EASL CONGRESS
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ALXN1840 (tiomolibdate choline) stabilizes liver disease and improves neurological symptoms as well as quality of life in treatment-experienced Wilson disease patients

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Wilson Disease (WD)

- **Wilson disease** is a rare autosomal recessive disorder of impaired copper (Cu) transport
- Cu accumulates in the **liver** and **brain**, causing organ damage
- Inadequately treated or untreated, Cu accumulation leads to **neuropsychiatric manifestations, hepatic failure**, and ultimately **death**
- Standard of care therapies (D-penicillamine, trientine, and zinc) carry safety risks such as paradoxical neurological worsening[1]

~1 in 30,000

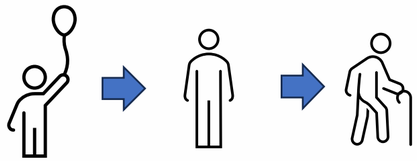
Estimated prevalence worldwide[1]

~25%

Of patients with neurologic WD paradoxically worsen on chelator therapy[2,3]

Lifelong

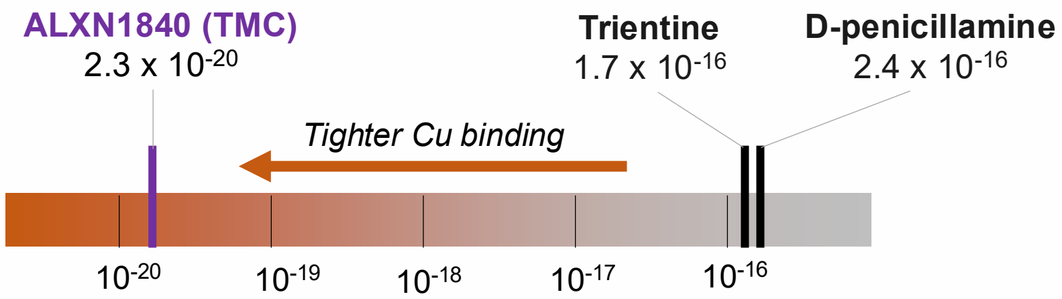
Treatment burden — requires cumbersome multi-dose daily regimen, separated from food



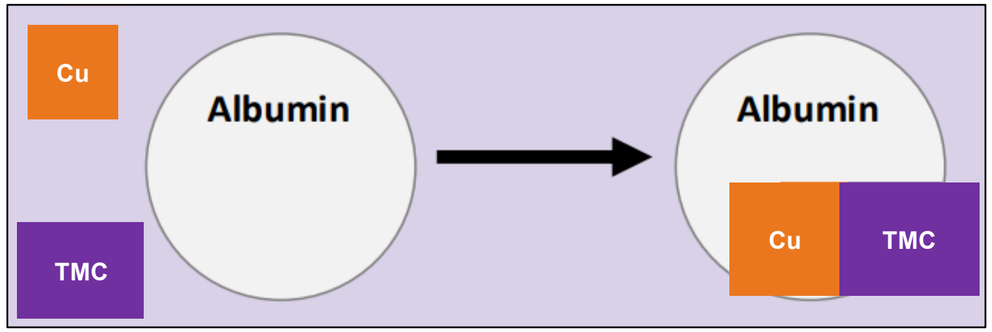
1. European Association for the Study of the Liver. *J Hepatol*. 2025 Feb 22:S0168-8278(24)02706-5. 2. Brewer GJ et al. *Arch Neurol*. 1987 May;44(5):490-3. 3. Antos A et al. Neurol Sci. 2023 Oct;44(10):3443-3455.

Tiomolibdate Choline (TMC; ALXN1840)

CU-BINDING AFFINITY (K_D) OF WD THERAPIES



TMC-CU-ALBUMIN FORMS A TRIPARTITE COMPLEX



Tiomolibdate choline (TMC, ALXN1840) demonstrates **superior Cu binding affinity**[1] and specificity compared to currently approved chelators

Tiomolibdate choline is an albumin tripartite complex (ATC) activator, binding Cu and albumin to form a stable tripartite complex — **mobilizing** and **sequestering** hepatic Cu[2]

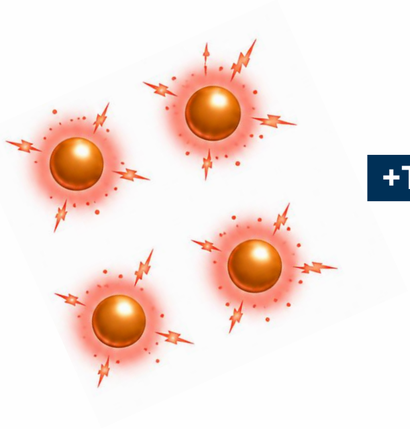
1. Kim P, et al. *Biomedicines*. 2021;9(12):1861. 2. Zhang L, et al. *Biochemistry*. 2009;48(5):891–897.

TMC Protects the Liver by Binding and Neutralizing Hepatic Cu

Differentiated from SoC, TMC's binding affinity is strong enough to **inhibit reactivity of free Cu** and **remove Cu from metallothionein[1]** — directly protecting the liver

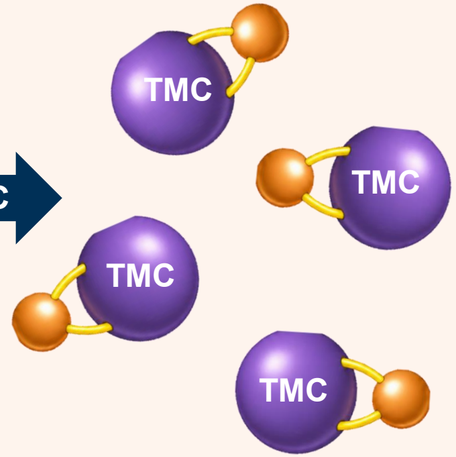
TMC AND REACTIVE FREE CU

Excess **reactive free Cu** causes tissue **toxicity**



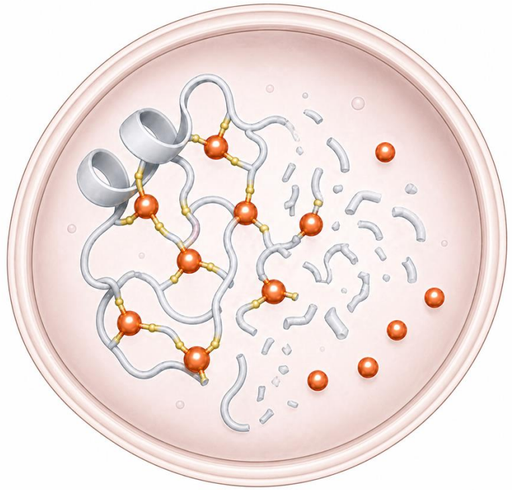
+TMC

TMC directly binds Cu, **preventing redox reactivity[2]**



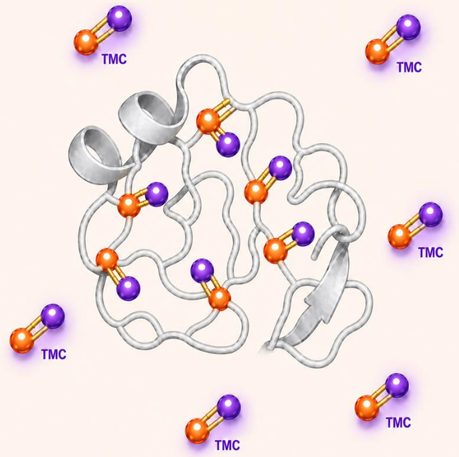
TMC AND METALLOTHIONEIN (MT)

Catabolism of Cu–MT **releases reactive Cu[3]**



+TMC

TMC prevents reactive Cu release by both **binding Cu and removing it from MT[4]**



1. Smirnova J et al. *Sci Rep*. 2018 Jan 23;8(1):1463. 2. Data on file. 3. Klein D et al. *Eur J Clin Invest*. 1998 Apr;28(4):302-10. 4. Czachor JD et al. *J Inorg Biochem*. 2002 Jan 15;88(2):213-22.

48-week Liver Biopsy Study Methods

Open-label, multicenter, pathologist-blinded trial of TMC monotherapy in **treatment-experienced** (≥ 1 year) patients with WD

SCREENING	PRIMARY TREATMENT PERIOD	OPTIONAL EXTENSION PERIOD
< 4 weeks	**48 weeks**	**48 weeks**
Eligibility	TMC 15–30 mg/day	TMC 15–30 mg/day

Baseline liver biopsy:
Week 0
(pre-treatment)

Follow-up liver biopsy:
Week 48
(post-treatment)

LIVER BIOPSY ENDPOINTS

Biopsy endpoints assessed by pathologist **blinded to treatment status**

Hepatic Cu concentration *Primary Endpoint*

Fibrosis *(NASH CRN Fibrosis Stage, NAS total score)*

Steatosis (*NAS steatosis grade, hepatocellular ballooning)*

Inflammation (*lobular inflammation, portal inflammation)*

OTHER ENDPOINTS

Neurologic
(Unified Wilson Disease Rating Scale)

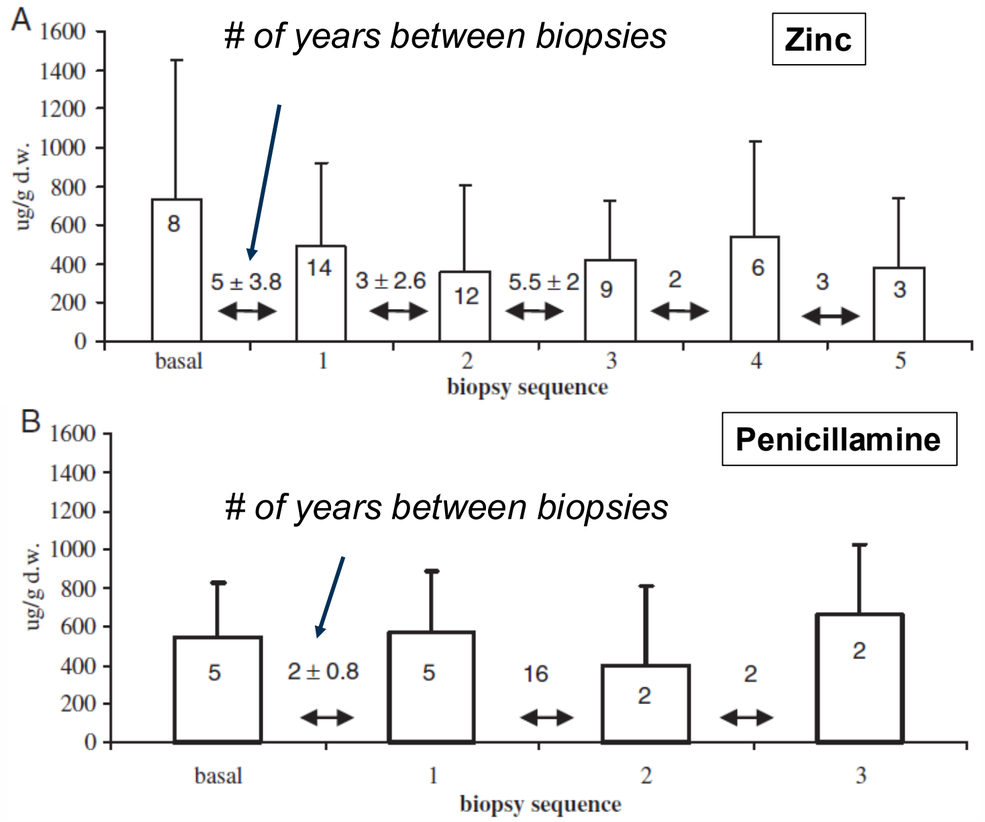
Global
(Clinical Global Impressions scale)

Quality of Life
(EuroQol-5D-5L)

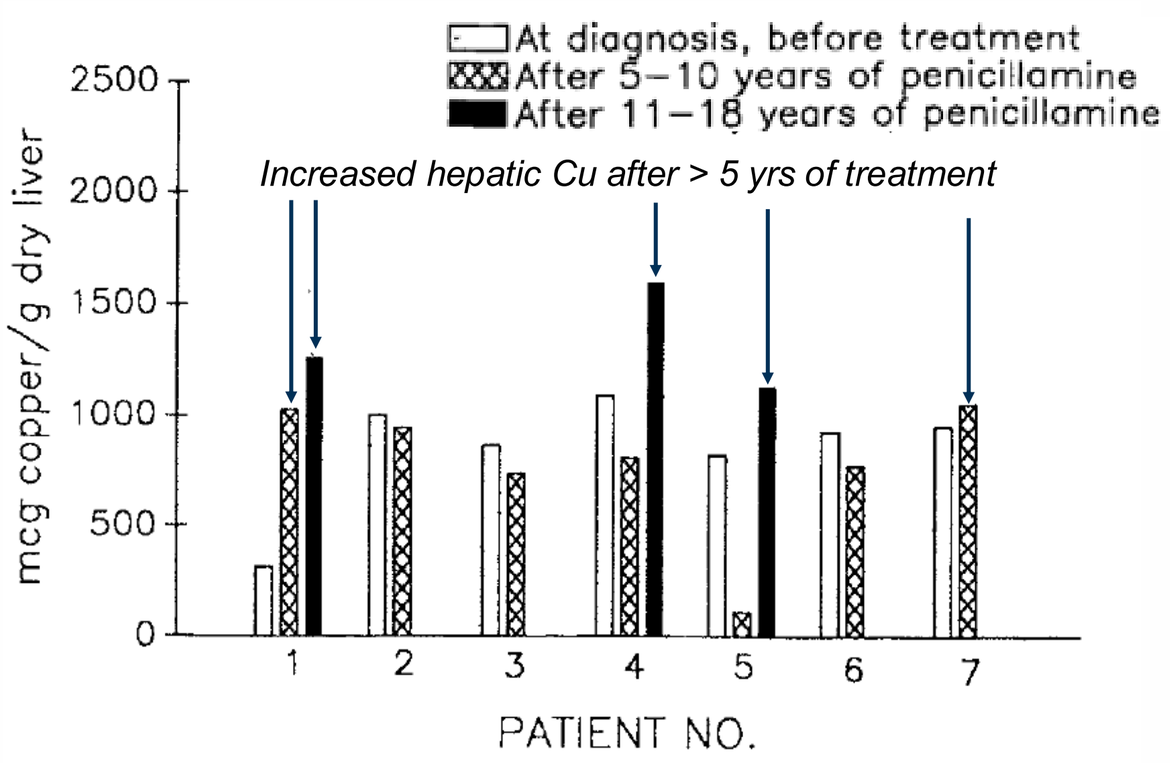
Safety
(adverse events, physical exam)

Literature Shows Stable/Increased SoC Hepatic Cu Change

Serial liver biopsy studies of SoC show **stable/increased hepatic Cu** over years on treatment



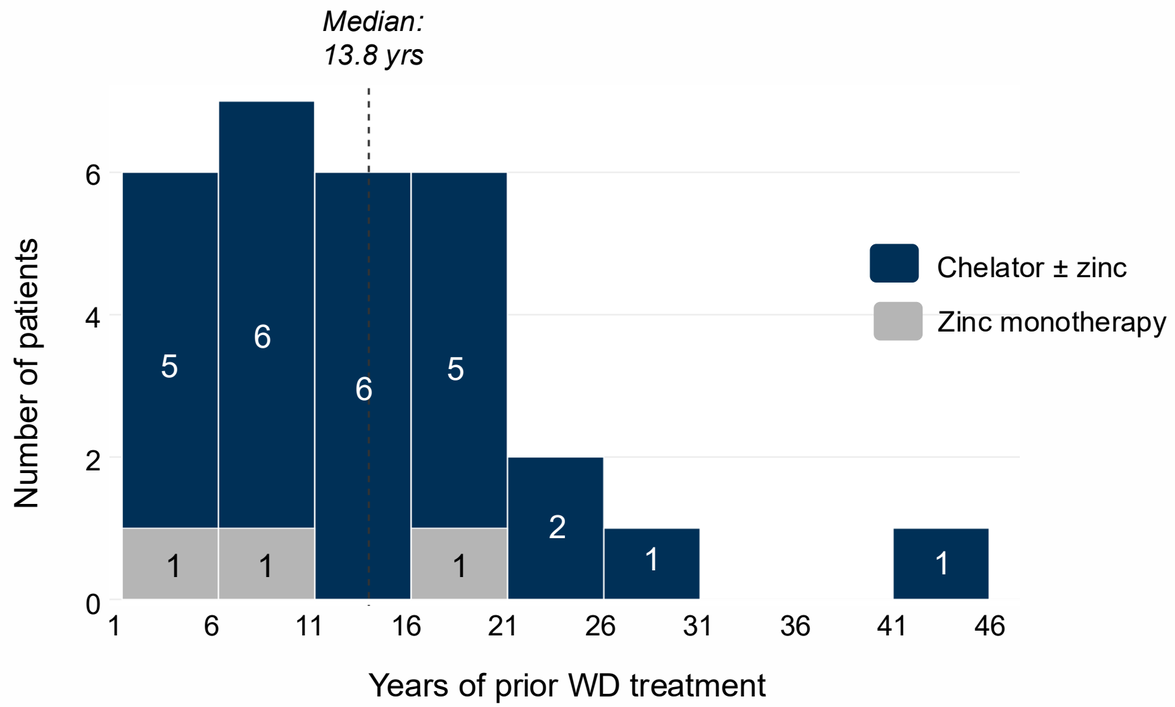
Adapted from Medici V et al. *J Clin Gastroenterol*. 2006 Nov-Dec;40(10):936-41.



Adapted from Scheinberg IH et al. *Lancet*. 1987 Jul 11;2(8550):95.

Study Enrolled a Heavily Pre-treated Population

CUMULATIVE DURATION OF PRIOR WD TREATMENT



Prior WD treatment	n	Median (yrs)	Min (yrs)	Max (yrs)
Chelator ± zinc	26	13.9	1.2	41.9
Zinc monotherapy	3	8.7	3.4	19.8

PATIENT ENROLLMENT

Enrolled w/ Baseline Biopsy

n = 29

Study discontinuations

Adverse event	n = 3
Subject withdrawal	n = 1
Physician withdrawal	n = 1

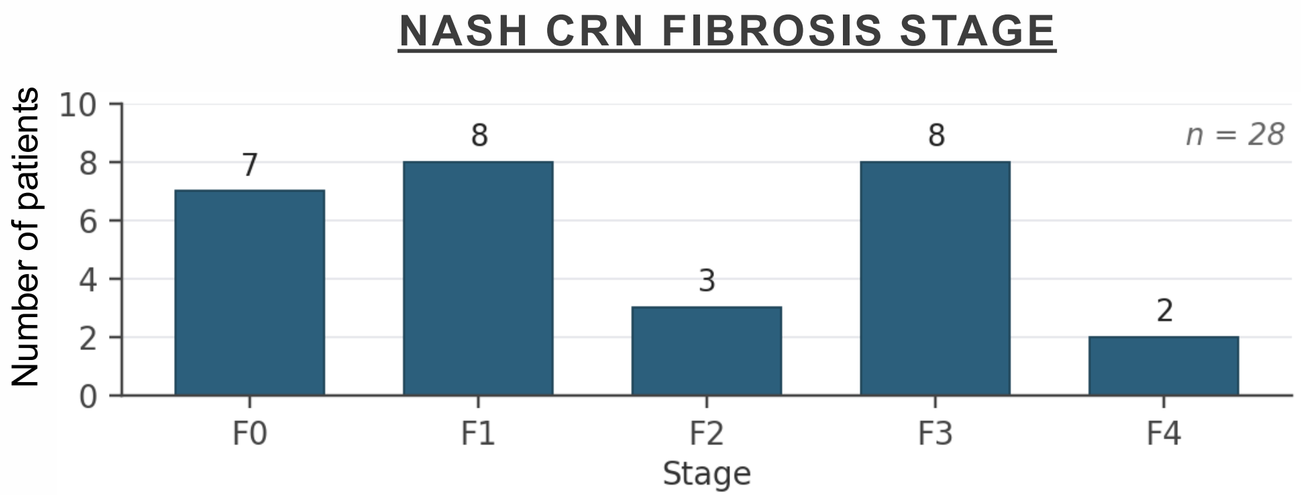
Week 48 Biopsy Obtained

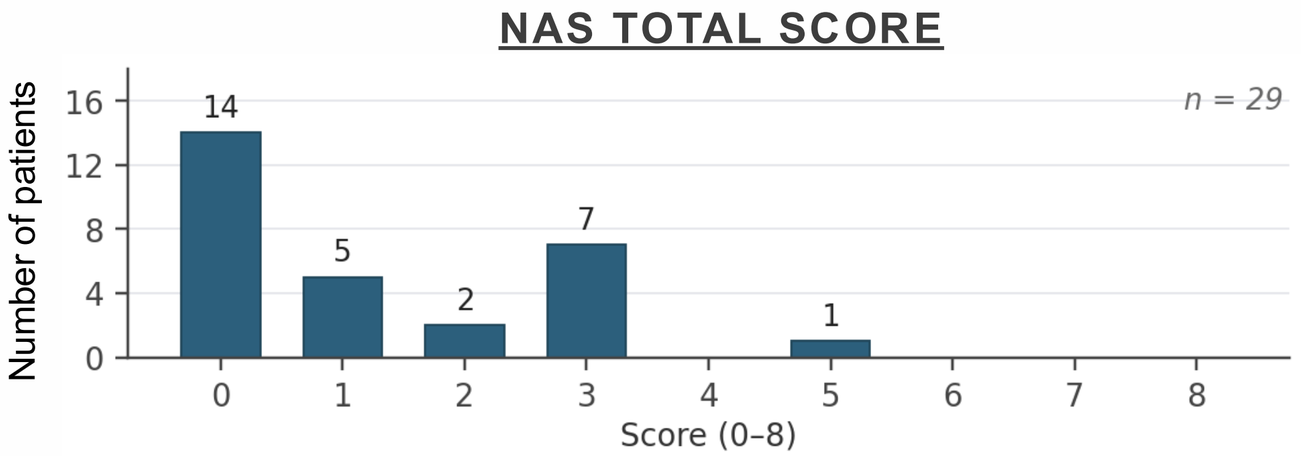
n = 24

Numbers above are for the full analysis set (n=29); 31 enrolled but 2 had no baseline liver biopsy

Baseline Demographics and Characteristics

	Enrolled patients n=29
Demographics	
Male sex, n (%)	19 (65.5%)
Age in years, median (IQR)	35.0 (17.0)
Clinical characteristics	
Years of prior WD treatment, median (IQR)	13.8 (10.9)
Medical history of cirrhosis, n (%)	12 (41.4%)
Abnormal liver ultrasound, n (%)	8 (27.6%)
UWDRS Part III score, median (IQR)	4.0 (9.0)
MELD score, median (IQR)	7.0 (2.0)

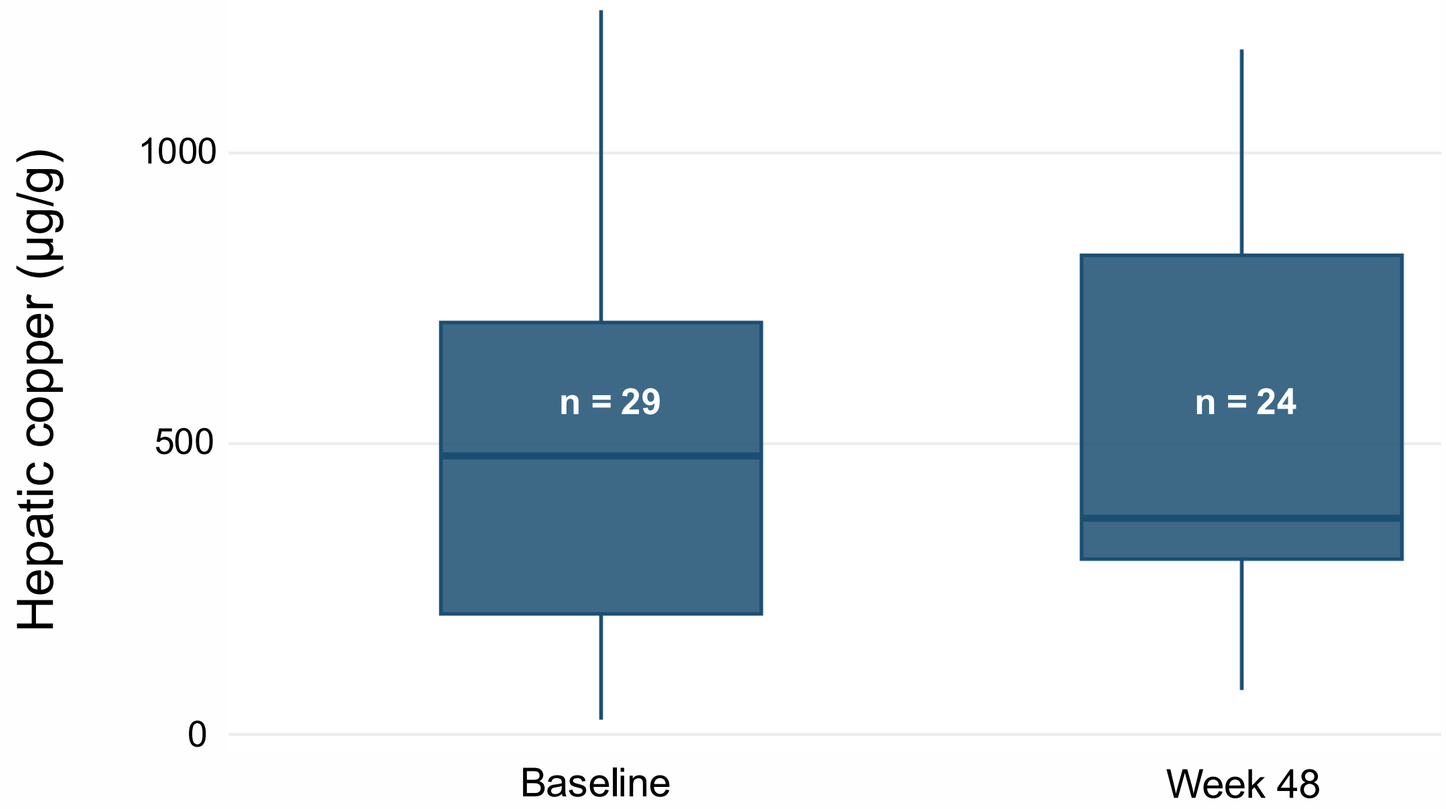




TMC Also Shows No Significant Change in Hepatic Cu

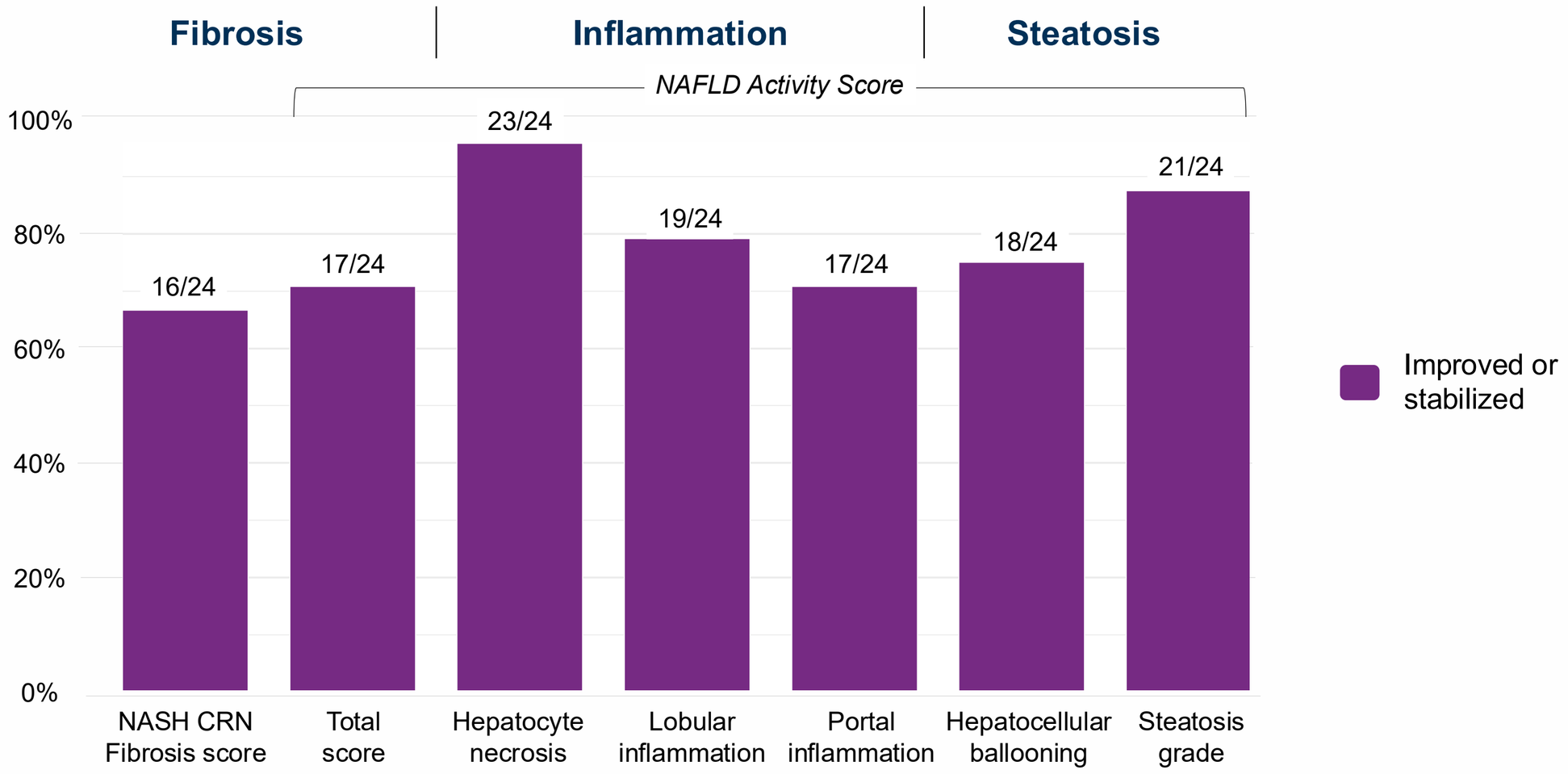
No statistically significant difference in hepatic Cu concentration after 48 weeks of treatment, **consistent with expected results** in heavily pre-treated patients

OBSERVED CHANGE FROM BASELINE IN HEPATIC CU CONCENTRATION (µg/g)



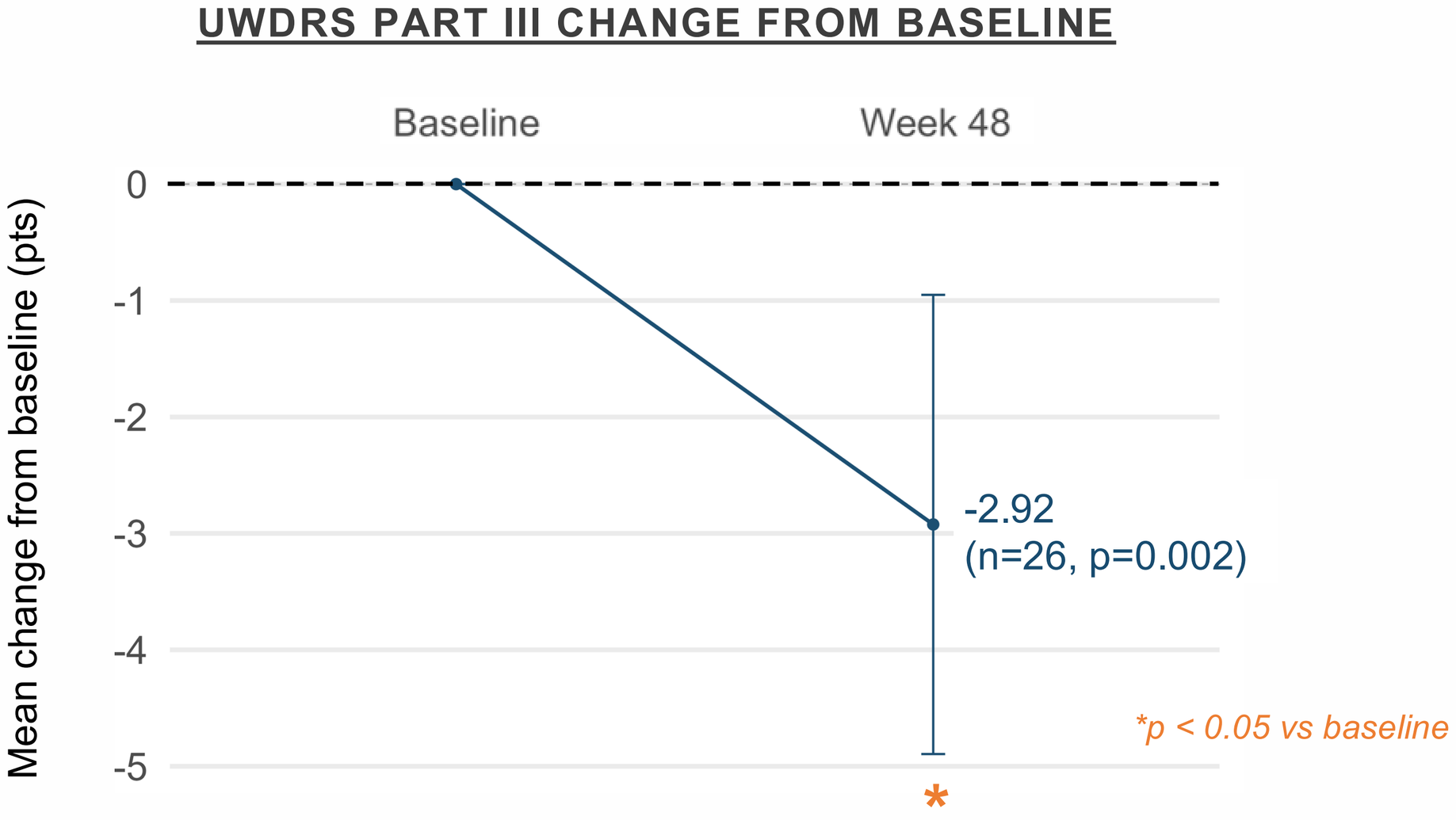
TMC Treatment Leads to Hepatic Stabilization and Improvement

By Week 48, most patients demonstrated **stabilization or improvement** in:

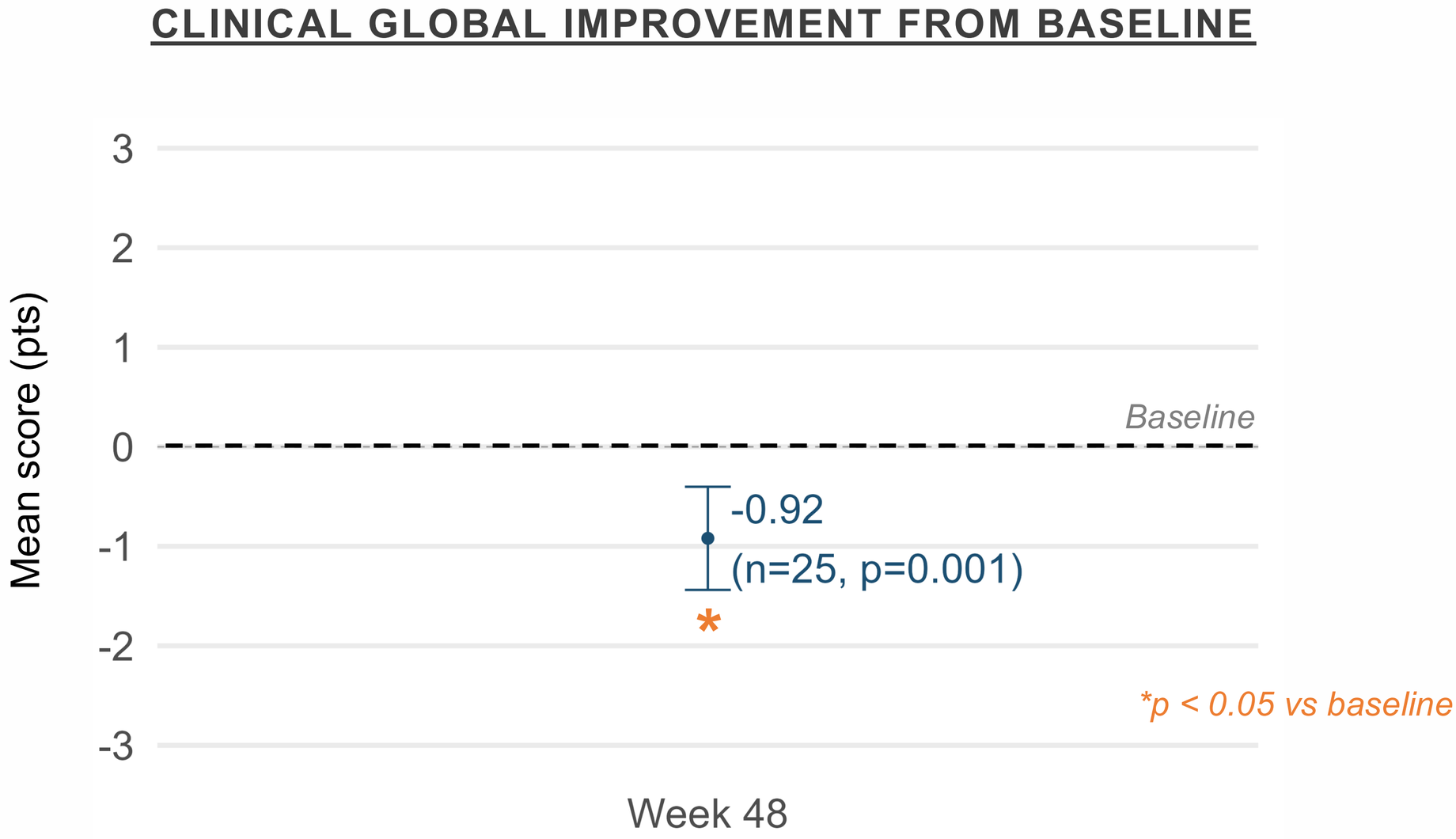


Improved/stabilized from baseline to Week 48:	NASH CRN Fibrosis score	Total score	Hepatocyte necrosis	Lobular inflammation	Portal inflammation	Hepatocellular ballooning	Steatosis grade
	67%	71%	96%	79%	71%	75%	88%

Neurological WD Symptoms Significantly Improved at Week 48

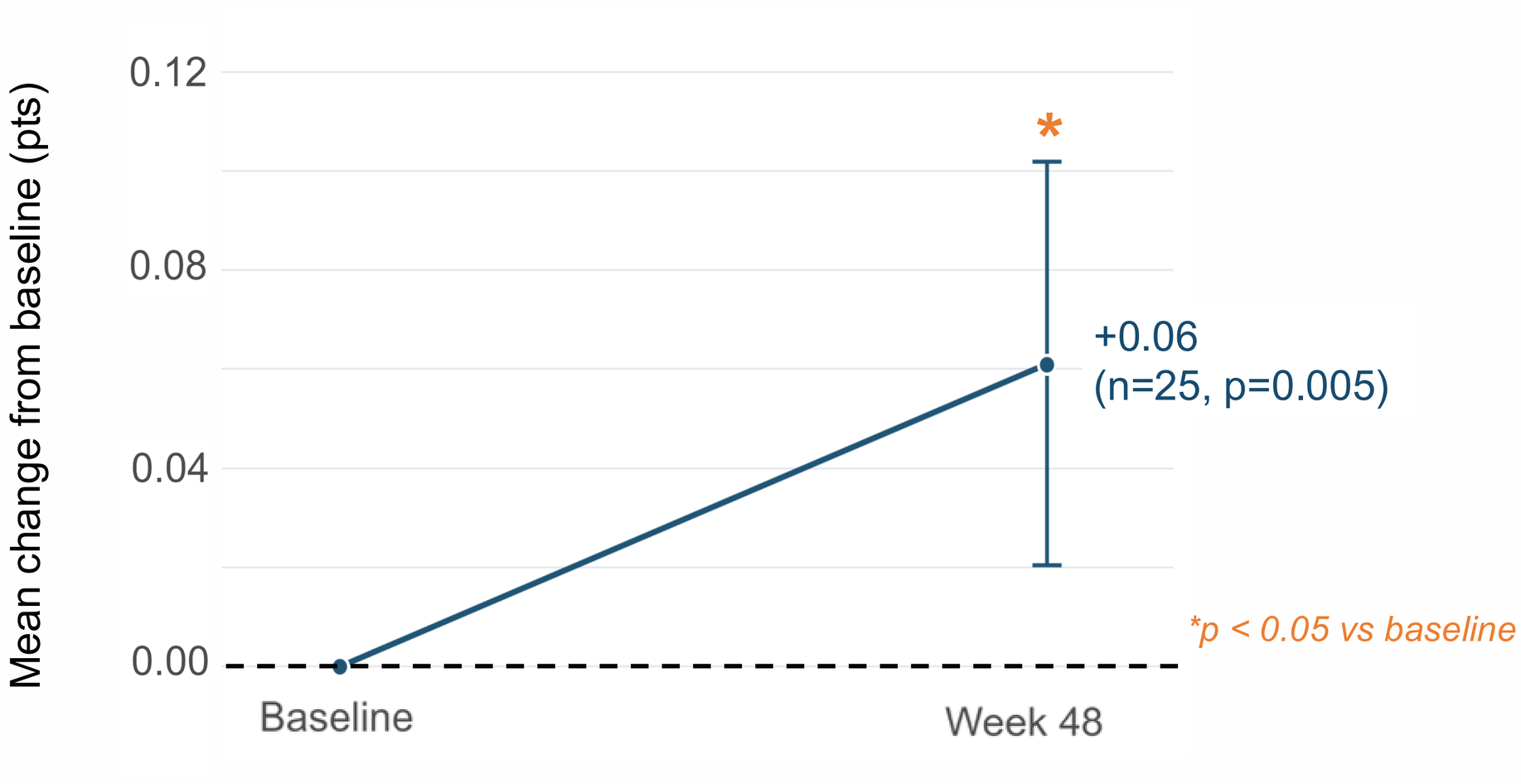


Global Clinical Disease Burden Significantly Improved at Week 48



Patient-reported Quality of Life Significantly Improved at Week 48

EUROQOL-5D UK HEALTH INDEX CHANGE FROM BASELINE



TMC is Well Tolerated, with Few Severe Adverse Events

- TMC was generally well tolerated; most treatment-emergent adverse events (TEAEs) were **nonserious** and **Grade 1 or 2** in severity
- No deaths were reported
- One event of DILI was reported
  - Patient was stable on TMC until Week 47; developed UTI and initiated on ciprofloxacin with DILI onset very shortly after
  - Adjudicated by independent panel as unlikely relationship to TMC

TEAEs IN SAFETY POPULATION (N=31)

	Primary period n=31	Extension period n=25
TEAEs	30 (96.8%)	19 (76.0%)
Related	24 (77.4%)	3 (12.0%)
Grade 1	17 (54.8%)	3 (12.0%)
Grade 2	16 (51.6%)	0
Grade 3	5 (16.1%)	0
Grade 4	0	0
Grade 5	0	0

Safety population (n=31) includes all patients who received ≥ 1 dose of TMC, including 2 patients enrolled without an evaluable baseline liver biopsy (full analysis set, n=29). Severity grade counts are subject-level and not mutually exclusive.

Conclusions

- Hepatic Cu concentration was **stable** after 48 weeks of TMC, consistent with published serial liver biopsy studies of WD patients treated with standard-of-care
- Treatment with TMC in heavily pre-treated patients resulted in **hepatic stabilization/improvement**
- TMC treatment **significantly improved neurological symptoms, global clinical status,** and **patient-reported quality of life**
- With the unique ability to **bind Cu with high affinity**, **remove excess Cu** from metallothionein, and **activate albumin-tripartite-complex (ATC) formation,** TMC has the potential to provide a therapeutic advantage over standard-of-care for the long-term treatment of WD

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Questions?