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Efficacy and safety of ALXN1840 versus standard of care in Wilson disease: primary results from an ongoing phase 3, randomized, controlled, rater-blinded trial

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Background and aims: ALXN1840 is an oral, copper (Cu)-binding agent that forms a stable tripartite (tetrathiomolybdate-Cu-albumin) complex. This study investigated the efficacy and safety of ALXN1840 for treating Wilson disease (WD) using a novel plasma biomarker of Cu sequestration.

Method: Patients with WD aged ≥12 years (Leipzig score ≥4; model for end-stage liver disease score ≤13) were randomized 2:1 to ALXN1840 at a starting dose of 15 mg QD with dose adjustments up to 60 mg QD permitted, or standard of care (SoC; penicillamine, trientine and/or zinc) for 48 weeks (W).

Prior SoC for >28 days and 0–28 days determined enrolment to Cohorts 1 and 2, respectively. Primary end point: mean daily area under the effect-time curve of directly measured non-ceruloplasmin-bound Cu 0–48W (dNCC $AUEC_{0-48W}$). Secondary end points: 0–48W change in neurological Unified WD rating scale (UWDRS) Part II and III scores, and Clinical Global Impression-Improvement (CGI-I) scores. A pre-specified hierarchical statistical testing method was used to control multiplicity across primary and key secondary end points. Adverse events (AEs) were summarized.

Results: 214 patients enrolled; all had preserved liver function and 79% had neurological symptoms. 207 were treated, 137 with ALXN1840 and 70 with SoC; mean age was 34.3 and 32.1 years, and 59.9% and 52.9% were male, respectively. Mean daily dNCC $AUEC_{0-48W}$ (μmol/L) was 3.2 times greater with ALXN1840 than with SoC overall (least-squares mean [LSM] difference, 2.18 [standard error (SE), 0.244], $p < 0.0001$), and 2.5 times greater with ALXN1840 for Cohort 1, despite a mean prior SoC duration of >12 years (Figure). UWDRS scores reduced modestly from 0 to 48W (mean [95% confidence interval] change in Part III score for symptomatic patients: ALXN1840, −2.91 [−4.74, −1.09]; SoC, −1.17 [−3.20, 0.86]). No significant between-group differences occurred by 48W. Transformed CGI-I scores improved with ALXN1840 vs SoC at 48W; LSM difference, −0.3 [SE, 0.15], $p = 0.0316$; outside the multiplicity testing sequence). For 0–48W, 100.1 (ALXN1840) and 86.5 (SoC) patients experienced AEs per 100 patient-years. Most AEs (ALXN1840, 94.1%; SoC, 92.7%) were not serious. The most frequent AE with ALXN1840 was alanine aminotransferase increase (14.6%). Two deaths, considered unrelated to ALXN1840, were reported.

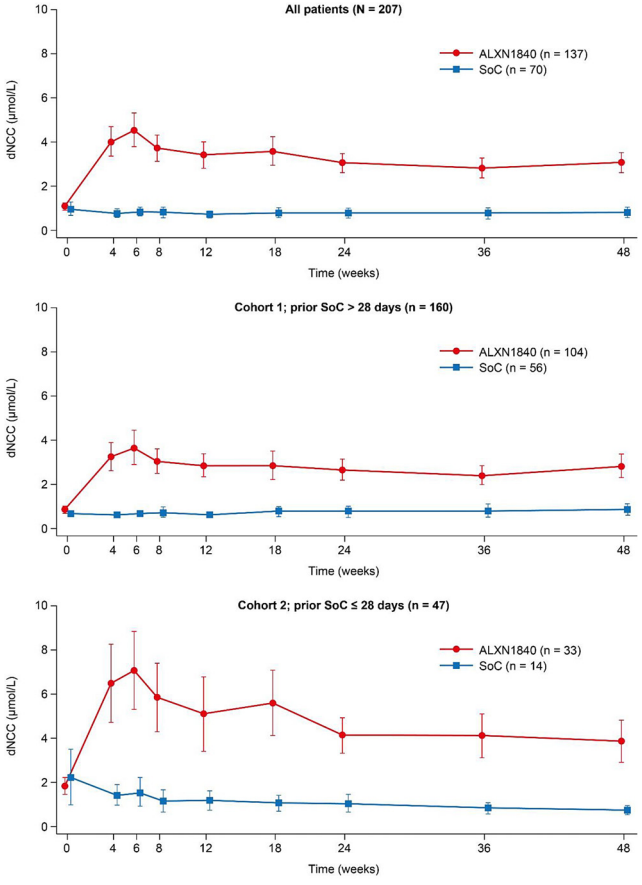

Figure: dNCC values by treatment group from 0 to 48 weeks.
dNCC, directly measured non-ceruloplasmin-bound copper; SoC, standard of care.

Conclusion: ALXN1840 treatment for 48W provided superior Cu control to SoC and was generally well tolerated. Future data analysis of the 60-month open-label extension of this study will evaluate long-term efficacy and safety of ALXN1840.

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