Poster #

Neutral Molybdenum Balance and Lack of Molybdenum Toxicity in Subjects Treated with Tiomolibdate Choline Supports Safety Profile of TMC

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BACKGROUND

- Tiomolibdate choline (TMC; ALXN1840) is an oral, once-daily, novel mechanism albumin-tripartite-complex (ATC)-activator in development for Wilson disease (WD)[1]
- TMC contains tetrathiomolybdate, a molybdenum (Mo)-containing high affinity Cu-binding moiety
- Excess Mo exposure presents with hyperuricemia and gout-like symptoms[2], so progressive Mo accumulation and serum uric acid levels were assessed for chronic TMC treatment in the Phase 2&3 TMC clinical trials

OBJECTIVE

We present results from:

- Mo balance study conducted in healthy volunteers administered TMC (HV-108)
- Long-term serum uric acid and adverse event (AE) data in WD patients from the Phase 2&3 TMC clinical trials

METHODS

- 17 healthy volunteers were started on a Mo-controlled diet, had a 4-day pretreatment period, and received TMC once daily for 15 days followed by a 15-day drug withdrawal period (HV-108)
- In the Phase 3 trial (WTX101-**301**), patients with WD were given standard of care (SoC) or TMC for 48 weeks
- Serum uric acid concentrations were evaluated over the study duration and during long-term follow-up
- Serum uric acid concentrations were also collected in the Phase 2 WTX101-**201** trial and included in the analyses (n=235 total)
- For AEs, data from the Phase 2 ALXN1840-WD-204 and ALXN1840-WD-205 trials were additionally included (n=266)

RESULTS

- Following initiation of TMC, daily Mo balance:
  - Increased transiently, then progressively declined (as urinary and fecal Mo elimination increased) **(Figure 1)**
  - Reached neutral quickly (Day 13) even with continued TMC dosing **(Figure 1)**
- Serum uric acid concentrations were not elevated for patients receiving ALXN1840 over 6 years of treatment **(Figure 2)**
- No hyperuricemia or gout-related AEs observed during 6 years of treatment

Figure 1. Mean Daily Net Molybdenum Balance (±95% CI) for Study Days −4 to 30 in Healthy Volunteers on TMC (n=17)

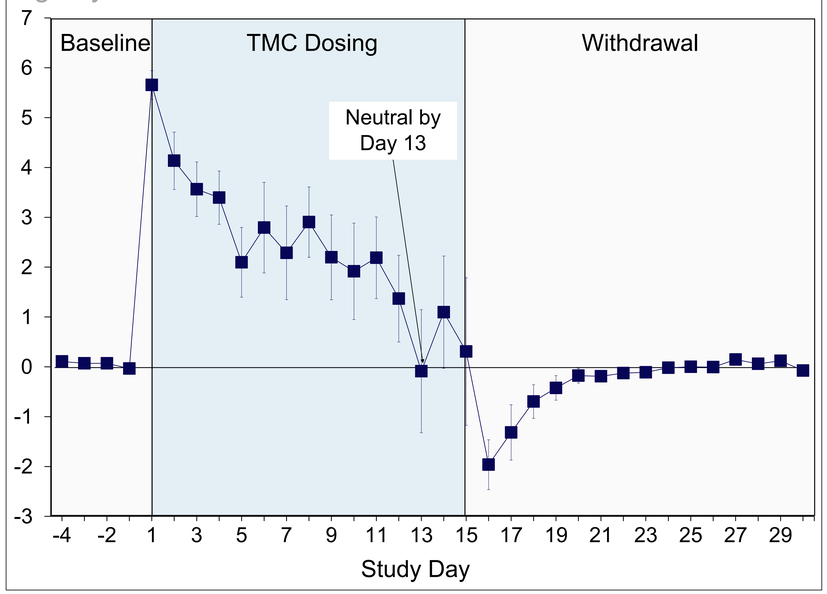
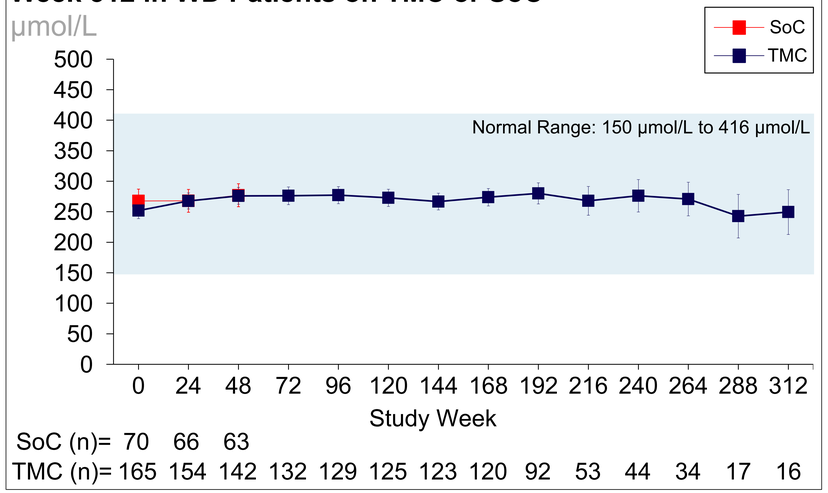


Figure 2. Mean Serum Uric Acid (±95% CI) from Baseline to Week 312 in WD Patients on TMC or SoC



CONCLUSIONS

- In HV-108, the Mo balance returned to neutral despite ongoing TMC treatment (consistent with ATC formation mechanism)
- Mean serum uric acid remained stable and in normal range over 6-year treatment (201 and 301)
- No hyperuricemia or gout-related AEs observed during period
- Together, these findings show no evidence of progressive Mo accumulation and the absence of Mo-related toxicity during chronic TMC treatment

IMPLICATIONS

These findings contribute to the understanding of the safety of the novel mechanism of TMC

References:

1. Borchard S. et al., *Life Sci Alliance*. 2021.
2. Novotny JA., *Molybdenum Nutriture in Humans*. 2011.

Acknowledgments:

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