Letter to the Editor

JOURNAL
OF HEPATOLOGY

Oral bis-choline tetrathiomolybdate rapidly improves copper balance in patients with Wilson disease

To the Editor:

The previous sponsor of bis-choline tetrathiomolybdate (TTM, ALXN1840) concluded that a study of copper balance in nine patients with Wilson disease treated with once daily oral TTM did not appear to demonstrate the elimination of copper and subsequently terminated the program.[1] In this Letter to the Editor, we provide new evidence directly contradicting that conclusion – data showing that TTM rapidly improves copper balance in patients with Wilson disease.

With the encouraging prospective 6-year-long efficacy and safety data for TTM in patients with Wilson disease recently shared at EASL Congress 2025 as a Late-Breaker, we revisited the 2024 *Journal of Hepatology* publication by Kirk *et al.*[2,3] This study by Kirk *et al.* demonstrated a dual mechanism of TTM: inhibition of dietary copper absorption and prevention of copper deposition in the liver and brain. These data clearly suggest that TTM administration may enhance copper elimination rather than promote its accumulation.

This led us to revisit the copper balance trial and the conclusions of the previous sponsor. In doing so, we discovered a methodological limitation in the previous sponsor's copper balance equation, which quantified copper excretion as solely being through feces and urine, neglecting and failing to account for other routes of copper loss. Studies have demonstrated that significant copper losses also occur via sweat, tears, hair loss, and skin desquamation.[4–6] Interestingly, a recent copper balance study of 17 healthy volunteers, conducted at the same main clinical trial site and using the same equation that accounted only for feces and urine, demonstrated a positive mean daily copper balance of 0.516 mg/day.[7] Their mean dietary copper intake was 1.67 mg/day, yielding a 30.9% retention of copper in these healthy individuals. Considering the estimated average adult copper intake in the US and EU ranges from 1.2–1.7 mg/day, if analytically correct, the finding of positive copper balance in healthy individuals indicates that a substantial fraction of ingested copper is retained in healthy individuals.[8,9] If this was truly the case, one would expect to see toxic copper overload observed in the real world general healthy population, which it is not.

These copper balance studies are inherently difficult to conduct. It is nearly impossible to fully capture and measure all routes of copper excretion. Further, enrollment is limited by the rarity of Wilson disease and feasibility of recruitment for a study that requires voluntary confinement to a clinical research facility for multiple weeks. Due to sample collection challenges, these studies tend to be restricted to measuring copper loss through feces and urine only.

To account and control for routes of copper loss other than those measured in the feces and urine, we evaluated the change from baseline in the eight TTM-treated patients with Wilson disease who completed the copper balance study (the ninth patient was discontinued from the study on Day 4 due to a major protocol violation – failing to stop penicillamine treatment). Interestingly, this patient's baseline copper balance while still on penicillamine, which they had been on for years, was higher than the baseline average of the other patients). Using the prior sponsor's reported daily copper balance values, we evaluated the change for these patients from their pre-treatment baseline during both the TTM 15 mg/day treatment periods (study days 1-8 and 25-28) and the overall treatment period (includes days 31-39, in which some patients dose escalated to 30 mg/day and others dose reduced to 15 mg every other day).

Their baseline mean (SD) daily copper balance was 1.10 mg (0.36). The mean change from baseline in daily copper balance was statistically significant in both the 15 mg/day treatment period (mean difference, -0.367 mg; $p = 0.005$) and the overall treatment period (mean difference, -0.289 mg; $p = 0.023$). The improved (decreased) copper balance was driven almost entirely by increased fecal copper excretion. By study end, the cumulative mean change from baseline in copper balance for days on study was -6.08 mg (95% CI -10.18 to -1.98, Fig. 1A; individual data are presented in Fig. 1B; all primary data and calculations can be found in the supplementary material).

In summary, TTM treatment led to statistically significantly improved (decreased) copper balance in patients with Wilson disease, primarily driven by measured increased fecal copper excretion. These results may largely be driven by systemic copper chelation rather than inhibition of dietary copper absorption, considering that patients had to fast for 10 hours before through to 2 hours after TTM administration. If TTM were administered in a non-fasting state, copper balance may further improve.

The findings in this Letter, in conjunction with the long-term prospective efficacy and safety data recently presented at EASL Congress 2025, support the therapeutic potential of TTM as a novel next-generation treatment option for Wilson disease.

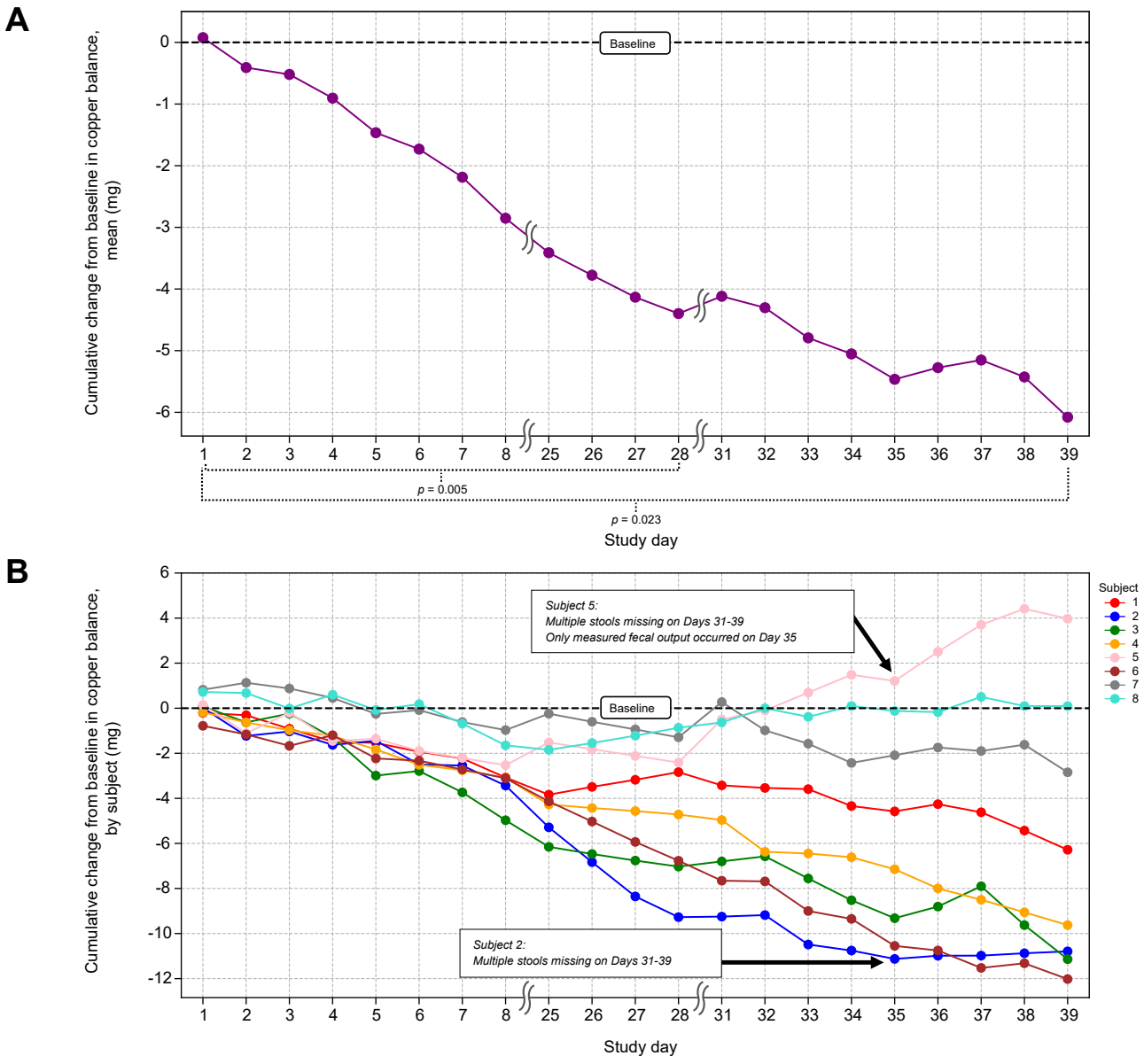

Fig. 1. Cumulative change from baseline in daily copper balance of Wilson disease patients treated with TTM. Results are presented for all participants who completed the study (n = 8, the ninth patient was withdrawn early on for failure to discontinue penicillamine treatment). (A) Mean change from baseline for all participants. (B) Individual change from baseline for all participants. The underlying primary data, as well as the calculations for the individual and mean changes from baseline, presented in these figures are provided in the supplementary material. *p*-values were calculated using two-tailed paired t-tests.

Aftab Ala[1,*]
Fred Askari[2]
Karl Heinz Weiss[3]
Valentina Medici[4]
Thomas Damgaard Sandahl[5]
[1]*Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom*
[2]*Michigan Medicine, Ann Arbor, MI, USA*
[3]*Salem Medical Center, Heidelberg, Germany*
[4]*Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of California, Davis, CA, USA*
[5]*Aarhus University Hospital, Aarhus, Denmark*
[*]Corresponding author. Address: Institute of Liver Studies, King's College Hospital NHS Foundation Trust, Denmark Hill, London, United Kingdom; Tel.: +44 203 299 3713.
E-mail address: aftab.ala1@nhs.net (A. Ala)

Received 4 July 2025; Received in revised form 5 September 2025; Accepted 8 September 2025; Available online xxx
https://doi.org/10.1016/j.jhep.2025.09.006

Financial support

The copper balance study was funded by Alexion, AstraZeneca Rare Disease. Monopar Therapeutics Inc. licensed bis-choline tetrathiomolybdate after study completion and is responsible for future development.

Conflict of interest

AA has received grants or contracts (paid to institution) from Orphalan, Alexion/AstraZeneca Rare Disease, Univar Solutions, Ultragenyx, Vivet Therapeutics, and from Alexion/AstraZeneca Rare Disease (paid to self); consulting fees from ArborMed, Alexion/AstraZeneca Rare Disease, Univar Solutions, and Orphalan; honoraria from Orphalan and Univar Solutions; support for attending meetings from Alexion/AstraZeneca Rare Disease, ArborMed, Orphalan, and Univar Solutions; advisory board payments from Alexion/AstraZeneca Rare Disease, ArborMed, Orphalan, Vivet Therapeutics, Univar Solutions, and Ultragenyx; and non-financial support from the Wilson Disease Association, Wilson's Disease Support Group, British Association for the Study of the Liver, and the British Liver Trust. FA has received grants or contracts (paid to institution) from Alexion/AstraZeneca Rare Disease, Orphalan, Ultragenyx, and Vivet Therapeutics; research support and advisory board payments (paid to institution) from Wilson Therapeutics, Alexion/AstraZeneca Rare Disease; support for attending meetings from Wilson Therapeutics, Alexion/AstraZeneca Rare Disease, and Orphalan; support for participation on data safety monitoring boards and/or advisory boards (unpaid) from Wilson Therapeutics, Alexion/AstraZeneca Rare Disease, Orphalan, Monopar Therapeutics, Vivet Therapeutics, and Ultragenyx; and non-financial support from the Wilson Disease Association. KW has received grants or contracts consulting fees from Univar Solutions, Alexion/AstraZeneca Rare Disease, Orphalan, Vivet Therapeutics, and Prime Medicine; honoraria from AbbVie, Indiogen, Orphalan, and Univar Solutions; and support for participation on data safety monitoring boards and/or advisory boards from Ultragenyx. VM has received grants or contracts from Alexion/AstraZeneca Rare Disease, Orphalan, Ultragenyx, ArborMed, Vivet Therapeutics, and Eton Pharmaceuticals; consulting fees from Alexion, AstraZeneca Rare Disease, ArborMed, Eton Pharmaceuticals, and Orphalan; honoraria from Alexion, AstraZeneca Rare Disease; support for attending meetings from Orphalan; support for participation on data safety monitoring boards and/or advisory boards from ArborMed, Orphalan, and Eton Pharmaceuticals; and receipt of equipment, materials, or other services from Mars. TS has received consulting fees from ArborMed; honoraria from Orphalan; support for attending meetings from Alexion/AstraZeneca Rare Disease; and support for participation on data safety monitoring boards and/or advisory boards from Ultragenyx and Vivet Therapeutics.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed to the Letter, critically reviewed content, and provided final approval of the Letter.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2025.09.006.

References

[1] Copper and molybdenum balance in participants with Wilson disease treated with ALXN1840. ClinicalTrials.gov identifier: NCT04573309. Updated June 24, https://clinicaltrials.gov/study/NCT04573309. [Accessed 16 May 2025].
[2] Weiss KH, Sandahl T, Medici V, et al. LBP-032 Sustained long-term clinical improvement in Wilson disease patients on tiomolybdate choline. J Hepatol 2025;82:S86–S87. https://doi.org/10.1016/s0168-8278(25)00450-7.
[3] Kirk FT, Munk DE, Swenson ES, et al. Effects of tetrathiomolybdate on copper metabolism in healthy volunteers and in patients with Wilson disease. J Hepatol 2024 Apr;80(4):586–595. https://doi.org/10.1016/j.jhep.2023.11.023.
[4] Molin L, Wester PO. The estimated daily loss of trace elements from normal skin by desquamation. Scand J Clin Lab Invest 1976 Nov;36(7):679–682. https://doi.org/10.1080/00365517609054495.
[5] Kumakli H, Duncan AV, McDaniel K, et al. Environmental biomonitoring of essential and toxic elements in human scalp hair using accelerated microwave-assisted sample digestion and inductively coupled plasma optical emission spectroscopy. Chemosphere 2017 May;174:708–715. https://doi.org/10.1016/j.chemosphere.2017.02.032.
[6] Jacob RA, Sandstead HH, Munoz JM, et al. Whole body surface loss of trace metals in normal males. Am J Clin Nutr 1981 Jul;34(7):1379–1383. https://doi.org/10.1093/ajcn/34.7.1379. PMID: 7258128.
[7] Copper balance in healthy participants administered ALXN1840. ClinicalTrials.gov identifier: NCT04594252. 2024. August 19, https://clinicaltrials.gov/study/NCT04594252. [Accessed 16 May 2025].
[8] Blumberg JB, Frei B, Fulgoni VL, et al. Contribution of dietary supplements to nutritional adequacy in various adult age groups. Nutrients 2017 Dec 6;9(12):1325. https://doi.org/10.3390/nu9121325.
[9] Sadhra SS, Wheatley AD, Cross HJ. Dietary exposure to copper in the European Union and its assessment for EU regulatory risk assessment. Sci Total Environ 2007 Mar 15;374(2–3):223–234. https://doi.org/10.1016/j.scitotenv.2006.12.041.