Rapidly Improved Copper Balance in Wilson Disease Patients on Tiomolybdate Choline

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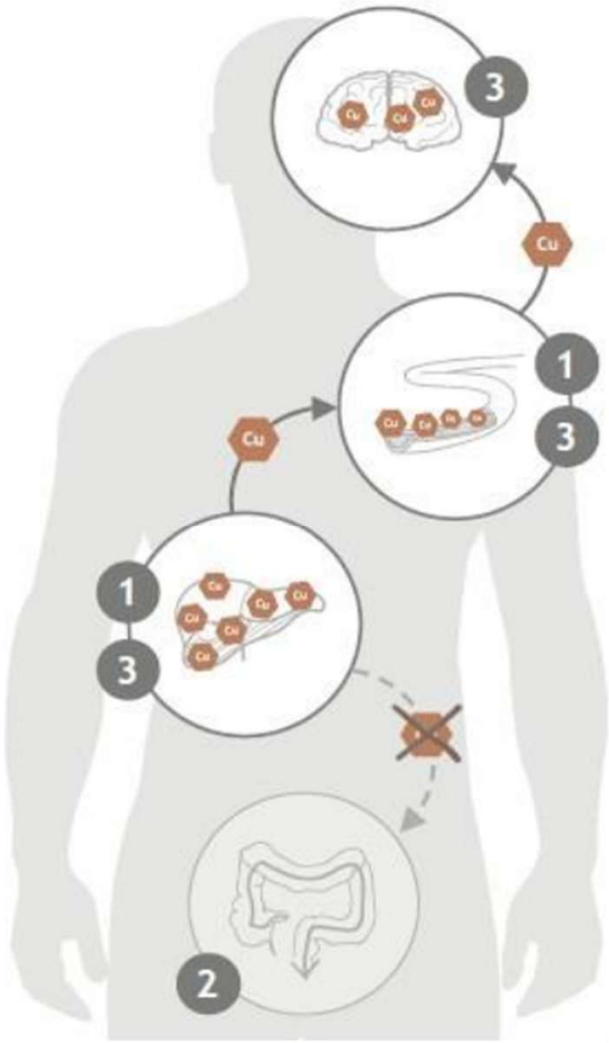
Wilson Disease (WD)

Wilson disease is a rare genetic disorder of impaired copper (Cu) transport

Cu accumulates in the **liver** and **brain**, causing organ damage

Standard-of-care (SoC) therapies have **numerous limitations**:

- paradoxical neurological worsening
- complex, multi-per-day dosing
- slow onset of action



1. Diminished loading of Cu onto the ceruloplasmin (Cp) protein in liver leads to suboptimal transport of Cp- bound Cu into blood
2. Diminished excretion of excess Cu through the bile into feces
3. **Increased levels of free Cu (toxic) in blood, liver, brain and other organs**

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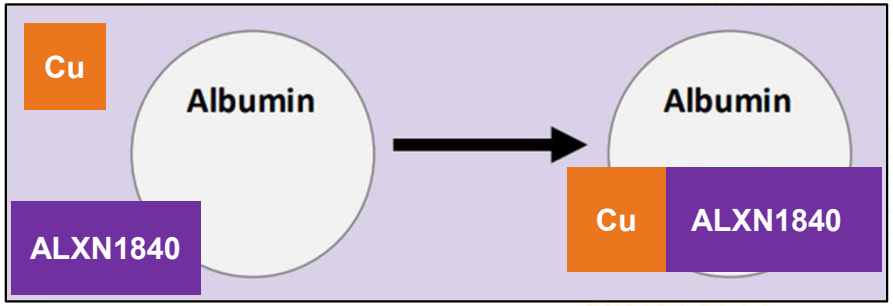
ALXN1840 is a Once Daily Oral Small Molecule Therapy for WD

ALXN1840 Tightly Binds Cu

Cu binding affinity (K_d)	
D-penicillamine	2.4×10^{-16}
Trientine	1.7×10^{-17}
ALXN1840	**2.3×10^{-20}**

ALXN1840 (MoS_4^{2-}, tiomolybdate choline) demonstrates superior Cu specificity and binding affinity compared to currently approved chelators

ALXN1840-Cu-albumin Forms a Tripartite Complex



Cu-ALXN1840 forms a strong tripartite complex with albumin, **mobilizing and sequestering** toxic Cu, reducing uptake in the liver and brain[1-3]

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1. Zhang L *et al. Biochemistry*. 2009;48(5):891-897; 2. Kim P *et al. Biomedicines*. 2021;9(12):1861. 3. Kirk *et al. J Hepatol*. 2024 Apr;80(4):586-595

Recap of Recently Presented ALXN1840 Clinical Data

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Sustained Long-term Clinical Improvement Over 6 Years

Efficacy

Unified Wilson Disease Rating Scale Results Show Long-term Benefit

Fig 1: UWDRS Part II (Patient-reported)

Least squares mean and standard error – Ph2 & Ph3

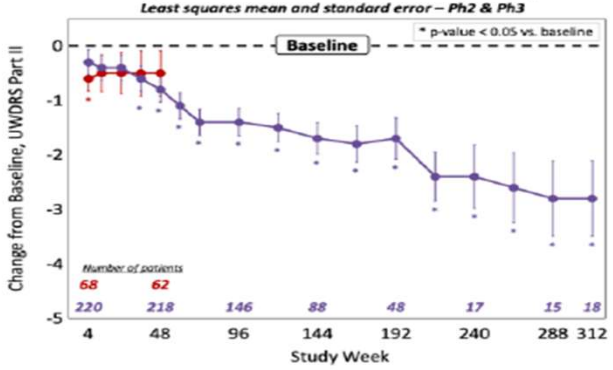
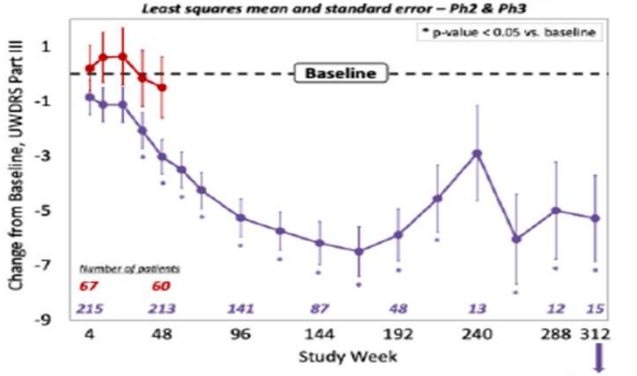


Fig 2: UWDRS Part III (Physician-assessed)

Least squares mean and standard error – Ph2 & Ph3



ALXN1840 — Standard of Care

CGI-I & TSQM-9 Show Disease Improvement, Patient-Reported Benefit

Fig 3: Transformed CGI-I By Visit

Least squares mean and standard error – Ph2 & Ph3

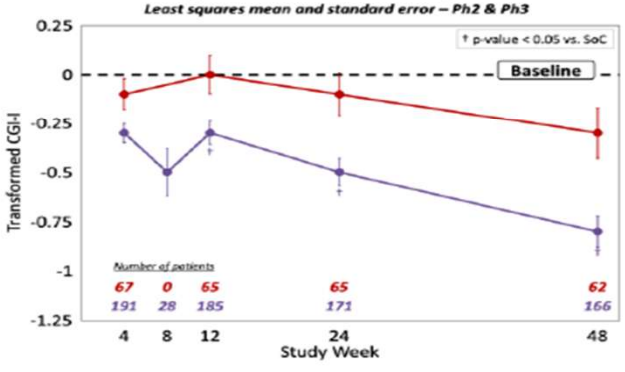
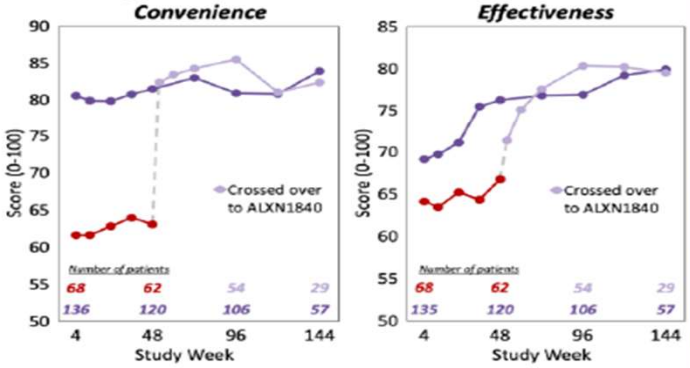


Fig 4: TSQM-9 Treatment Satisfaction Scores – Ph3



Treatment Satisfaction Questionnaire for Medication-9

Safety

ALXN1840 has a Favorable Safety Profile

Table 2: Serious Adverse Events (SAEs) on ALXN1840

data thru 01-Sep-2022

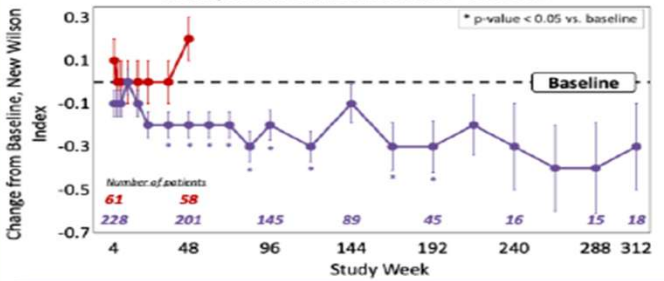
N	266
Patient-years (PYs)	645.6
Patients with any ALXN1840-related SAEs	13 (4.9%)
Renal/Urinary System-related SAEs	0 (0%)
Liver-related SAEs	8 (3.0%)

- Only 2 patients (0.8%) had ALXN1840-related renal/urinary AE
- No deaths occurred due to ALXN1840

61 Ph3 cross-over patients from SoC to ALXN1840 had no change in psychiatric AE rate: 4.3% (3/70, 62.4 PYs) vs. 4.9% (3/61, 55.4 PYs)

Fig 5: New Wilson Index

Least squares mean and standard error – Ph2 & Ph3



New Wilson Index (based on bilirubin, AST, INR, leukocytes, albumin) improved for patients on ALXN1840 treatment over 6 years

Conclusions

Clinical data from 255 WD patients on ALXN1840 treatment show sustained clinical improvement over 6 years of treatment. Combined with long-term safety, this analysis supports the potential use of ALXN1840 as a treatment for Wilson disease.

References & Acknowledgements

The authors would like to thank the patients and their families for their participation in the studies, as well as all participating sites

Source: Weiss KH *et al.* Poster presented at: EASL 2025; May, 2025; Amsterdam, NL.

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Sustained Long-term Neurologic and Psychiatric Benefit

Neurologic benefit reproduced across independent trials

UWDRS Minimum Clinically Important Difference **(MCID)**

- Previous studies have reported a Part III MCID of **4 – 6.9 pts**[2-4]
- Calculated UWDRS Part III MCID from Ph2 & Ph3 (n=255): **4.69 pts**

UWDRS Part III (Physician-assessed)

MCID responder rate (change from baseline to Week 48) – Ph2 & Ph3

	ALXN1840				SoC
Study ID *(n enrolled)*	201 (n=29)	205 (n=31)	301** (n=137)	ISE (n=255)	301** (n=70)
Improved* (%)	94	57	45	50	32
Worsened (%)	5	4	8	7	13

**Calculated from patients eligible to improve (baseline score ≥ MCID)*

*** Physician rater-blinded*

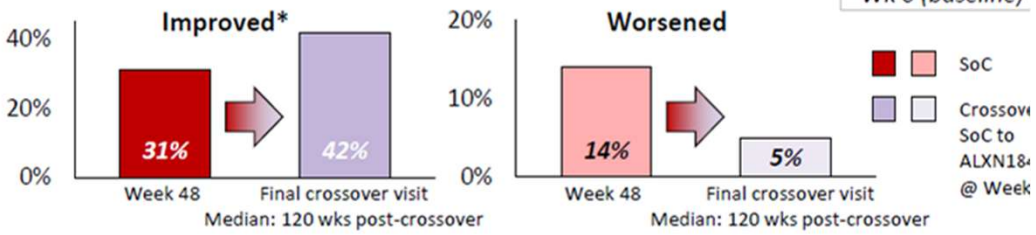
Patients who switch from SoC to ALXN1840 further improve

UWDRS Part III (Physician-assessed)

MCID responder rate – Ph3

SoC-Crossover Patients (n=56)

All changes vs. Wk 0 (baseline)



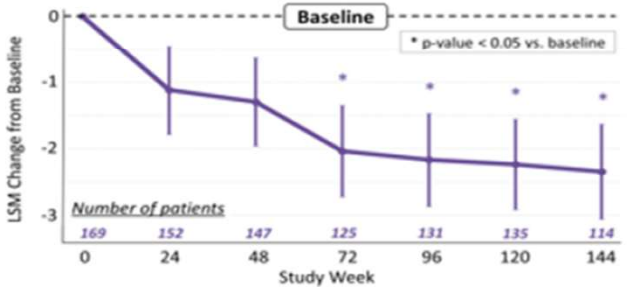
Mean △ from Wk 0*: *-1.9 pts* → *-4.8 pts*

**Calculated from patients eligible to improve (baseline score ≥ MCID)*

Sustained psychiatric benefit

Brief Psychiatric Rating Scale
(Clinician-assessed)

Least squares mean (LSM) ± standard error – Ph3



Favorable safety profile

Adverse Events

Data through 01-Sep-2022 Ph2 & Ph3

Drug-related Serious Adverse Events (SAEs)	
Number of patients	266
Total **patient-years (PYs)**	645.6
Patients with **any drug-related SAEs**	13 (4.9%)
Patients with **drug-related neurological SAEs**	2 (0.8%)
Patients with **drug-related psychiatric SAEs**	1 (0.4%)

M. Lorincz[1], A. Poujois[2], C. Robinson[3], D. Tuffy[3], A. Kelly[3], T. Litwin[4], A. Członkowska[4]

[1]University of Michigan Health System, Ann Arbor, United States; [2]Department of Neurology, Rothschild Foundation Hospital, Paris, France; [3]Monopar Therapeutics, Wilmette, United States; [4]2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland.

Source: Lorincz M *et al.* Poster presented at: ANA 2025; September, 2025; Baltimore, MD.

Copper Balance in Patients with Wison Disease

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Efficacy End Point: *Mean Daily Cu balance*

= ***Cu intake*** *(food and drink)* **– *Cu output*** *(feces + urine)*

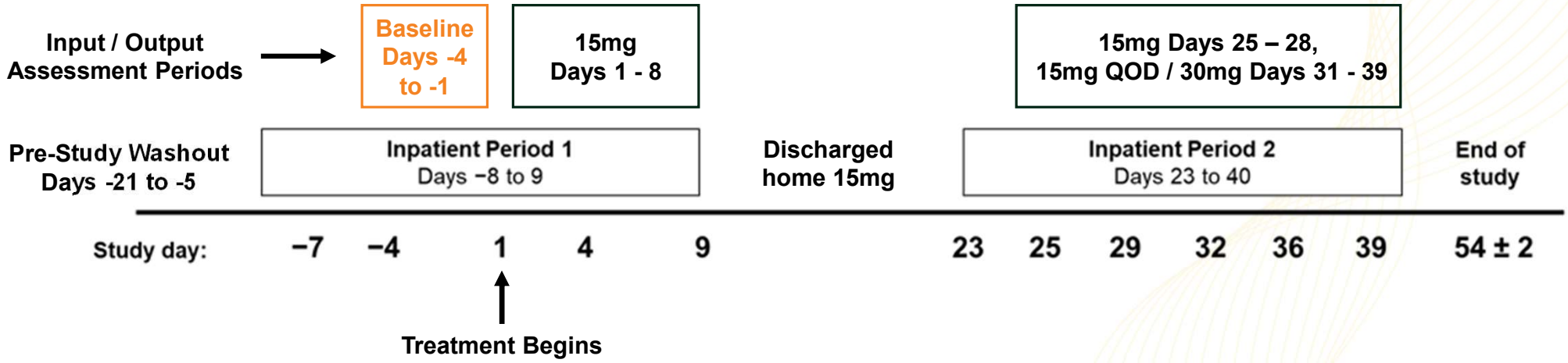
Copper Balance Study Baseline Demographics and Characteristics

Enrolled Wilson Disease Subjects (n=9)†	
Demographics	
Clinical site location	
United Kingdom (Richmond Pharmacology Ltd)	6 (66.7%)
New Zealand (University of Auckland)	3 (33.3%)
Male sex	7 (77.8%)
Race	
White	8 (88.9%)
Asian	1 (11.1%)
Age, mean (SD)	34.1 (12.0) years
Baseline characteristics	
Time since WD diagnosis, mean (SD)	15.1 (16.2) years
Prior WD therapy	
Penicillamine (± zinc)	5 (55.6%)
Trientine (± zinc)	1 (11.1%)
Penicillamine + trientine (± zinc)	1 (11.1%)
Zinc monotherapy	1 (11.1%)
None	1 (11.1%)
Cirrhosis at baseline	
Absent	5 (55.6%)
Present	3 (33.3%)
Unknown	1 (11.1%)

†One subject was withdrawn on Study Day 3 due to failure to discontinue standard-of-care therapy.

Source: ALXN1840-WD-204 – Copper balance clinical trial

Cu Balance Study Design (ALXN1840-WD-204) IN WILSON DISEASE PATIENTS



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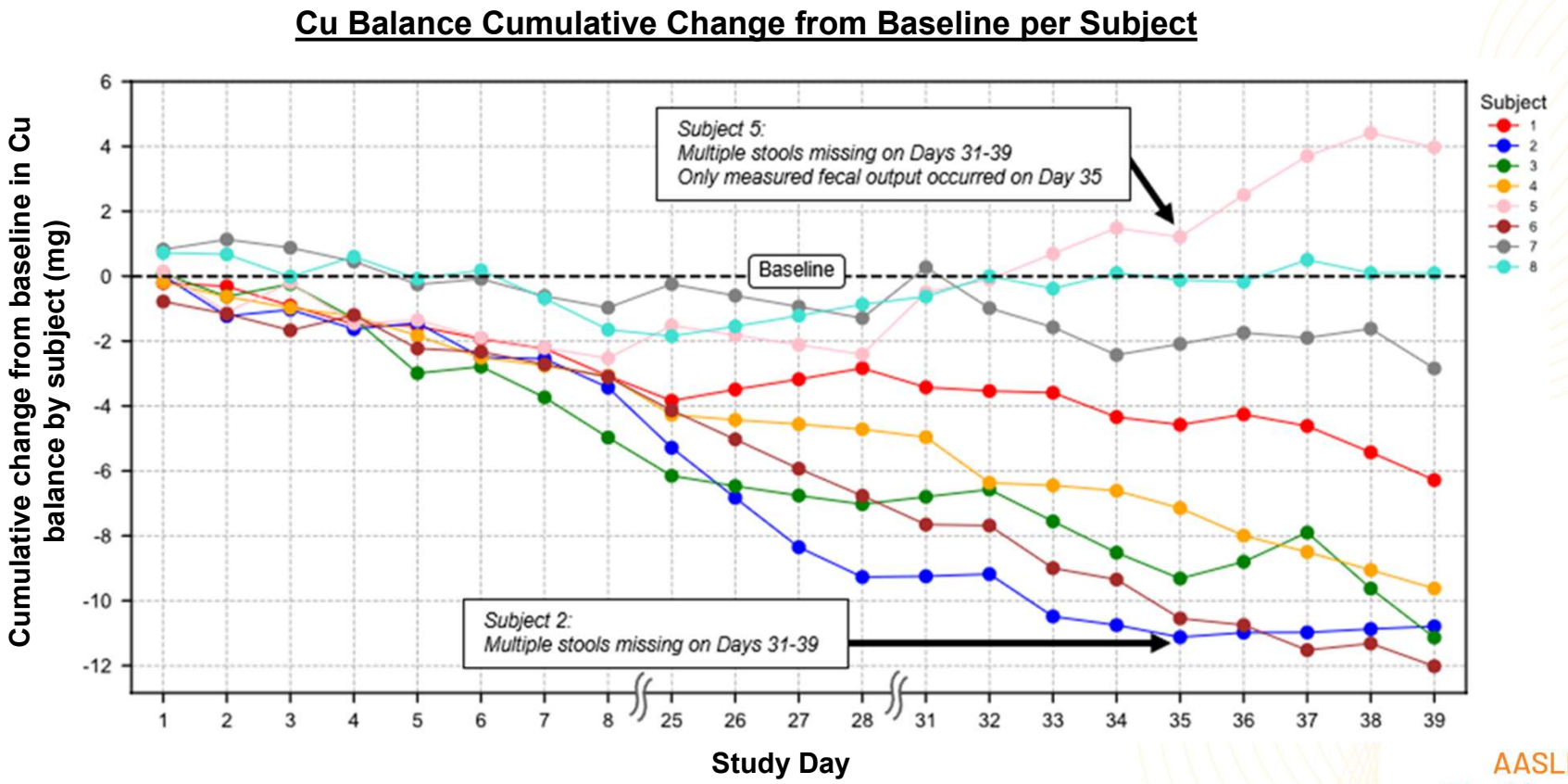
Source: ALXN1840-WD-204 – Copper balance clinical trial

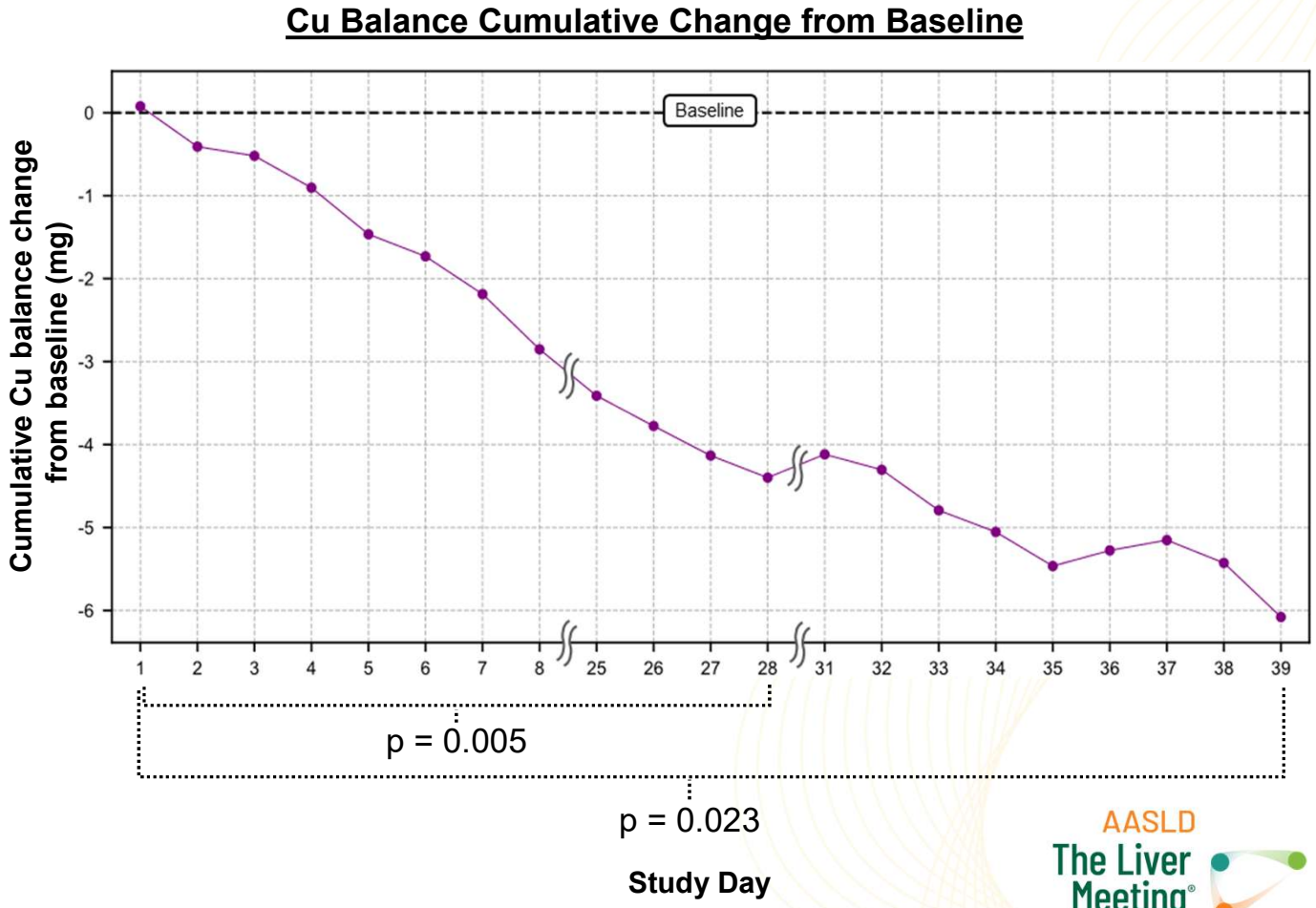
Encouraging Patient-Level Improvement in Copper Balance



Source: Ala A *et al. J Hepatol.* 2025;S0168-8278(25)02483-3.

Rapid Significant, Sustained Improvement in Copper Balance on ALXN1840

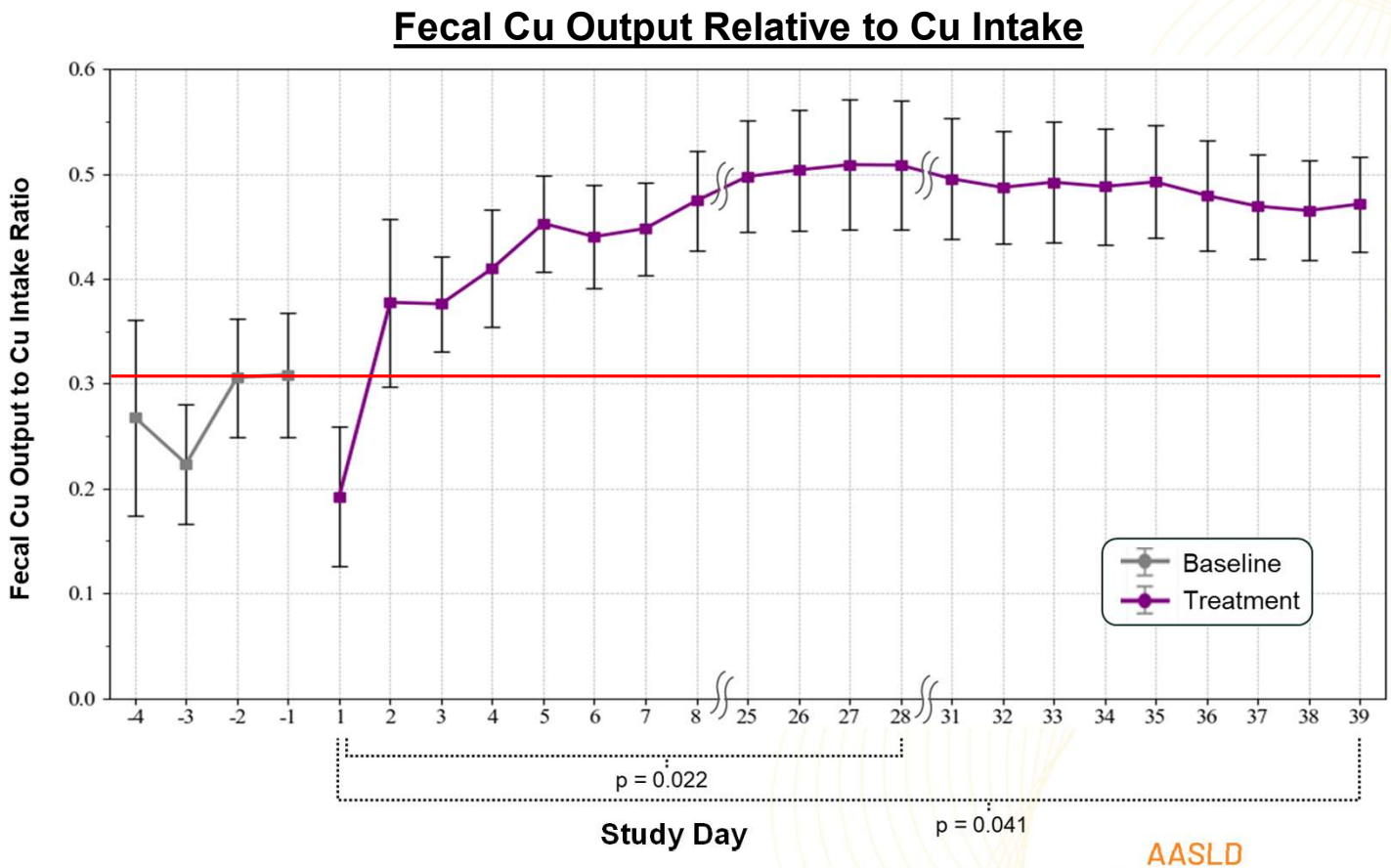
Increased fecal Cu excretion results in **statistically significantly improved Cu balance** on ALXN1840



Source: Ala A *et al. J Hepatol.* 2025;S0168-8278(25)02483-3.

ALXN1840 Statistically Significantly Increases Human Fecal Copper Excretion

ALXN1840 treatment **significantly increased fecal Cu excretion** by ~50% vs. pre-treatment baseline *(red line)*



Data presented as a rolling average and error bars represent standard error about the mean

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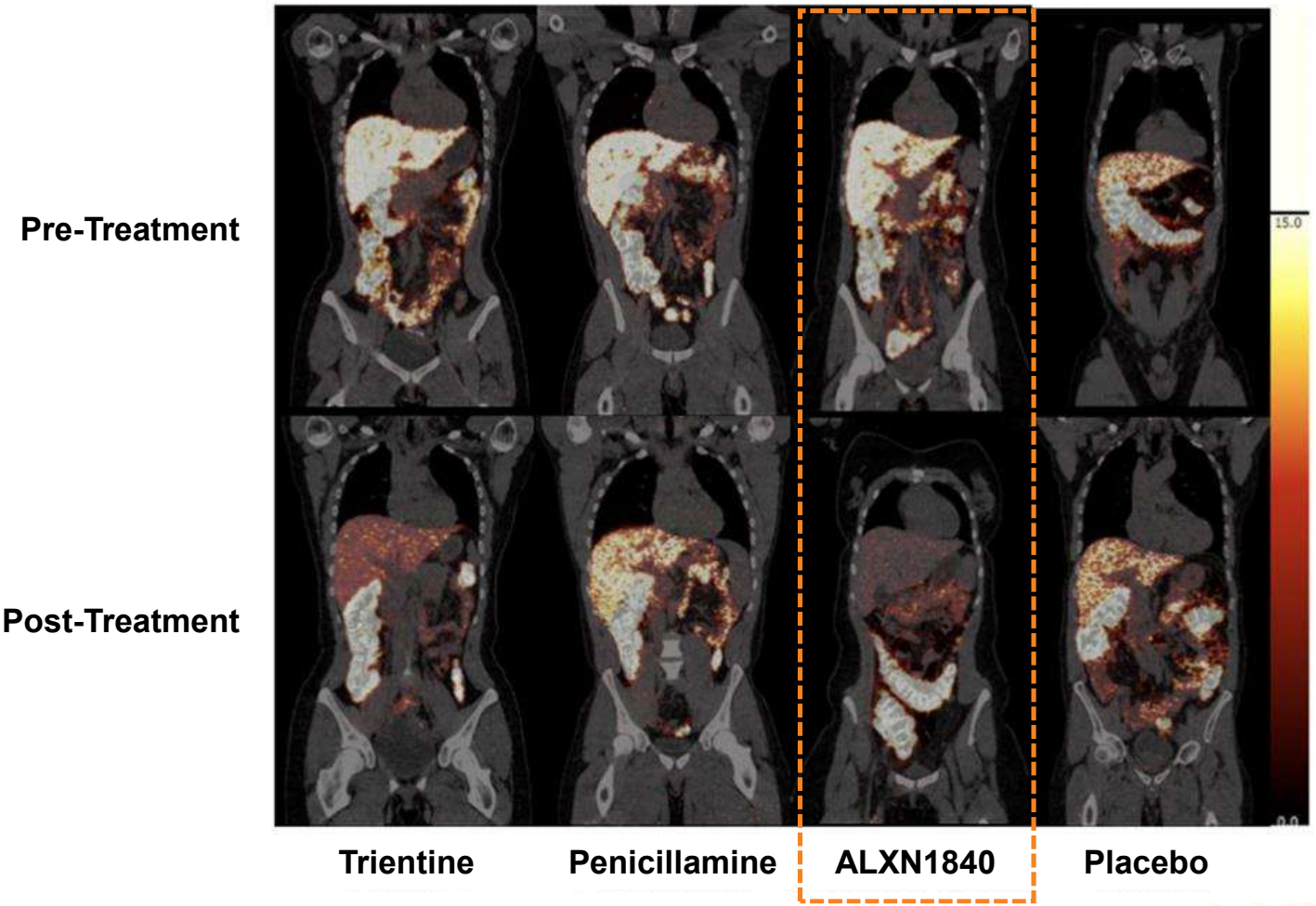
Source: ALXN1840-WD-204 – Copper balance clinical trial

ALXN1840 Strongly Blocks Dietary Copper Uptake in Humans

15 hours post oral ^{64}Cu ingestion

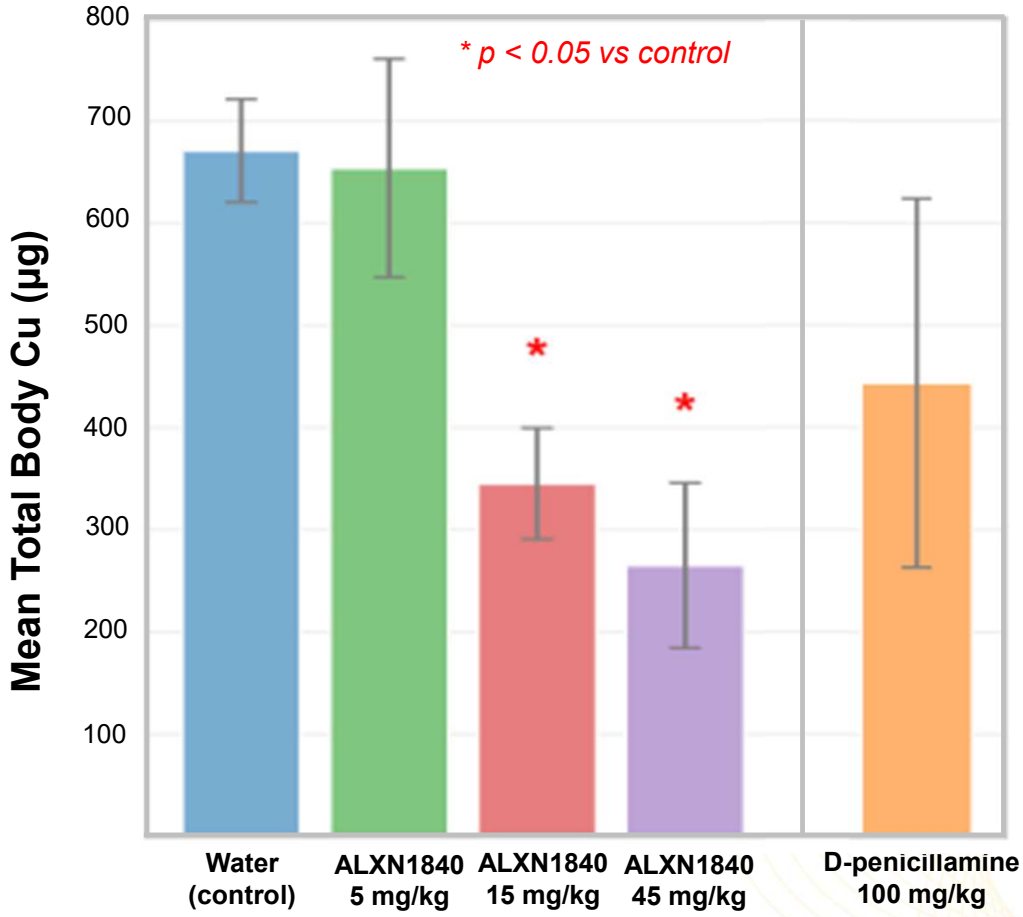


Source: Kirk *et al*. *J Hepatol*. 2024;80(4):586-595; Sandahl 2022 Aarhus University Hospital

Marked Decrease in *Total Body Copper* in WD Mice on ALXN1840 at 8 weeks

Total body Cu is **significantly lower** after 8 weeks in WD mice treated with ALXN1840

(n = 5 mice per group)



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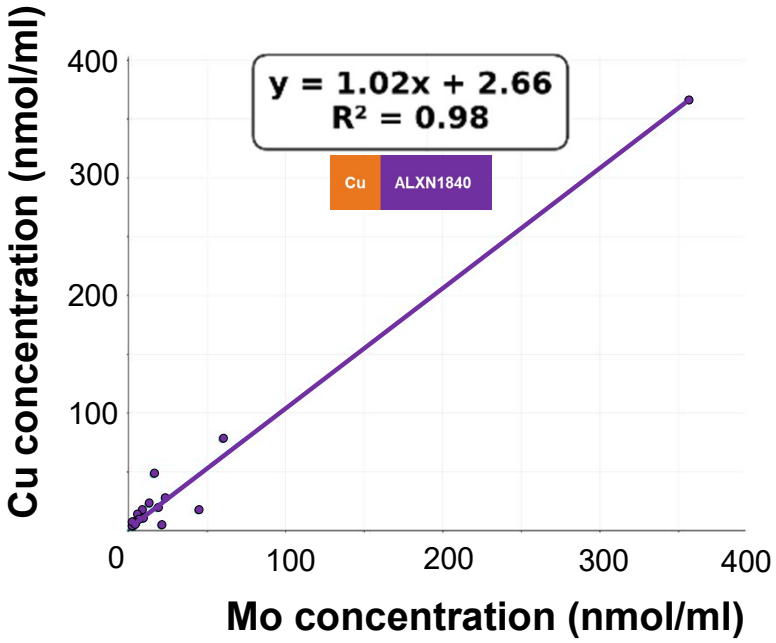
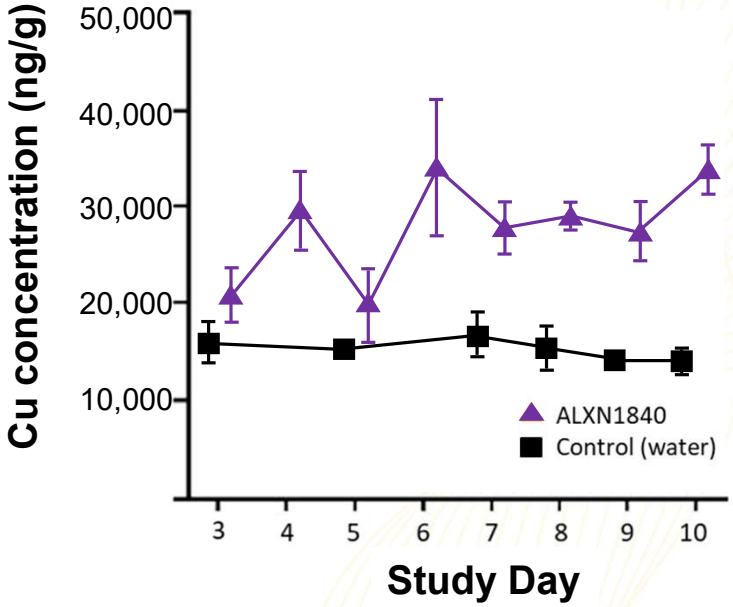
Source: RTR-0051 Additional Analysis – Alexion Pharmaceuticals Preclinical Study in WD Mice (Toxic Milk Mouse model)

MoA: Oral ALXN1840 Induces 1:1 *Biliary Excretion* with Cu in WD Rats

Cu and Mo (nmol/ml) Correlation in Bile[1]



Fecal Cu (ng/g)[1]



Once bound, Cu-ALXN1840 is **excreted intact in bile at a 1:1 molar ratio** ($p < 0.001$) in WD rats, *consistent with literature.*[2]

Fecal Cu excretion was significantly increased with ALXN1840 vs. control

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1. Source: RTR-0052 Additional Analyses – Alexion Pharmaceuticals Preclinical Study in Long Evans Cinnamon (LEC) Rat model
2. Komatsu *et al*. *Chem Biol Interact*. 2000 Feb;124(3):217-231

Supportive New ALXN1840 Data

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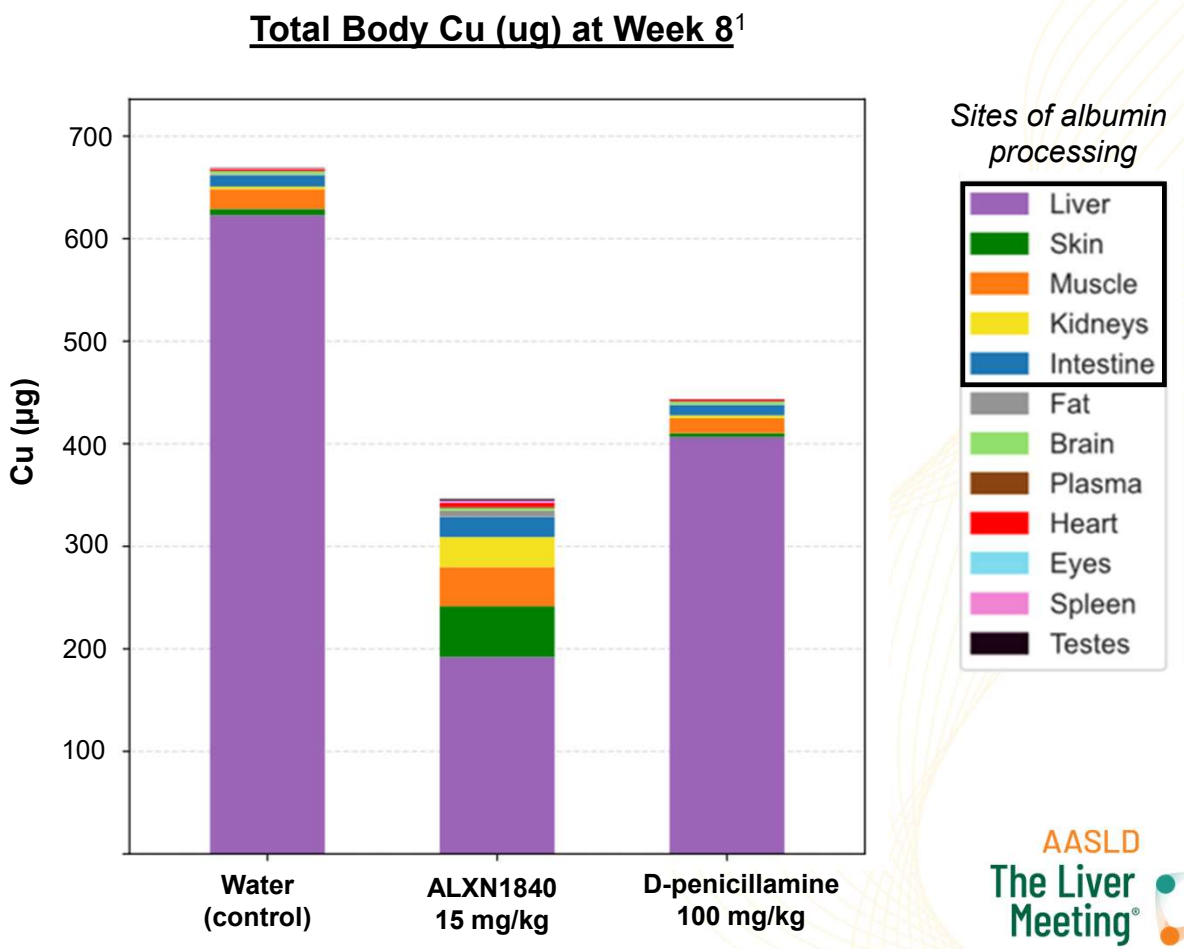
Cu Transits Through Sites of Albumin Processing – Does Not Accumulate

Cu **transits with albumin** (as ALXN1840-Cu-albumin complex) **through sites of albumin processing** before excretion in WD mice



Albumin processing includes catabolism, FcRn recycling, degradation, and renal reabsorption[2-4]

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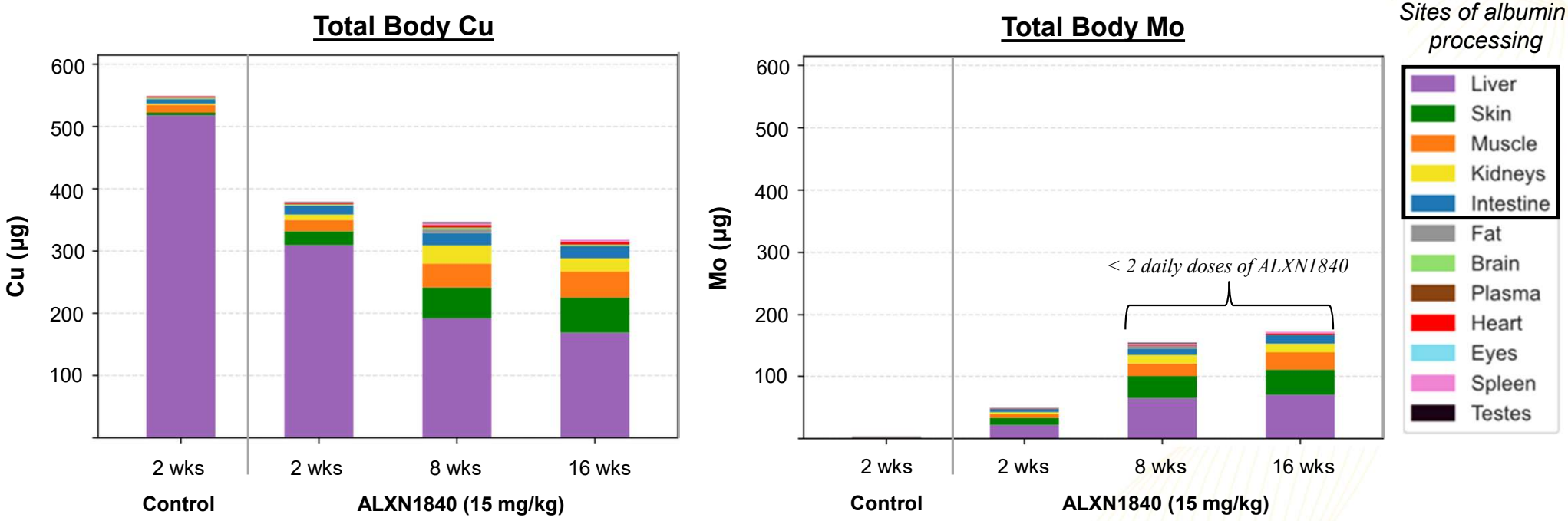
1. Source: RTR-0051 Additional Analysis – Alexion Pharmaceuticals Preclinical Study in WD Mice (Toxic Milk Mouse model);
2. Levitt G *et al. Int J Gen Med*. 2016;9:229-55; 3. Baynes JW *et al. Arch Biochem Biophys.* 1981;206(2):372-9; 4. Yedgar S *et al. Am J Physiol.* 1983;244(1):E101-7.

Mo Transits Thru Sites of Albumin Processing – Does Not Accumulate

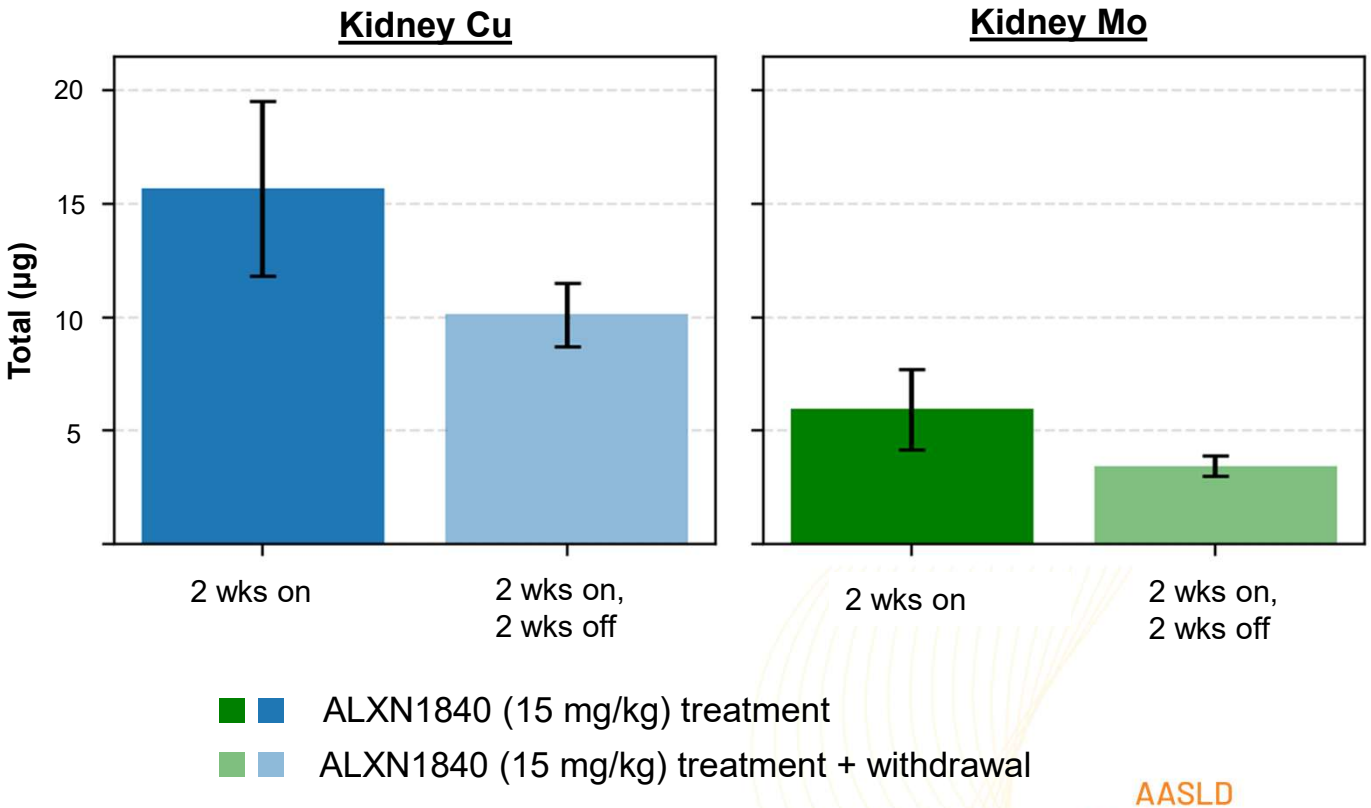


Molybdenum and copper **travel together**; after 112 days of daily dosing, **< 2 daily doses worth of ALXN1840 (Mo)** is present in mice

Source: RTR-0051 Additional Analysis – Alexion Pharmaceuticals Preclinical Study in WD Mice (Toxic Milk Mouse model)

Cu and Mo (ALXN1840) Transit Thru Tissue is Non-toxic and Reversible

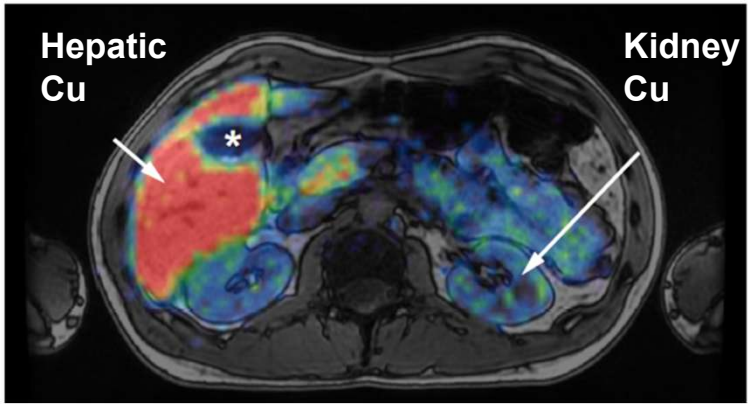
After a 2-week withdrawal period in WD mice, kidney Cu and Mo levels **decrease in parallel**



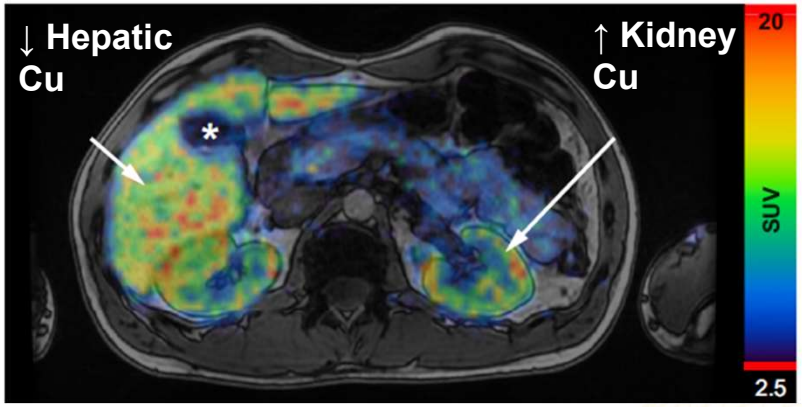
Source: RTR-0054 Additional Analysis – Alexion Pharmaceuticals Preclinical Study in WD Mice (Toxic Milk Mouse model)

Clinical Data Corroborate Nonclinical Findings; TPC Transit Appears Safe

Before ALXN1840



After ALXN1840



ALXN1840 **blocks Cu uptake** in liver[1]; **transits** through the **kidney in a manner that appears safe**

Drug-related Adverse Events[2]	
Number of patients	266
Patient-years (PYs)	645.6
Renal/urinary SAEs	0 (0%)
Renal/urinary AEs	2 (0.8%)

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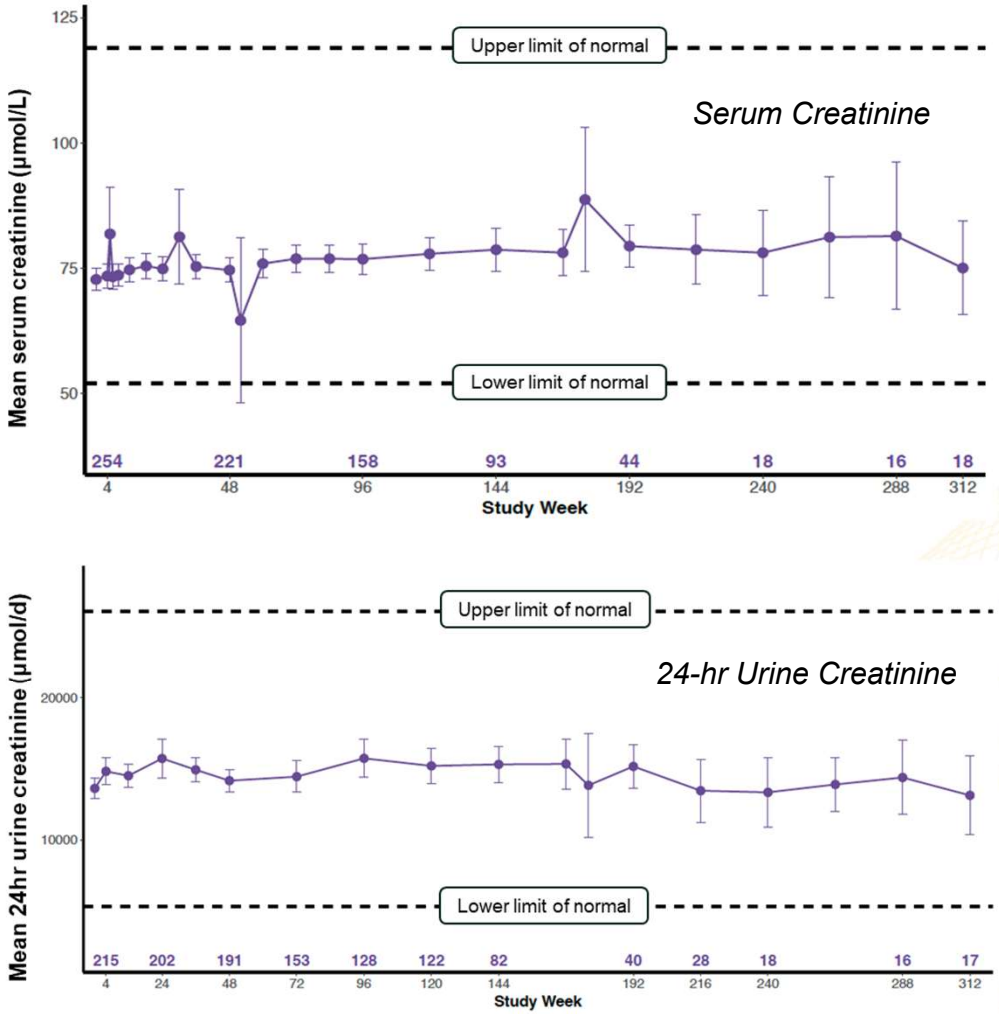
TPC = ALXN1840-Cu-albumin tripartite complex

1. Kirk *et al*. *J Hepatol*. 2024;80(4):586-595; 2. Source: Pooled Phase 2/3 Safety Analysis

No Impact on Kidney Function in Humans Across 6 Years of Treatment

Mean serum creatinine (top) and mean 24-hour urine creatinine (bottom) were **within normal limits across 6 years** on ALXN1840



Source: Pooled Phase 2/3 Safety Analysis

Clean SAE Profile at Sites of Albumin Processing

SAEs from Phase 3 Clinical Trial (48-weeks)

	All SAEs		Related only	
System Organ Class	**ALXN1840 (n=137)**	**SoC (n=70)**	**ALXN1840 (n=137)**	**SoC (n=70)**
Gastrointestinal disorders	1 (0.7%)	2 (2.9%)	0	0
Musculoskeletal and connective tissue disorders	1 (0.7%)	2 (2.9%)	0	0
Renal and urinary disorders	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0

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Source: WTX101-301 – Phase 3 Randomized Controlled Trial

Key Take-aways

ALXN1840 improves copper balance in Wilson disease patients through **increased fecal copper excretion**

Demonstrated **in humans a potent blocking of dietary copper uptake**

Pre-clinical studies demonstrate **reduction in total body Cu** and **biliary co-excretion of Cu-ALXN1840 (Mo) complex**

New Sponsor is planning to submit an **NDA in early 2026**

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Acknowledgements

We would like to thank the patients and their families for their participation in the studies, as well as all participating sites

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Thank You !

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