	0.922 (0.863, 0.985) n = 142	1.01 (0.930, 1.10)	0.781
p-tau 181 (fg/mL)	1.28 (1.19, 1.39) n = 132	1.26 (1.14, 1.38) n = 90	1.02 (0.900, 1.15)	0.762
SPP1 (pg/mL)	1.17 (1.13, 1.20) n=204	1.12 (1.07, 1.16) n=139	1.04 (0.991, 1.10)	0.103

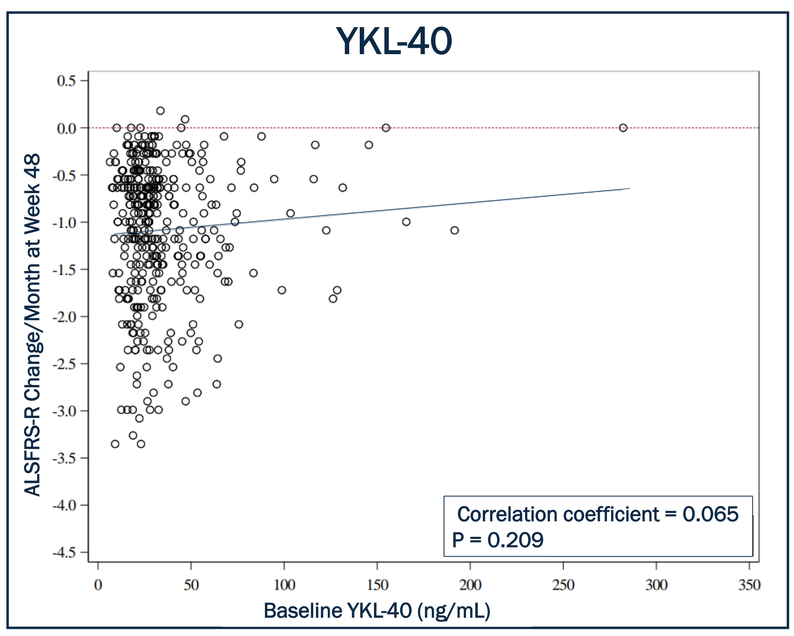
PHOENIX CENTAUR-Like Subgroup

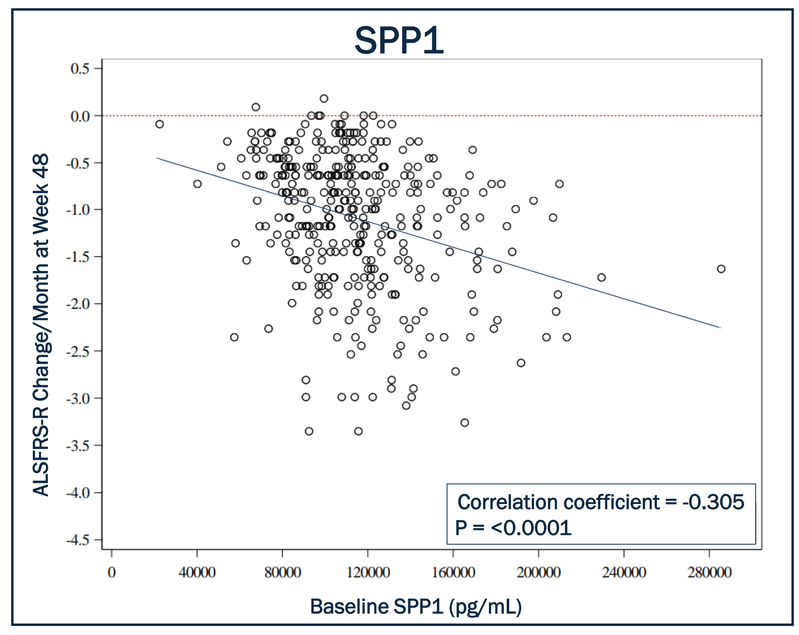
Biomarker	Geometric Mean Ratio to Baseline (95% CI) PB&TURSO N = 100	Geometric Mean Ratio to Baseline (95% CI) Placebo N = 68	Geometric Mean Ratio (95% CI)	p-value
NfL (pg/mL)	0.941 (0.870, 1.02) n = 49	0.945 (0.856, 1.04) n = 32	0.996 (0.878, 1.13)	0.952
YKL-40 (ng/mL)	1.05 (0.935, 1.17) n = 49	1.13 (0.981, 1.30) n = 30	0.926 (0.774, 1.11)	0.400
CRP (ng/mL)	1.49 (1.07, 2.10) n = 48	0.897 (0.591, 1.36) n = 29	1.66 (0.979, 2.81)	0.060
Total tau (fg/mL)	0.978 (0.879, 1.09) n = 49	1.04 (0.914, 1.19) n = 32	0.940 (0.794, 1.11)	0.463
p-tau 181 (fg/mL)	1.39 (1.20, 1.62) n = 29	1.31 (1.10, 1.55) n = 23	1.07 (0.848, 1.34)	0.579
SPP1 (pg/mL)	1.15 (1.04, 1.26) n=46	1.08 (0.968, 1.22) n=32	1.06 (0.913, 1.23)	0.442

- YKL-40 levels were **12% lower** at Week 48 in AMX0035 group compared to placebo in PHOENIX overall population (p=0.003)
- No difference in YKL-40 in CENTAUR-like subgroup
- No other biomarker differences in overall PHOENIX population or PHOENIX CENTAUR-like subgroups were seen

Biomarker Results from PHOENIX at Week 48: Correlation Plots for ALSFRS-R Slope and Baseline Biomarkers







Key Takeaways

- PHOENIX biomarker findings were generally consistent with CENTAUR
  - CENTAUR: both YKL-40 and CRP lowered; PHOENIX: only YKL-40 lowered (no CRP) and only in overall population
  - Key limitation: PHOENIX and CENTAUR utilized different neurofilament assays, preventing comparison
- PB&TURSO has lowered YKL-40 compared to placebo in 2 ALS trials and in 1 AD trial
  - Further research needed to understand mechanism and meaningfulness
- In PHOENIX, baseline NfL and SPP1 correlated with ALSFRS-R slope, but YKL-40 did not

Abbreviations

ALS, amyotrophic lateral sclerosis; ALFRS-R, ALS Functional Rating Scale – Revised; CI, confidence interval; CRP, C-reactive protein; MMRM, mixed model for repeated measures; NfH, neurofilament heavy chain; NfL, neurofilament light chain; p-tau, phosphorylated tau; SPP1, secreted phosphoprotein 1; YKL-40, chitinase-3-like protein 1.

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References

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Based on results from the PHOENIX trial, Amylyx has started a process with the FDA and Health Canada to voluntarily discontinue the marketing authorizations for PB&TURSO. This will remove the product from the market in the U.S. and Canada.

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