A Phase 1, Open-label Study to Assess Copper Balance in Healthy Participants Following Administration of ALXN1840

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TITLE PAGE

Protocol Title: A Phase 1, Open-label Study to Assess Copper Balance in Healthy Participants Following Administration of ALXN1840

Protocol Number: ALXN1840-HV-108

Amendment Number: 2

Compound: ALXN1840 (bis-choline tetrathiomolybdate)

Study Phase: 1

Short Title: Copper Balance in Healthy Participants Administered ALXN1840

Sponsor Name:

Alexion Pharmaceuticals, Inc.

Legal Registered Address:

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Regulatory Agency Identifier Number(s)

EudraCT: 2019-003010-14

Approval Date:

Original Protocol	**10 Mar 2020**
Amendment 1	**07 Apr 2020**
Amendment 2	**29 May 2020**

Sponsor Signatory:

PPD

01-Jun-2020

PPD

Date

Medical Monitor Name and Contact Information can be found in the Study Contact List.

INVESTIGATOR'S AGREEMENT

I have read the study protocol amendment 2 and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	10 Mar 2020
Amendment 1	07 Apr 2020
Amendment 2	29 May 2020

Amendment 2 (29 May 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The main reason for preparation of this amendment was to remove contradictory text on the assessment of intensity of serious adverse events and to include language on the collection of pregnancy information. Additional changes are included in the table below.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Title Page	Change of Sponsor signatory	To reflect a change in Alexion Medical Monitor
Section 5.1 Inclusion Criteria	Edits to text in inclusion criterion 7 regarding requirements for contraception	To improve the flow of text and remove duplicate text that is also present in Section 10.4 of the protocol
Section 6.1 Study Intervention Administration	Text in Table 5 edited with respect to labeling of study intervention.	Wording regarding labeling amended to reflect that the study is planned to be conducted in the UK
Section 10.3.3 Recording and Follow-Up of AE and/or SAE	Removal of contradictory text on the assessment of intensity of AEs and /or SAEs	Assessment of the intensity of AEs and/or SAEs and assignment to a category should be performed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 Nov 2017. The section has been revised to remove unnecessary duplication in assessment
Section 10.4 Contraceptive Guidance and Collection of Pregnancy Information	Addition of language on collection of pregnancy information	Reporting procedures were added in order to collect pregnancy information as well as information regarding exposure of infants to ALXN1840 during breastfeeding
Section 2 Introduction Section 2.2 Background Section 2.3.2 Overall Benefit: Risk Conclusion Section 10.5 Appendix 5: Abbreviations	Removal of text relating to primary biliary cholangitis	To reflect that development of ALXN1840 is for Wilson disease
Appendix 10.6 Appendix 6: Protocol Amendment History	Addition of details of the previous amendment to the protocol	To include details of the changes that were made in the previous amendment, Amendment 1
All	Minor editorial changes	For consistency and to correct minor typographical errors

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-label Study to Assess Copper Balance in Healthy Participants Following Administration of ALXN1840

Short Title: Copper Balance in Healthy Participants Administered ALXN1840

Rationale:

The principal aim of this study is to assess the change from baseline in mean daily copper (Cu) balance in healthy participants with repeat-dose administrations of ALXN1840 over 2 weeks to demonstrate that ALXN1840 promotes a net negative Cu balance through enhanced fecal elimination of Cu. If observed, these data will support the ALXN1840 decoppering mechanism of action ie, liver decoppering with subsequent biliary excretion and fecal elimination. A secondary aim of this study is to characterize the steady state absorption, distribution, metabolism, and excretion (ADME) (mass balance) of total molybdenum (Mo), which is a surrogate measure of ALXN1840 disposition.

ALXN1840 contains the active anion tetrathiomolybdate (TTM) and has been shown to cause negative Cu balance when administered to healthy animals as well as decopper the liver in animal models of Wilson Disease (WD) (Mills, 1981; Czachor, 2002). In Study WTX101-201, which assessed the safety and efficacy of ALXN1840 in patients with WD, ALXN1840 demonstrated enhanced Cu control as measured by reduced plasma non-ceruloplasmin bound Cu (NCC) corrected for the stable tetrathiomolybdate-Cu-albumin complex (tripartite complex; TPC) ($NCC_{corrected}$) (Weiss, 2017).

Depletion of Cu by ALXN1840 has been shown to occur primarily through fecal elimination in both healthy and WD animal models. In contrast, Cu chelators (current standard of care [SoC] such as trientine and penicillamine) enhance urinary Cu output and penicillamine has been shown to drive a net negative Cu balance in most patients with WD and in healthy participants (Strickland, 1971; Walshe, 1973).

Published literature support that a Cu balance study may be conducted in healthy participants to investigate the mechanism of action of decoppering agents such as ALXN1840. Copper balance is assessed through measurement of all Cu intake (food and drink) and measurement of all Cu output (urine and feces) and is classically considered the most objective measure of decoppering ability with a decoppering agent able to drive a net negative Cu balance (Hill, 1986; Strickland, 1971; Walshe, 1973). Because participants may have different baseline Cu balance values and may include values that are both mildly positive or negative, the primary objective of the study will be to assess the change from baseline in Cu balance in healthy participants treated with ALXN1840. This approach will allow an assessment of change in Cu balance due to ALXN1840 treatment. Secondarily, the study will also assess whether a mean net negative Cu balance is achieved following ALXN1840 treatment. Taken together, these 2 complementary Cu balance endpoints will allow an assessment of the role of ALXN1840 on Cu balance and study its mechanism of action of decoppering, mostly of liver, through urine and fecal excretions.

As part of the secondary objective, the study has been designed to descriptively assess the total Mo mass balance (as a measure of ALXN1840 balance). A Mo mass balance study in healthy

participants is sufficient to characterize the ADME profile for ALXN1840 and for comparisons to the results from Long-Evans Agouti (LEA; normal Wistar) and Long-Evans Cinnamon (LEC; Wilson disease model) rats.

Objectives and Endpoints

Objectives	Endpoints
Primary Assess change from baseline in copper (Cu) balance over 2 weeks of repeated daily ALXN1840 dosing	Change in mean daily Cu balance from pretreatment baseline period to ALXN1840 treatment period, as measured by the calculated difference between Cu intake (in food and drink), and Cu output (in feces and urine)
Secondary Assess net Cu balance over 2 weeks of repeated daily ALXN1840 dosing	Mean daily Cu balance during ALXN1840 treatment period where Cu balance is measured by the calculated difference between Cu intake (in food and drink), and Cu output (in feces and urine)
Assess steady-state molybdenum (Mo) balance after 2 weeks of repeated daily ALXN1840 dosing	Mean daily Mo balance at ALXN1840 pharmacokinetic (PK) steady state, as demonstrated through measurement of Mo intake (in food, drink, and ALXN1840), and Mo output (in feces and urine)
Assess extent of Mo excretion in urine and feces	Quantify total Mo excretion in urine and feces following ALXN1840 treatment compared with baseline
Determine the steady-state plasma PK of ALXN1840 after 2 weeks of repeated daily ALXN1840 dosing	PK parameters for plasma total Mo and plasma ultrafiltrate (PUF) Mo including terminal elimination for Mo after steady-state dosing
Investigate the effect of ALXN1840 on the disposition of Cu after 2 weeks of repeated daily ALXN1840 dosing at steady state	Cu quantified in food, feces, and urine over 2 weeks of ALXN1840 dosing including plasma total and labile bound Cu (LBC) at steady state
Investigate the effect of ALXN1840 on the disposition of Cu over 2 weeks of repeated daily ALXN1840 dosing and through the post-treatment period	Cu quantified in food, drink, feces, and urine
Investigate the effect of ALXN1840 on the disposition of Mo over 2 weeks of repeated daily ALXN1840 dosing and through the post-treatment period	Mo quantified in ALXN1840 doses given and in food, drink, feces, and urine
Safety Evaluate the safety and tolerability of repeated dose administration of ALXN1840	Safety parameters: Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs)

	Clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis) Physical examinations Heart rate, intervals (PR, QRS, QT and QTc), and clinically significant ECG findings as determined by triplicate 12-lead ECG Vital sign assessments (blood pressure and heart rate)
Exploratory Assess the effects of ALXN1840 on ceruloplasmin, ceruloplasmin-bound Cu, and LBC profiles in plasma	Absolute and percent changes in ceruloplasmin, ceruloplasmin-bound Cu, ceruloplasmin-bound Cu:ceruloplasmin ratio, and LBC during treatment period and post-treatment compared with predose baseline
Assess the effects of repeated daily ALXN1840 dosing on Cu:Mo ratio in plasma at steady state	Measure plasma Cu:Mo ratios during treatment period and post-treatment compared with predose baseline
Assess the effects of ALXN1840 on Cu:Mo ratio in urine and feces	Measure the average daily Cu:Mo ratio in urine and feces during treatment and post-treatment compared with predose
Assess the effects of ALXN1840 on the time course of Cu balance over 2 weeks	Evaluate the effect of time on change in average daily Cu balance

Overall Design

This is a single-arm, open-label, repeat-dose (30 mg/day) study designed to assess the effects of ALXN1840 administration on Cu balance in healthy participants. The safety and tolerability of ALXN1840 in healthy participants will also be assessed. ALXN1840 pharmacokinetics (PK) in plasma as measured via total Mo and plasma ultrafiltrate (PUF) Mo will be determined after single and repeated dosing along with total Mo mass balance at steady state.

Disclosure Statement: This is an open-label, 2-period study with 1 arm.

Number of Participants:

Approximately 17 enrolled participants will receive study intervention to ensure 13 participants complete the study.

This study will be conducted in a minimum of 2 groups. The first group will consist of approximately 6 participants and no more than 8 participants. The second group may be initiated after the Safety Review Committee (SRC) reviews safety information (all adverse events [AEs], safety laboratory data, and vital signs) through Day 18 and agrees that it is safe to continue enrollment to complete the study. If ceruloplasmin concentrations or AE findings are suggestive of Cu depletion, the SRC may propose a dose reduction to 15 mg/day for the remainder of the study population.

Note: "Enrolled" means all participants who sign the ICF, are eligible for the study, and are registered on Day -7 when participants are assigned a subject number.

Intervention Groups and Duration:

This is a single arm study. Following screening and enrollment, participants will have a Run-in Period to support diet equilibration (Day -7 through Day -5) and measurement of pretreatment Cu and Mo balance (Day -4 through Day -1). Following the Run-in Period, participants will be administered ALXN1840 at 30 mg/day for 15 days (Day 1 through Day 15). ALXN1840 will be administered orally after an overnight fast and participants will remain fasted for a minimum of 2 hours following each dose administration. Following completion of the 15-day dosing period, participants will remain in the clinical research unit (CRU) for an additional 16 days until discharge on Day 31.

Total intake and output will be measured continuously from Day -4 through Day 30 with Day 1 through Day 15 representing the ALXN1840 treatment period and Day 16 through Day 30 representing the post-treatment period. The collection period will support assessment of Cu and Mo mass balance including assessment of steady state and terminal elimination.

Participants will return to the CRU for a final study visit on Day 43 ± 2 days, approximately 28 days after the final dose of ALXN1840, to conclude the safety follow up period.

If participants withdraw from the study early, they will be seen and assessed by the Investigator or study physician and whenever possible, will undergo the procedures associated with the end of study (EOS) Visit. Participants may be replaced at the discretion of Alexion.

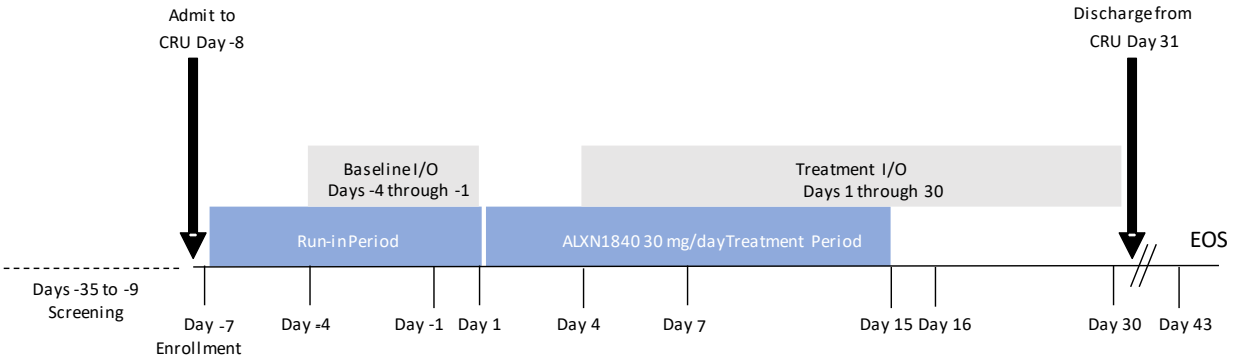
Safety Review Committee:

An SRC, composed of a minimum of the Investigator and Alexion's medical monitor, will review safety information from the first group (approximately 6-8 participants) through Day 18 including all AEs, safety laboratory data, and vital sign assessment and agree that it is safe to continue enrollment to complete the study. If ceruloplasmin concentrations or AEs findings are suggestive of Cu depletion, the SRC may propose a dose reduction to 15 mg/day for the rest of the enrolled study participants.

1.2. Schema

The study design is presented in Figure 1.

Figure 1: Study Design Schematic



Participants will be admitted to the CRU on Day -8 and discharged on Day 31.
Participants eligible for the study will be enrolled (assigned a subject number) on Day -7. A Cu- and Mo-controlled diet will be initiated on Day -7 and will be continued through Day 30.
Participants will be administered ALXN1840 at a dose of 30 mg/day on Day 1 through Day 15, with post-treatment period starting at Day 16.
Total intake and total output (I/O) samples for measurement of Cu and Mo will be collected during the baseline (Day -4 through Day -1), treatment (Day 1 through Day 15), and post-treatment periods (Day 16 through Day 31). I/O defines the period in which all intake (food and drink) and all output (urine and feces) will be collected for the measurement of Cu and Mo.
Intensive PK/PD sampling will occur on Day 1 and Day 15. Pre-dose PK/PD samples will be collected on Days 2 (Day 1, Hour 24), 3, 5, 8, 11, and 14. During the post-treatment period, PK/PD samples will be collected on Days 16, 18, 21, 24, 27, and 30.
Abbreviations: CRU = clinical research unit; EOS = end of study; I/O = input/output.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities

Study Procedures	**Screening**[a]	**Check-in**[b]																						**EOS or ET**[c]
Days	**-35 to -9**	-8	-7	-6 to -5	-4 to -1	1	2	3	4	5	6-7	8	9-10	11	12-13	14	15	16-17	18	19-20	21-29	30	31	EOS Day 43 ± 2
Eligibility																								
Informed consent	X																							
Admit to unit		X																						
Discharge from unit																							X[d]	
Inclusion/exclusion	X	X	X																					
Discuss/document contraception	X	X																						X
Follicle stimulating hormone (post-menopausal females)	X																							
Alcohol test	X	X																						
Urine drug screen	X	X																						
HIV, hepatitis B and C screen	X																							
Study Administration																								
Medical history/demographics[e]	X	X																						
Physical examination[f]	X	X																					X	X
Height[g], weight, and BMI	X	X																						
Enrollment																								
Enrollment (prior to administration of study intervention)			X																					
Administration of Study Intervention																								
ALXN1840[h]						X	X	X	X	X	X	X	X	X	X	X	X							
PK Analyses																								
ALXN1840 (total Mo) and PUF Mo PK[i]						X[j]	X[k]	X[k]		X[k]		X[k]		X[k]		X[k]	X[j]	X[k]	X[k]		X[k,n]	X[k]		
Safety Assessments/Laboratory Analyses																								
Chemistry[l], Hematology, Coagulation	X	X			X[m]		X			X		X		X			X		X		X[n]		X	X
Urinalysis	X	X																						X

Study Procedures	**Screening**[a]	**Check-in**[b]																						**EOS or ET**[c]
Days	**-35 to -9**	-8	-7	-6 to -5	-4 to -1	1	2	3	4	5	6-7	8	9-10	11	12-13	14	15	16-17	18	19-20	21-29	30	31	EOS Day 43 ± 2
Pregnancy test[o]	X	X																						X
Serum ceruloplasmin and Cu	X											X					X						X	X
Retained sample (safety)[p]			X																					
Vitals sign measurements[q]	X		X			X	X			X		X		X		X	X							X
12-lead ECG (triplicate)[q]	X		X			X[j]	X			X		X		X		X	X[j]							X
AE monitoring	←																							→
Balance assessments																								
Cu/Mo controlled meals[r]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Light exercise regimen			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urination and bowel movement monitoring, menstruation check[o]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
24-hour urine for Cu and Mo[s]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Feces for Cu and Mo[t]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Plasma total Cu, PUF Cu ceruloplasmin, ceruloplasmin-bound Cu, and LBC						X[j]	X[k]	X[k]		X[k]		X[k]		X[k]		X[k]	X[j]	X[k]	X[k]		X[k,n]	X[k]		X
Other																								
Concomitant medication review	←																							→

[a] Within 35 days of ALXN1840 administration (or within approximately 28 days of enrollment)

[b] Participants will be admitted to the CRU at least 10 hours prior to enrollment and initiation of Cu- and Mo-controlled diet

[c] Participants are required to return to the CRU approximately 28 days (±2 days) after final ALXN1840 dose administration. In the event of early termination, the procedures listed at the end of the study are performed prior to participant discharge. Additional follow-up for participants who undergo early termination are allowed per the Investigator's discretion.

[d] Discharge from the CRU may occur after completion of all procedures on Day 31 and after investigator has reviewed all safety assessment (including safety labs) and confirmed that participant is appropriate for discharge.

[e] Parameters include age and sex. Race and ethnicity will be collected where permitted by local regulations.

[f] A full physical examination will be performed at screening, at check-in for the study, and at the end of the study or upon early termination. A physical examination should also be performed on any participant with ongoing AEs prior to discharge from the unit. Otherwise, a symptom-driven physical examination may be performed at other times, at the Investigator's discretion.

[g] Height at screening only.
[h] Study intervention will be administered after an overnight fast (ie, at least 10 hours) at the same time every morning; ALXN1840 is to be administered with 240 mL of water. Participants will remain fasted for a minimum of 2 hours following each dose administration.
[i] Blood samples will be collected pre-dose on dosing days for PK. On Days 1 and 15, intensive blood sampling for PK/PD will occur at the timepoints described in Table 2. Blood samples for PK/PD on Days 16 (Day 15 24-hour time point), 18, 21, 24, 27, and 30 (non-dosing days) will be collected at approximately 0800 and before breakfast.
[j] See Table 2 for PK/PD blood sampling and ECG schedules on Days 1 and 15.
[k] Procedures will occur pre-dose on Day 1 through Day 15; starting on Day 16, procedure will occur at approximately 0800 and before breakfast
[l] Samples for serum chemistry will be obtained following a fast of at least 8 hours at screening, and of at least 6 hours at check-in. In case of dropouts, rechecks, and postdose serum chemistry, participants may not have fasted for 6 or 8 hours before the serum chemistry sample is taken.
[m] Day -1 only.
[n] Laboratory assessment including chemistry, hematology, and coagulation parameters should be performed on Days 21, 24, and 27; blood sampling for plasma PK (total and PUF Mo) and PD (total and PUF Cu, ceruloplasmin, ceruloplasmin-bound Cu, and LBC) should occur at approximately 0800 or before breakfast on Days 21, 24, and 27.
[o] Menstruation check is for women only; Women of childbearing potential should only be enrolled after a negative serum pregnancy test result at screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRBs/IEC (Section 10.2).
[p] A single 15 mL serum sample will be retained for evaluation in the event of an unexpected safety finding; retained samples may be destroyed after completion of the clinical study report
[q] Vital signs measurements and ECGs should be performed predose, unless otherwise specified. Vitals signs include body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure.
[r] Cu and Mo controlled meals will be initiated after enrollment (Day -7 breakfast) and continued through Day 30; during this time participants will be strongly encouraged to complete all meals. If a participant is unable to eat 100% of the food, the remaining food will be weighed and reported in the CRF to support Cu/Mo determination as a fraction of total meal (Table 4).
[s] For each intake/output balance period, 24-hour urine samples are to be collected for measurement of Cu and Mo. 24-hour collection volumes will be recorded in the CRF. The 24-hour collection period is defined as relative to the first ALXN1840 dose administration.
[t] For fecal samples, each individual sample will be independently collected with record of date, time and weight of the sample.

Abbreviations: AE = adverse event; BMI = body mass index; CRF = case report form; CRU = clinical research unit; Cu = copper; EOS/ET = End of Study or Early Termination; HR = heart rate; Mo = molybdenum; PK = pharmacokinetics; PUF = plasma ultrafiltrate; LBC = labile bound copper.

Note: When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, study intervention administration, and meal

Table 2: Schedule of Pharmacokinetic/Pharmacodynamic and Safety Assessments on Day 1 and Day 15

Time point (h)[a]	Predose[b]	0	1	2	3	4	5	6	8	12	24
ALXN1840 (total Mo) and PUF Mo PK	X		X	X	X	X	X	X	X	X	X
Plasma total Cu, ceruloplasmin, ceruloplasmin-bound Cu, and LBC	X		X	X	X	X	X	X	X	X	X
ECG (triplicate)	X					X					

a Time points are relative to dosing (0 hours) on Day 1 and Day 15.
b Pre-dose should be collected within 1 hour prior to dosing.
Note 1: Windows for PK/PD time points will be defined as ± 10% of the nominal time point.
Note 2: The 24-hour PK/PD samples after Day 1 and Day 15 dosing are to be collected at pre-dose on Day 2 and at approximately 0800 am on Day 16.
Note 3: When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, study intervention administration, and meal.
Abbreviations: Cu = copper; LBC = labile-bound copper; Mo = molybdenum; PK = pharmacokinetic; PUF = plasma ultrafiltrate.

2. INTRODUCTION

ALXN1840 (bis-choline tetrathiomolybdate; formerly known as WTX101) is a novel, first-in-class, copper (Cu)-protein binding agent in development for the treatment of Wilson disease (WD).

2.1. Study Rationale

The principal aim of this study is to assess the change from baseline in mean daily copper (Cu) balance in healthy participants with repeat-dose administrations of ALXN1840 over 2 weeks to demonstrate that ALXN1840 promotes a net negative Cu balance through enhanced fecal elimination of Cu. If observed, these data will support the ALXN1840 decoppering mechanism of action ie, liver decoppering with subsequent biliary excretion and fecal elimination. A secondary aim of this study is to characterize the steady state absorption, distribution, metabolism, and excretion (ADME) (mass balance) of total molybdenum (Mo), which is a surrogate measure of ALXN1840 disposition.

ALXN1840, which contains the active anion tetrathiomolybdate (TTM) and has been shown to cause Cu depletion when administered to healthy animals as well as decopper the liver in animal models of WD (Mills, 1981; Czachor, 2002). In Study WTX101-201, which assessed the safety and efficacy of ALXN1840 in patients with WD, ALXN1840 demonstrated enhanced Cu control as measured by reduced plasma non-ceruloplasmin-bound Cu (NCC) corrected for the stable tetrathiomolybdate -Cu-albumin complex (tripartite complex; TPC) ($NCC_{corrected}$) (Weiss, 2017).

Studies in both healthy and WD animal models showed that treatment with tetrathiomolybdate results in removal of Cu from the liver. Tetrathiomolybdate administered to healthy mice by intraperitoneal injection resulted in a dose-dependent reduction in liver Cu concentration over a treatment range of 0-6 mg/kg/day (human equivalent dose [HED] by body surface area [BSA] scaling: 0-1 mg/kg/day). The results of these studies indicated that only 30-40% of Cu remained after 5 weeks of treatment. Similar liver decoppering (approximately 40-60%) was also reported in toxic milk mice (a WD animal model) at 5 mg/kg/ day for 14 days (HED by BSA scaling: 0.4 mg/kg/day; Mills, 1981; Czachor, 2002). In Long-Evans Cinnamon (LEC) WD model rats, 25 mg/kg/day of ALXN1840 (HED by BSA scaling: 4 mg/kg/day) administered by oral gavage for 10 days, resulted in an approximately 50% decrease in liver Cu concentration.

Mechanistic work in vitro and in vivo has shown that tetrathiomolybdate is capable of removing Cu directly from metallothionein (MT), which may enhance its ability to decopper the liver compared with other decoppering agents (Suzuki, 1995). The Cu removed from the liver is believed to be excreted into the blood or bile as a soluble tetrathiomolybdate -Cu-albumin complex or TPC (Komatsu, 2000).

Depletion of Cu by ALXN1840 has been shown to occur primarily through fecal elimination in both healthy and WD animal models.

Sheep injected with 30 mg/day of tetrathiomolybdate for 5 days were shown to have an elevation of fecal Cu during the treatment period increasing from a baseline of approximately 3 mg/day up to approximately 7 mg/day during the treatment period before returning to baseline concentrations (Mason, 1988). Similarly, LEC rats were injected intra-peritoneally with a saline solution of tetrathiomolybdate at a dose of 10 mg/kg body weight daily for 8 consecutive days (Ogra, 2000). The amounts of both Cu and Mo excreted into the feces increased significantly

during treatment with tetrathiomolybdate, which suggest that Cu is excreted in complex with tetrathiomolybdate into the feces. While fecal Cu increased with tetrathiomolybdate administration, the amount of Cu excreted into the urine decreased and that of Mo increased significantly during treatment with tetrathiomolybdate. Mo in the urine does not bind to Cu (data on file). These findings are in-line with other studies showing enhanced biliary and/or fecal excretion of Cu and Mo upon administration of tetrathiomolybdate in rats and sheep (Komatsu, 2000; Ogra, 1995; Mason, 1988). In contrast, Cu chelators (current standard of care [SoC] for WD such as trientine and penicillamine) enhance urinary Cu output, and have been shown to drive a net negative Cu balance in most patients with WD and in healthy participants (Strickland, 1971; Brewer, 1995; Walshe, 1973). These data support that a Cu balance study may be conducted in healthy participants to investigate the mechanism of action of decoppering agents such as ALXN1840.

As both healthy and WD animal models have supported the characterization of tetrathiomolybdate's mechanism of action, namely liver Cu depletion through mobilization of Cu into plasma and bile and excretion into feces, healthy participants are adequate for assessing the mechanism of action of ALXN1840 on Cu balance, which is the primary objective of this study.

Copper balance is assessed through measurement of all Cu intake (food and drink) and measurement of all output (urine and feces) and is classically considered the most objective measure of decoppering ability with a decoppering agent able to drive a net negative Cu balance (Hill, 1986; Strickland, 1971; Walshe, 1973). Because participants may have different baseline Cu balance values and may include values that are both mildly positive and/or negative, the primary objective of the study will be to evaluate the change from baseline in Cu balance in healthy participants treated with ALXN1840. This approach will allow an assessment of change in Cu balance due to ALXN1840 treatment. Secondarily, the study will also assess whether a net negative Cu balance is achieved following ALXN1840 treatment. Taken together, these 2 complementary Cu balance endpoints will allow an assessment of the role of ALXN1840 on Cu balance or its mechanism of action.

As part of the secondary objective, the study has been designed to descriptively assess the total Mo balance (as a surrogate measure of ALXN1840 balance). A dedicated, single-dose study of ALXN1840 was performed in normal (Long Evans Agouti [LEA]) rats and LEC WD model rats (Plitz, 2018). The rats were treated with 1.5 mg/kg intravenous tetrathiomolybdate single injection and placed in a metabolic cage to support collection of urine and feces over 7 days. During the 7-day (168 hours) collection period in LEA rats, approximately 87% of the dose was accounted for with approximately 79% total Mo dose (as a measure of ALXN1840) excreted in the urine and approximately 7% in the feces. Conversely, in the LEC rats, less than half the 1.5 mg/kg dose was excreted in the 7-day (168 hours) period with approximately 30% remaining in the liver and 5-10% in the kidney. A Mo mass balance in healthy participants is sufficient to characterize the ADME profile for ALXN1840 and for comparisons to the results from LEA and LEC rats.

2.2. Background

ALXN1840 has been selected for development in WD due to its improved stability properties over ammonium tetrathiomolybdate, which has previously been studied in patients with WD and

other indications. Ammonium tetrathiomolybdate as well as bis-choline tetrathiomolybdate non-clinical and clinical data reported to date support the efficacy and safety of ALXN1840.

ALXN1840 rapidly forms irreversible tetrathiomolybdate -Cu-albumin tripartite complexes (TPC), which stabilize free Cu leading to a reduction in the NCC concentrations after correction for free Cu bound to TPC ($NCC_{corrected}$).

In the Phase 2 proof of concept Study WTX101-201 in patients with WD, ALXN1840 demonstrated a sustained control of free Cu as measured by $NCC_{corrected}$. Importantly, ALXN1840 treatment resulted in improvements in disability and neurologic symptoms as measured by the Unified Wilson's Disease Rating Scale (UWDRS, Parts II and III) and stabilization of liver function (Weiss, 2017). Treatment with ALXN1840 resulted in an acceptable safety and tolerability profile when initiated at 15 mg daily with Investigator-driven, individual patient titration of dose based on safety, $NCC_{corrected}$, and symptoms.

ALXN1840 is currently being evaluated in a Phase 3 multicenter, randomized study to assess the efficacy of ALXN1840 compared with SoC on plasma toxic Cu control as measured by $NCC_{corrected}$. Toxic Cu in this study can be measured via PUF and/or LBC or assessed via $NCC/NCC_{corrected}$ methods.

Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of ALXN1840 are provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits, risks, and reasonably expected adverse events (AEs) of ALXN1840 may be found in the IB. Information about the known or potential risks and benefits are detailed in the sections following.

Table 3: Potential Risks and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
ALXN1840		
Dose-dependent elevations in transaminases (ALT and AST)	**Generally mild to moderate in severity, asymptomatic and reversible with dose adjustments were reported, usually after 3-6 weeks of treatment.** Results obtained from studies of ALXN1840 and ammonium tetrathiomolybdate in patients with WD; see the IB	Regular monitoring of liver function tests. Dose modification or discontinuation (Section 6.6)
Anemia	Anemia has been observed in patients with WD, attributed to overtreatment and resultant Cu depletion, see the IB	Monitoring complete blood count. Dose modification or discontinuation (Section 6.6)
Low white blood cell count (leukopenia, bone marrow toxicity)	**Leukopenia and bone marrow toxicity (myelosuppression) have been observed in patients with WD, attributed to overtreatment and resultant Cu depletion.** Results obtained from studies of ALXN1840 and ammonium tetrathiomolybdate in patients with WD; see the IB	Monitoring of complete blood count. Dose modification or discontinuation (Section 6.6)
Neurological dysfunction	**Neurological worsening may occur due to Cu mobilization. Peripheral neuropathy may be seen with over-decoppering; however, symptoms such as myelosuppression is typically seen earlier**	Neurologic dysfunction is not anticipated in HV population.
Study Procedures		
Risks associated with the study design and procedures	Participants will undergo repeated blood draws to measure the PK of the study intervention and metabolism. Blood draws may result in ecchymosis, redness and minor pain to the site. On rare occasion, infection or thrombophlebitis can occur	Blood draws are optimized for PK. A cannula may be placed to minimize needle sticks; however, a catheter may not be left in place for longer than 72 hours, and should be flushed a minimum of every 8 hours

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; Cu = copper; IB = Investigator's Brochure; PK = pharmacokinetics; WD = Wilson Disease.

2.3.1. Benefit Assessment

This is a healthy participant study, and there is no direct benefit to study participants.

2.3.2. Overall Benefit: Risk Conclusion

Taking into account the measures implemented to minimize risk to participants participating in this study, the potential risks identified in association with ALXN1840 are justified by the anticipated benefits that may be afforded to patients with WD.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Assess change from baseline in copper (Cu) balance over 2 weeks of repeated daily ALXN1840 dosing	Change in mean daily Cu balance from pretreatment baseline period to ALXN1840 treatment period, as measured by the calculated difference between Cu intake (in food and drink), and Cu output (in feces and urine)
Secondary Assess net Cu balance over 2 weeks of repeated daily ALXN1840 dosing	Mean daily Cu balance during ALXN1840 treatment period where Cu balance is measured by the calculated difference between Cu intake (in food and drink), and Cu output (in feces and urine)
Assess steady-state molybdenum (Mo) balance after 2 weeks of repeated daily ALXN1840 dosing	Mean daily Mo balance at ALXN1840 pharmacokinetic (PK) steady state, as demonstrated through measurement of Mo intake (in food, drink, and ALXN1840), and Mo output (in feces and urine)
Assess extent of Mo excretion in urine and feces	Quantify total Mo excretion in urine and feces following ALXN1840 treatment compared with baseline
Determine the steady-state plasma PK of ALXN1840 after 2 weeks of repeated daily ALXN1840 dosing	PK parameters for plasma total Mo and plasma ultrafiltrate (PUF) Mo including terminal elimination for Mo after steady-state dosing
Investigate the effect of ALXN1840 on the disposition of Cu after 2 weeks of repeated daily ALXN1840 dosing at steady state	Cu quantified in food, feces, and urine over 2 weeks of ALXN1840 dosing including plasma total and labile bound Cu (LBC) at steady state
Investigate the effect of ALXN1840 on the disposition of Cu over 2 weeks of repeated daily ALXN1840 dosing and through the post-treatment period	Cu quantified in food, drink, feces, and urine
Investigate the effect of ALXN1840 on the disposition of Mo over 2 weeks of repeated daily ALXN1840 dosing and through the post-treatment period	Mo quantified in ALXN1840 doses given and in food, drink, feces, and urine
Safety Evaluate the safety and tolerability of repeated dose administration of ALXN1840	Safety parameters: Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs) Clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis) Physical examinations

	Heart rate, intervals (PR, QRS, QT and QTc), and clinically significant ECG findings as determined by triplicate 12-lead ECG Vital sign assessments (blood pressure and heart rate)
Exploratory Assess the effects of ALXN1840 on ceruloplasmin, ceruloplasmin-bound Cu, and LBC profiles in plasma	Absolute and percent changes in ceruloplasmin, ceruloplasmin-bound Cu, ceruloplasmin-bound Cu:ceruloplasmin ratio, and LBC during treatment period and post-treatment compared with predose baseline
Assess the effects of repeated daily ALXN1840 dosing on Cu:Mo ratio in plasma at steady state	Measure plasma Cu:Mo ratios during treatment period and post-treatment compared with predose baseline
Assess the effects of ALXN1840 on Cu:Mo ratio in urine and feces	Measure the average daily Cu:Mo ratio in urine and feces during treatment and post-treatment compared with predose
Assess the effects of ALXN1840 on the time course of Cu balance over 2 weeks	Evaluate the effect of time on change in average daily Cu balance

4. STUDY DESIGN

4.1. Overall Design

This is a single-arm, open-label, repeat-dose (30 mg/day) study designed to assess the effects of ALXN1840 administration on Cu balance in healthy participants.

This study will be conducted in a minimum of 2 groups. The first group will consist of approximately 6 participants and no more than 8 participants. The second group may only be initiated after the Safety Review Committee (SRC; defined in Section 9.7) reviews safety information (all AEs, safety laboratory data, and vital signs) through Day 18 and agrees that it is safe to continue enrollment to complete the study. If ceruloplasmin concentrations or AE findings are suggestive of over-depletion of Cu, the SRC may propose a dose reduction to 15 mg/day for remainder of the study population.

This is a single arm study. Following screening and enrollment, participants will have a Run-in Period to support diet equilibration (Day -7 through Day -5) and measure of pretreatment Cu and Mo balance (Day -4 through Day -1). Following the Run-in Period, participants will be administered ALXN1840 at 30 mg/day for 15 days (Day 1 through Day 15). ALXN1840 will be administered orally after an overnight fast, and participants will remain fasted for a minimum of 2 hours following each dose administration. Following completion of the 15 days dosing period, participants will remain the clinical research unit (CRU) for an additional 16 days until discharge on Day 31.

Total intake and output will be measured continuously from Day -4 through Day 30 with Day 1 through Day 15 representing the ALXN1840 treatment period and Day 16 through Day 30 representing the post-treatment period. The collection period will support assessment of Cu balance and Mo mass balance including assessment at steady state and terminal elimination.

Participants will return to the CRU for a final study visit on Day 43 ± 2 days, approximately 28 days after the final dose of ALXN1840, to conclude the safety follow-up period.

Participants meeting all study entry criteria prior to Cu/Mo controlled diet initiation are eligible for enrollment. At the time of enrollment, participants will be assigned a subject number for the study.

Throughout the period in the CRU, participants will remain on a Cu- and Mo-controlled diet with a limited selection of meals utilized for breakfast, lunch and dinner throughout the study to ensure Cu/Mo control (Table 4). During the intake and output collection periods, daily urine will be pooled (24-hour collection) with volumes recorded for each 24-hour period. Fecal samples will be individually collected; each sample will include a collection date, time, and weight. To support accurate determination of daily Cu/Mo content for each 24-hour period, participants should be encouraged to provide urine and fecal sample (if appropriate) prior to 0800 or the dosing time each morning. To support assessment of daily Cu/Mo balance, on Days -4 through Day 30, at every mealtime, an additional meal will be prepared from the same batch as the meals being given to the study participants and will be analyzed for Cu and Mo content. A minimum of 3 complete meals from each prepared batch will be sent for analysis.

Copper balance is defined as the difference between the measured Cu input in food and drink, and the measured Cu elimination in urine and feces, and will be calculated as the average daily

Cu balance over the collection period. For assessment of ALXN1840 effect on Cu balance, the time period for analysis will take into consideration the average bowel transit of approximately 40 hours (male: 33 hours; female: 47 hours) (Camilleri, 1986; Metcalf, 1987; Weaver, 1984). Collection over the entire 15 days of ALXN8140 treatment allows a robust average assessment of Cu balance and ensures a complete assessment of Mo ADME. The study assumes insensible loss due to sweat does not change significantly with ALXN1840 treatment and is therefore not measured. While menstruation is not anticipated to significantly impact Cu/Mo balance, it may have minor impact on interpretation of the urine data. Dates of menstruation should be collected to help support data interpretation.

Mo mass balance, as a measure of ALXN1840 ADME, will be calculated in an analogous fashion to Cu balance; however, the Mo balance will also include the Mo content in ALXN1840 as part of the Mo intake in the calculation. Following the final ALXN1840 dose administration on Day 15, intake and output collection will continue through Day 30 to characterize the extent of Mo and Cu elimination, which may allow for better understanding of Mo and Cu elimination after dose discontinuation.

Intensive blood sampling for PK/PD will occur over the 24-hour dosing periods on Day 1 and Day 15. Additional PK/PD sampling will occur as noted in the Schedule of Activities (Table 1).

4.2. Scientific Rationale for Study Design

As both healthy and WD animal models have supported the characterization of tetrathiomolybdate's (ALXN1840) mechanism of action, namely liver Cu depletion through mobilization of Cu into plasma and bile and excretion into feces, healthy participants are adequate for assessing the mechanism of action of ALXN1840 on Cu balance, which is the primary objective of this study. The inclusion and exclusion criteria for this study are consistent with typical Phase 1 clinical pharmacology studies for assessing the medication of interest. To limit the risk of Cu depletion in healthy participants (or the risk of recruiting participants with abnormal Cu metabolism), only participants with serum Cu and ceruloplasmin above the lower limit of normal will be included.

The 15-day duration for ALXN1840 dosing is supported by both preclinical and clinical data. Preclinical models suggest that Cu excretion in feces may be increased or at least sustained with repeated-dose administration over 5-8 days. With gastrointestinal transit in humans being somewhat longer than most animal models (Mason, 1988; Ogra, 2000), a 15-day repeat dose is considered reasonable. Based on studies in oncology patients, a dose of 30 mg/day for 28 days resulted in a substantive reduction in ceruloplasmin (Lin, 2013). Copper-containing ceruloplasmin, known has holo-ceruloplasmin, has a half-life of approximately 5 days, and serum ceruloplasmin concentrations (largely determined by holo-ceruloplasmin) are indicative of reduction in total body Cu load (Harris, 1997; Sternlieb, 1961). Taken together, a dose of 30 mg/day for 15 days is expected to result in a net negative Cu balance in healthy participants with an acceptable safety profile.

Following ALXN1840 administration, the active drug moiety tetrathiomolybdate rapidly binds Cu to form TPC in the liver and blood and presents as such in the systemic circulation. If TPC is not rapidly formed, tetrathiomolybdate spontaneously undergoes serial hydrolysis to form molybdate, the most common form of nutrient Mo, and is excreted in the urine. Total Mo concentration has been measured as a surrogate of ALXN1840 PK; however, total Mo

concentration cannot distinguish whether the Mo is complexed with Cu and albumin (as in TPC), free active ALXN1840 drug, intermediate hydrolysis products, or molybdate which may be from ALXN1840 hydrolysis. To better characterize the amount of non-TPC bound ALXN1840 and its degradation products, plasma ultrafiltrate Mo (PUF Mo), which represents the free parent drug (ALXN1840), short-lived intermediate hydrolysis products, and molybdate, will be measured. Total Mo and PUF Mo concentrations also include physiologic molybdate concentrations from dietary micronutrient molybdate intake. While it is not feasible to separate and quantify ALXN1840 directly in the plasma, total Mo PK and PUF Mo PK provide surrogate measures to characterize ALXN1840 exposure. To better characterize the ADME of ALXN1840, the PK of both total Mo and PUF Mo will be characterized and described.

Single dose administration of the enterically-coated ALXN1840 under fasted conditions in healthy participants resulted in a peak total Mo concentration, as stable TPC, at approximately 4.54 hours with a half-life of approximately 51 hours. In Study WTX101-HV-106, a 60-mg dose demonstrated a total Mo time to maximum concentration (T_{max}) of approximately 6 hours with up to 14% of the total Mo represented as PUF Mo, which also peaked at approximately 6 hours post dose. By 24 hours, PUF Mo had declined to approximately 3-5% of the total Mo. These findings are consistent with results from the Phase 2 Study WTX101-201 in patients with WD. Given the much longer half-life of total Mo, a repeat dose study of 15 days duration will support steady state assessment of ALXN1840 ADME (as measured by total Mo and PUF Mo). In addition, complete collection of Mo over the ALXN1840 treatment period as well as the 15-day terminal elimination period may support a complete assessment of Mo balance for the study.

As this study represents the first repeat dose study in healthy participants, dosing duration will be limited to 15 days. Safety laboratory tests will be monitored at least every 3 days with individual and cohort stopping criteria in place if significant safety risks are identified. In addition, if findings of Cu depletion or toxicity are identified in the initial study group by Day 18, the dose of ALXN1840 may be reduced to 15 mg/day for the remainder of the enrolled participants.

4.2.1. Participant Input into Design

Not applicable as this is a study in healthy participants.

4.3. Justification for Dose

The 30-mg dose selected for this study in healthy participants is within the 15 to 60 mg daily dose range that has demonstrated an acceptable safety profile in healthy volunteers and patients with WD in Phase 1 to Phase 3 clinical studies.

Repeated doses between 15 and 60 mg/day have been tested in the Phase 2 Study WTX101-201 and are being tested in the ongoing Phase 3 Study WTX101-301. A single oral dose of 60 mg has been tested in healthy volunteers in Phase 1 Studies WTX101-101, WTX101-102, and WTX101-HV-106, and has been well tolerated.

While most studies used high doses (120-300 mg/day or greater) of tetrathiomolybdate to rapidly deplete total body Cu as measured by ceruloplasmin, Lin et al reported use of bis-choline tetrathiomolybdate (ALXN1840) at a more modest dose of 30 mg/day in prostatic malignancy administered in 28-day cycles (Lin, 2013). At this dose, only a moderate reduction in ceruloplasmin was reported with the median value remaining just above 20 mg/dL (reference

range: 20-35 mg/dL). Only one Grade 3 hematologic finding of leukopenia was reported at this dose (during the study, which included up to four 28-day cycles of ALXN1840). The proposed dosing period for this study is half that of a single 28-day cycle, for which reports indicate that the safety risk is acceptable with adequate monitoring and management (Lin, 2013).

In addition to its use in both patients with WD and healthy volunteers, tetrathiomolybdate, the active anion in ALXN1840, has been used in a substantive number of oncology programs, and based on published data, bis-choline tetrathiomolybdate (ALXN1840) has been well tolerated up to a maximum tolerated repeated dose of 300 mg/day (Lowndes, 2008). Early oncology programs employed an induction approach with the use of high doses of tetrathiomolybdate followed by lower maintenance doses and used serum ceruloplasmin as a marker for depletion of total body Cu, with a target ceruloplasmin concentration between 5 and 15 mg/dL (Lowndes, 2008; Brewer, 2000; Lin, 2013; Pass, 2008; Henry, 2006). The most commonly reported AEs in oncology programs include fatigue, dizziness, myelosuppression (anemia, leukopenia, neutropenia, lymphocytopenia and/or thrombocytopenia), and gastrointestinal complaints (nausea, vomiting, diarrhea, constipation, flatulence, sulfur burps, anorexia). With the exception of the gastrointestinal complaints, reported AEs have largely been associated with over-decoppering. Myelosuppression is monitorable and has been shown to be reversible with correction of Cu deficiency. Occasional reports of liver function test abnormalities were also noted (Lin, 2013; Lowndes, 2008).

Based on the above safety and ceruloplasmin data, a dose of 30 mg/day for 15 days has been chosen for this study. The dose of 30 mg/day is 1/10th of the MTD identified in oncology patients. In addition, the reduction in ceruloplasmin concentration, which is considered a measure of total body Cu, suggests that a 30 mg/day dose may be sufficient to drive a net negative Cu balance during the treatment period.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA).

The end of the study is defined as the date the last participant completes the last visit shown in the SoA (Table 1).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Participants must be 18 to 45 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by medical evaluation with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluation (hematology, biochemistry, coagulation, and urinalysis) that are reasonably likely to interfere with the participant's participation in or ability to complete the study, or to potentially confound interpretation of study results, as assessed by the Investigator.
3. Have regular bowel movements (at least once per day)
4. Adequate venous access in the left or right arm to allow collection of study-required blood samples.
5. Willing and able to adhere to all dietary requirements of the study.

Weight

6. Body weight between 50 to 70 kg (inclusive) for female participants, and 65 to 85 kg (inclusive) for male participants, and body mass index (BMI) within the range 18 – 25 kg/m^2 (inclusive).

Sex

7. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    a. Male participants:

    - Male participants, if heterosexually active and with a female spouse or partner of childbearing potential or a pregnant or breastfeeding spouse or partner, must agree to use barrier contraception (male condom) for the duration of the study and for at least 3 months after the end of systemic exposure of the study intervention (ie, 3 months after the EOS Visit). Male participants must not donate sperm for at least 3 months after the end of systemic exposure of the study intervention (ie, 3 months after the EOS Visit).
    - Female spouses or partners of male participants who are of childbearing potential must use highly effective contraception as defined below and in Section 10.4, starting at least 1 menstrual cycle before (the male participant's) first study intervention administration and continuing until at least 3 months after the end of their male

partner's systemic exposure to the study intervention (ie, 3 months after the EOS Visit).

- Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy. For male participants who have had a vasectomy (with documented evidence of azoospermia if possible) and agree to use a barrier method (male condom) for the stated time period, no additional contraceptive method is required by their female partner.

b. Female participants:

- Female participants or female partners of male participants of childbearing potential (including breastfeeding females), if heterosexually active, must be willing to follow protocol specified contraception guidance starting at least 1 menstrual cycle before first study intervention administration and continuing for at least 3 months after the end of systemic exposure of the study intervention (ie, 3 months after the EOS Visit). Female participants must not donate ova for at least 3 months after the EOS (ie. 3 months after the EOS Visit).
- Female participants who are documented as being of non-childbearing potential as defined in Section 10.4 are exempt from contraception requirements.
- Highly effective contraceptive methods for female participants and female partners of male participants are described in Section 10.4:

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders, or psychiatric disorder. Any surgical or medical history which may significantly alter the absorption, metabolism, or elimination of drugs or constitute a risk when taking the study intervention; or interfering with the interpretation of data (eg, gastric bypass, cyclical vomiting, etc).
2. History or presence of gastrointestinal conditions including chronic constipation and irritable bowel syndrome
3. Supine blood pressure ≤ 90/60 mmHg or > 140/90 mmHg at Screening and on vital signs assessed prior to enrollment (Day -7); systolic or diastolic components outside of range should result in exclusion. Supine blood pressure should be taken after a minimum of 5 minutes in supine position. If vital signs are abnormal, two additional readings will be

taken. The mean of the 3 replicates will be recorded in the case report form (CRF) and used to determine inclusion.

4. Lymphoma, leukemia, or any malignancy except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
5. Breast cancer within the past 10 years
6. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin > upper limit of normal (ULN) of laboratory reference range at screening and at check-in (Day -8). At the discretion of the Investigator, a single repeat analysis may be performed per time point to assess eligibility. ALT, AST, and total bilirubin values on Day -1 must not exceed 1.3 x ULN to initiate ALXN1840 dosing on Day 1.
7. Serum Cu or serum ceruloplasmin below lower limit of normal on laboratory reference range at Screening
8. History of anemia or hemoglobin < 130 g/L for men and hemoglobin < 115 g/L for women at screening and at check-in (Day -8). At the discretion of the Investigator, a single repeat analysis may be performed per time point to assess eligibility.
9. History of benign ethnic neutropenia or absolute neutrophil count < 1500/uL; lymphocyte count below 1000/uL at check-in (Day -8). At the discretion of the Investigator, a single repeat analysis may be performed per time point to assess eligibility.
10. Blood donation or blood loss in excess of 500 mL in the 60 days prior to screening
11. ECG showing 120 ms > PR > 240 ms, QRS> 110 ms, and QTcF> 450 ms for men and QTcF> 480 ms for women at Screening and on Day -7 prior to enrollment. As with vital signs, if ECG interval measurements are abnormal, an additional 2 replicate measures will be performed with the mean of the 3 measured interval values used to confirm eligibility and recorded in the CRF.
12. Current or chronic history of liver disease or known hepatic or biliary abnormalities (except for asymptomatic gallstones). Participants with elevated total bilirubin or history of Gilbert's will be excluded from the study.
13. Any other significant disease or disorder which, in the opinion of the Investigator, may put the participant at risk or confound the interpretation of the results.
14. History of hypersensitivity to ALXN1840 or its excipients or any significant allergic reaction (eg, anaphylaxis or angioedema) to any product (eg, food, pharmaceutical).

Prior/Concomitant Therapy

15. Use or intended use of prescription medications (excluding oral contraceptives) within 14 days or 5 half-lives of the drug (whichever is longer) prior to Day -7, and/or intended use at any point over the duration of the study except with prior approval of Alexion.
16. Use of nonprescription/ over-the-counter medications, including herbal remedies and supplements, within 7 days or 5 half-lives of the drug (whichever is longer) prior to Day -7 and/or intended use at any point over the duration of the study.

Prior/Concurrent Clinical Study Experience

17. Exposure to more than 4 new chemical entities within 12 months prior to dosing
18. Current enrollment or past participation, within the last 90 days, before signing of consent in this or any other clinical study involving an investigational study intervention or any other type of medical research. Participants, involved in intervention studies using investigation or non-investigational drug with prolonged half-lives, are not eligible unless the time since last treatment has exceeded 90 days or 5 half-lives of the study intervention, whichever is longer. Those who participated in the non-interventional Cu/Mo balance test study C19029 conducted by Richmond Pharmacology Limited (RPL), London, the United Kingdom between 17 Oct 2019 and 27 Oct 2019 are eligible to participate in this study.

Diagnostic Assessments

19. Presence of hepatitis B surface antigen or positive hepatitis C antibody or RNA test result at screening or within 3 months prior to first dose of the study intervention.
    NOTE: Patients with positive Hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative Hepatitis C ribonucleic acid (RNA) test result is obtained. NOTE: The RNA test is optional and patients with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
20. Positive human immunodeficiency virus (HIV) antibody test

Other Exclusions

21. Female participants who are pregnant, as evidenced by a positive serum pregnancy test result at screening, or breastfeeding.
22. Prior exposure to ALXN1840.
23. Major surgery or hospitalization within 90 days prior to dosing on Day 1.
24. Use of tobacco in any form (eg, smoking, chewing or vaping), other nicotine-containing products in any form (eg, gum, patch, electronic cigarettes, or vapes), or any recreational inhalational product within 6 months prior to the planned first day of dosing.
25. Use of known drugs of abuse within 6 months prior to the planned first day of dosing.
26. History of significant alcohol abuse within 1 year prior to the screening visit, or clinical evidence of substance and/or alcohol abuse within the 2 years before screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (for both males and females), using the following NHS alcohol tracker http://www.nhs.uk/Tools/Pages/drinks-tracker.aspx.
27. Positive urine drug toxicology screen at Screening or on Day -8.
28. Alcohol consumption within 24 hours prior to study intervention administration or positive alcohol breath test at screening or on Day -8.
29. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

Participants must be able and willing to adhere to the lifestyle restrictions detailed in Table 4.

Table 4: Healthy Participant Lifestyle Considerations

Restrictions	Timeframe restriction applies	Restrictions end
Food Participants will remain on a Cu/Mo controlled diet. Standardized Cu- and Mo-controlled meals will be provided as described in the SoA (Table 1). Male participants will receive larger meals than female participants, with adequate meal size to ensure appropriate daily caloric intake. If a participant is unable to eat 100% of the food, the remaining food will be weighed and reported in the CRF to support Cu/Mo determination as a fraction of the total meal. Participants will be expected to fast overnight. During the dosing period (Day 1 through Day 15), participants will be administered ALXN1840 with 240 mL of water each morning; participants must remain fasted for a least 2 hours after dose administration. Participants must allow for collection of all stool and urine from Day -4 through Day 30)	Dietary restrictions will remain in place from Day -7 through Day 30	Participants may return to routine diet after completion of Day 30.
Fluids All participants will drink water from the same large water bottle dispenser. There will be no set maximum volume of water that the participants must consume, but there will be a minimal volume that they must consume each day (1.5 L). The precise volume that each participant consumes will be measured.	Water restrictions will remain in place from Day -7 through Day 30	Participants may return to routine fluid intake after completion of Day 30.
Tobacco in any form (eg, smoking or chewing), other nicotine-containing products in any form (eg, gum, patch, electronic cigarettes), or any recreational inhalational product.	From Screening to EOS visit.	Restrictions ends after completion of EOS visit.
Not consume any other substances known to be potent inhibitors or inducers of CYP450s. This includes food or drink products containing cranberry, pomegranate, star fruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits). Red wine should also not be consumed.	Within 7 days before check-in to the CRU (Day -8) until discharge on Day 31.	After discharge from the CRU.
Caffeine-containing or xanthine-containing products (eg, tea, coffee, cola drinks, and chocolate).	During each dosing period, 24 hours before check-in to the CRU (Day -8) through Day 30.	After collection of the final PK sample for the study (Day 30).
Energy drinks or drinks containing taurine, glucuronolactone (eg, Red Bull).	48 hours before check-in to the CRU (Day -8) through EOS visit.	Restrictions ends after completion of EOS visit.

Restrictions	Timeframe restriction applies	Restrictions end
Alcohol	48 hours before check-in to the CRU (Day -8) and until discharge (Day 31), and 48 hours before each study outpatient/Follow-up Visit.	Discharge from the clinical research unit and completion of EOS visit.
Physical Activity Participants will carry out daily scheduled light exercise. This is to help encourage regular bowel movements and for health benefits to the participants. Participants must refrain from strenuous activity four 24 hour prior to each for the duration of the study.	48 hours prior to check-in to the CRU (Day -8) and until discharge (Day 31).	Restrictions ends after completion of EOS visit.
Any prescription medication. Concomitant prescription medications may be used during the study to treat adverse events as deemed medically indicated by the investigator. The investigator or delegate will notify the Sponsor of any adverse events requiring administration of prescription medication(s) while on study. Note: Investigator in consultation with the Sponsor should determine participant's continued suitability to remain in the study.	14 days or 5 half-lives (whichever is longer) prior to Day -7 through EOS visit.	Restrictions ends after completion of EOS visit.
Any nonprescription/over-the-counter medication, including herbal remedies and supplements. For details, Section 6.5.1.	Nonprescription/over-the-counter medications may be used for adverse events under the direction and at the discretion of the investigator including up to 1000 mg/day of paracetamol/acetaminophen.	After the EOS visit.
Any herbal remedy or dietary supplement containing St John's Wort.	2 weeks before the planned first study intervention is administered.	After EOS visit.
Blood and plasma donation	Blood donation or blood loss in excess of 500 mL in the 60 days prior to screening (Section 5.2)	1 month after EOS visit.
Contraception: Participants must consistently and correctly use one or more of the appropriate contraceptive methods described in Section 10.4.	Start times for contraceptives vary according to method used (see inclusion criteria #7).	See Section 10.4.

Abbreviations: CRF = case report form; CRU = clinical research unit; Cu = copper; CYP450 = cytochrome CYP450; EOS = end of study; Mo = molybdenum; PK = pharmacokinetic.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details

(eg, failed eligibility criteria), and any AEs, including any serious adverse events (SAEs) and any related concomitant medication, occurring during the screening period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention Administered

Details of ALXN1840 administered in the study are provided in Table 5.

Table 5: Details of Study Intervention Administered

Arm Name	**Study Intervention**
Intervention Name	ALXN1840 (formerly WTX101)
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	15 mg ALXN1840 containing 7.8 mg of tetrathiomolybdic acid
Dosage Level(s)	Repeat dose 30 mg administered as 2 × 15 mg ALXN1840 tablets for 15 days
Route of Administration	Oral
Use	experimental/study intervention
IMP and NIMP	IMP
Sourcing	Provided centrally by Alexion
Packaging and Labeling	The labeling of study intervention will be in compliance with Good Manufacturing Practice specifications, as described in the Rules Governing Medicinal Products in the European Union, Volume 4, annex 13, Investigational Medicinal Products, and any other or local applicable regulations. Sample labels will be submitted to the UK health authorities according to the submission requirements.
Current/Former Name(s) or Alias(es)	Bis-choline tetrathiomolybdate

Abbreviations: IMP = investigational medicinal product; NIMP = noninvestigational medicinal product.

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
    a. The ALXN1840 treatment kits should be stored at refrigerated conditions, 2°C to 8°C (36°F to 46°F).
2. Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator and/or qualified delegate (ie, Pharmacist) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any product complaints to PPD within 1 business day. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies

related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical trial material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.

4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinding and randomization are not applicable. This is an open-label study in which all participants are expected to receive the same dose of ALXN1840.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and in the CRF (if the CRF is not the source document). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

For additional information on study intervention compliance and management, refer to the Pharmacy Manual.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest) that the participant is receiving from 14 days prior to study enrollment (Day -7) until the end of study visit must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant and/or prior therapy.

6.5.1. Allowed Medicine and Therapy

- Paracetamol/acetaminophen at doses of a maximum 1000 mg per day is permitted for use as an exception with the approval of the Investigator.
- As per the ALXN1840 IB, in this study, Investigators should use caution in the co-administration of drugs known to be substrates of cytochromes 2C9 and 2B6 (CYP2C9 and CYP2B6). Common substrates of CYP2C9 include ibuprofen, which is permitted in this study. The Investigator must use ibuprofen with caution during the

conduct of the study, and the ibuprofen dose must not exceed 1200 mg in any 24-hour period. Ibuprofen may only be used with approval of the Investigator.

- Concomitant procedures are not allowed unless medically indicated and/or permitted by Alexion or the Investigator or designee.
- Concomitant medications may be used during the study if deemed medically indicated by the Investigator. The Investigator or designee will notify Alexion of any AEs requiring administration of prescription medication(s) while on study.

6.5.2. Disallowed Medicine and Therapy

Participants must abstain from taking prescription medications within 14 days or 5 half-lives (whichever is longer) of Day -7 or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before Day -7 and until completion of the follow-up visit, except as described in Section 6.5.1.

6.6. Dose Modification

Asymptomatic elevations of hepatic transaminases and gamma glutamyltransferase have been reported in patients with WD treated with ALXN1840 and have occasionally been seen in ALXN1840 single dose studies in healthy volunteers, and in published data from oncology studies. Liver enzymes will be monitored a minimum of every 3 days throughout the study. In addition, chronic treatment with ALXN1840 may result in anemia, leukopenia or thrombocytopenia due to over-decoppering. As this is the first repeat-dose study to be conducted in healthy participants, complete blood count with platelets will also be monitored a minimum of every 3 days. Ceruloplasmin concentrations will be measured and may be used as appropriate to guide group dosing decisions.

If laboratory tests result in abnormal values, it will be expected that the tests are repeated to confirm those results. Depending on the severity of the abnormal values, laboratory tests may be checked as frequently as daily; it is at the discretion of the Investigator to track abnormal values. Results from non-scheduled safety laboratory assessments must be recorded in the CRF.

Alexion should be notified within 24 hours of any laboratory, vital sign, ECG abnormality or AE that are considered of clinical concern by the Investigator. Investigators must notify Alexion immediately of drug discontinuation. The decision to discontinue drug should not be delayed for causality assessment.

Following dosing of the first group of approximately 6-8 participants, if ceruloplasmin concentrations or AE findings are suggestive of Cu depletion, the SRC (Section 9.7) may reduce the dose to 15 mg/day for the remainder of the study population.

Dose modification guidelines will be specified as follows.

6.6.1. Adverse Reaction Rules

An adverse reaction is any treatment emergent adverse event (TEAE) that is considered related to the study medication (for a full definition of related TEAEs, see Section 10.3.3). When a TEAE occurs, timely determination of relatedness is not always feasible. In such cases, the

Investigator and Alexion should use judgment in protecting the individual patient and study population.

6.6.1.1. General Adverse Reaction Rules

The general adverse reaction rules refer to all adverse reactions, excluding those relating to the liver and hematology and QT interval prolongation. The Common Terminology Criteria for Adverse Events (CTCAE) may not give clear enough guidance, and grading may not be appropriate for this study in healthy volunteers; therefore, special study-specific rules have been created.

6.6.1.2. Individual Adverse Reaction Rules

An individual participant will not receive any further dose(s) of ALXN1840, if either of the following occurs:

- Participant experiences any CTCAE Grade 3 (or higher) adverse reaction, or a serious adverse reaction, irrespective of severity/CTCAE grade.
- Participant experiences any CTCAE Grade 1 or 2 adverse reaction considered to be related to ALXN1840 and considered a safety concern by the SRC.

6.6.1.3. Group Adverse Reaction Rules

Dosing will be suspended for all participants or potentially only in an affected dose group (in the event a dose reduction is employed for the second group), if either of the following occurs:

- One participant experiences a non-serious, severe (CTCAE Grade 3) adverse reaction.
- One participant experiences a serious adverse reaction, irrespective of severity/CTCAE grade.
- One participant experiences a Grade 2 or higher adverse reaction which is considered by the SRC of significant medical consequence to the remaining group to require discontinuation of dosing to the remainder of the group

In the event of suspension of dosing, continuation of the study will require a protocol amendment that has been approved by the MHRA and ethics committee.

6.6.1.4. Special individual Adverse Reaction Rules

Dosing in an individual participant will be suspended if they experience any of the following:

- Liver function test elevation
  - ALT or AST value > 3 × ULN in the presence or absence of symptoms. Grade 2 or higher by NCI CTCAE v 5.0.
  - Any possible Hy's law case will be considered a serious adverse event defined as ALT ≥ 3 × ULN AND total bilirubin ≥ 2 x ULN (or 35% increase in direct bilirubin) or INR > 1.5 (if measured)

  - Any ALT or AST or other liver function test elevation or trend in elevation that in the opinion of the Investigator and/or Alexion may place the participant at risk if dosing is continued

- Hematology
  - Hemoglobin reduction to an absolute value of 9.5 g/dL (95 g/L) or lower. Because of the repeated blood draws in the study, an addition 0.5 g/dL (5 g/L) over the Grade 2 CTCAE v 5.0 value may be tolerated at the investigator discretion and based on clinical judgment.
  - Platelet count reduction to an absolute value < 75,000/mm^3, defined as Grade 2 or higher by NCI CTCAE v 5.0
  - Any hematologic abnormality that in the opinion of the investigator and Alexion may place the participant at risk if dosing is continued
- QT interval prolongation
  - A prolongation of the QTcF interval of > 500 ms (using consistent, technically valid triplicate ECG)

6.6.1.5. Special group Adverse Reaction Rules

- For special group adverse reaction stopping rules (ie transaminase elevation, hematologic abnormalities and QT prolongation), dosing will be suspended for all participants or to the dosing group if any of the following occurs:
  - One or more participants experience a non-serious, severe (NCI CTCAE Grade 3) or higher adverse reaction.
  - One or more participants experience a serious adverse reaction, irrespective of severity/CTCAE grade
  - One or more participants experience a Grade 2 or higher adverse reaction that is considered by the SRC of significant medical consequence to the remaining group to require discontinuation of dosing to the remainder of the group

6.6.1.6. Safety Oversight and Implementation Stopping Rules

- If one or more participants fulfills criteria from either the individual adverse reaction rules (outlined in Section 6.6.1.2 and/or Section 6.6.1.4) or for group adverse reaction rules (outlined in Section 6.6.1.3 and/or Section 6.6.1.5), a SRC meeting will be arranged. At this meeting, a decision will be made regarding the continuation/discontinuation of dosing for the remaining participants as well as need for dose modification. Based on the severity and medical risk to other participants and on request of either the Investigator or Alexion, dosing for all participants will be temporarily suspended until the SRC meets.
- The SRC will meet following completion of Day 18 of Group 1 to confirm adequate safety to complete dosing at 30 mg/day. Dose reduction to 15 mg/day may be made

following review of Group 1 data if there is evidence of over-decoppering as determined by AEs and/or ceruloplasmin concentration.

- The SRC will be comprised of, at minimum, the Investigator and Alexion's Medical Monitor. Additional site staff and Alexion personnel may also be included and will be responsible for reviewing all safety data and making determination around dosing.
- In the event of suspension of dosing, continuation of the study will require a protocol amendment that has been approved by the MHRA and ethics committee.

6.7. Intervention After the End of the Study

This is a healthy participant study and no follow-up intervention is planned.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention. If the study intervention is definitively discontinued, the participant should remain in the study to be evaluated for safety follow-up. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in the Dose Modification criteria (Section 6.6) or if the Investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Participants must be considered for discontinuation from intervention if any of the following occur during the study:

- Serious hypersensitivity reaction;
- Severe uncontrolled infection;
- Use of disallowed medication;
- Pregnancy or planned pregnancy (see Section 8.2.6); or
- Alexion or the Investigator deems it is necessary for the participant.

See the SoA (Table 1) for samples and data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal From the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and CRF.
- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuation from the study, participants will be seen and assessed by the Investigator or study physician and whenever possible, will undergo the procedures associated with the early termination visit. as shown in the SoA. See the

SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

No efficacy assessments will be obtained during this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, study intervention administration, and meal.

PK collection should occur as close as possible to the scheduled time.

All routine safety laboratory samples should be drawn following a minimum of 8 hours fasting.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at Screening only) and weight (as per the SoA for physical examinations) will also be measured and recorded. A symptom-driven physical examination may be performed at other times, at the Principal Investigator's discretion.

8.2.2. Vital Signs

- Body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg) will be assessed using consistent methods and equipment to allow comparability and reproducibility throughout the study.
- Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and heart rate. Vital signs will consist of a single pulse and blood pressure measurement. If vital signs are abnormal as defined by inclusion/ exclusion criteria, 2 additional vital signs measurements will be made. The average of the 3 vital signs measurements will be recorded in the CRF and used to determine patient eligibility. The average of the blood pressure readings will be recorded in the CRF.

8.2.3. Electrocardiograms

- Triplicate 12-lead ECGs will be conducted as outlined in the SoA (see Section 1.3) to obtain heart rate, PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary. As with vital signs, if ECG interval measurements are abnormal, an additional 2 replicate measures will be performed with the mean of the 3 measured interval values used to confirm eligibility and recorded in the CRF.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant laboratory values are those deemed by the investigator to be clinically significant resulting in further evaluation or treatment or those associated with an AE or clinical signs or symptoms.
- All laboratory test results with values considered abnormal and clinically significant during participation in the study after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
  - All laboratory values from non-protocol specified laboratory assessments must also be recorded in the CRF.

8.2.4.1. Bowel and Urine Monitoring

Participants' bowel movements and urination will be monitored by the clinical staff. The clinical staff will record each time a fecal and urine sample is collected in the CRF. All urine and feces must be collected from Day -4 through Day 30. Day -4 through Day -1 will represent the pretreatment baseline, Day 1-15 will represent the treatment period and Day 16-30 will represent the post-treatment period.

8.2.4.2. Intake monitoring

To support accurate quantification of Cu/Mo intake, each participant's intake including both food and fluids will be monitored and recorded. Following each standardized meal, the clinical staff will record 100% completion of each meal including all liquids. If a participant is unable to eat 100% of the food for a given meal, the remaining food will be weighed and reported in the CRF to support accurate determination of Cu/Mo as a fraction of the total meal. Similarly, if participants do not complete 100% of non-water fluids with meal, the remaining volume will be measured and recorded in the CRF. In the case of water intake, the staff will record daily water volume intake in the CRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Not applicable to this study.

8.2.6. Pregnancy

- Pregnancy data from female participants and female spouses/partners of male participants will be collected from the signing of the ICF at the time points specified in the SoA. Any female participant who becomes pregnant while participating in the study will be discontinued from the study intervention. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.4.
- For all Alexion products, both in development or post-approval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The corresponding infant must be followed-up with for 3 months postpartum. Exposure of an infant to an Alexion product during breastfeeding must also be reported (see Section 10.3 for contact information).
- Pregnancy is not considered as an AE (Section 10.4) unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly) (Section 8.3). Elective abortions without complications should not be reported as AEs.

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

All AEs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until EOS visit.

All SAEs will be recorded and reported to Alexion or the designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and Investigators.

- Suspected unexpected serious adverse reactions (SUSARs) must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Adverse Events of Special Interest

There are no adverse events of special interest for this study.

8.3.6. Retained and Biobanked Sample

A single biobanked serum sample will be collected predose from each participant to serve as a retained sample during the study. Samples will remain on site and will be discarded following the completion of the clinical study report.

8.4. Treatment of Overdose

For this study, any dose of ALXN1840 greater than that specified in the protocol will be considered an overdose.

Alexion does not recommend specific treatment for an overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

In the event of an overdose or suspected overdose, the Investigator or treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

- Whole blood samples will be collected for the measurement of plasma concentrations of total Mo and PUF Mo as specified in the SoA (Table 1) via inductively coupled plasma mass spectrometry (ICP-MS).
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples will be used to evaluate the PK of ALXN1840. Samples collected for analyses of plasma concentrations may also be used to evaluate safety aspects related to concerns arising during or after the study.
- Excess/additional samples may be stored for up to 5 years and used for PD and/or diagnostic biomarker development and research to understand the pathways associated with the mechanism of action of ALXN1840. These samples will not be used for genetic analyses (ie, RNA or DNA analyses).
- Genetic analyses will not be performed on these whole blood samples. Participant confidentiality will be maintained.
- See also Section 8.7 for details of Mo measured in food, drinks, urine, and feces.

8.6. Pharmacodynamics

Plasma total Cu, ceruloplasmin, ceruloplasmin-bound Cu, and LBC will be assessed during the study.

Blood samples will be collected as described in the SoA (Table 1) for plasma isolation as per the Laboratory Manual. The isolated plasma will be stored at -20°C before analysis. Plasma samples will be used for ICP-MS measurement of total Cu, ceruloplasmin, ceruloplasmin-bound Cu, and toxic copper as measured by LBC and/or NCC at the time points indicated in the SoA (Table 1).

8.7. Copper and Molybdenum Balance Measurements

Copper and Mo balance measurements will be made on all intake (ie, investigational agent, food and fluids) and all output (urine and feces) from participants as indicated in the SoA. The Cu and Mo concentration of each sample will be determined by ICP-MS. Cu and Mo content of all intake and output will be calculated based on the volume or weight of intake and output and the concentration of representative samples.

8.7.1. Food and fluid collection for Cu and Mo concentrations

Samples of all meal and fluid batches will be collected and analyzed for measurement of Cu and Mo content. A minimum of 3 complete portions/meals from each food and liquid batch will be sent for analysis. All participants will drink water from the same large water bottle dispenser. Samples of water from this dispenser will be collected and analyzed for Cu and Mo content.

Samples will be collected, stored and shipped as detailed in the Laboratory Manual. All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage, and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail in the Laboratory Manual. Copper and Mo concentration of each food sample (ng/g) and each fluid sample (ng/ml) sample will be determined by ICP-MS.

8.7.2. Urine Collection for Measurement of Copper and Molybdenum content

Urine samples to measure Cu and Mo content will be taken on Day -4 through Day 30, as described in the SoA (Table 1). Samples will be collected, stored and shipped as detailed in the Laboratory Manual. For each 24-hour collection period, urine will be pooled for analysis and volumes will be recorded. All sample handling procedures, including the time of each sample

collection, the time of placement into frozen storage, and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail as described in the Laboratory Manual. Copper and Mo concentration (ng/mL) of each 24-hour urine sample will be determined by ICP-MS.

Fecal Collection for Measurement of Copper and Molybdenum content

Fecal samples to measure Cu and Mo content will be taken on Day -4 through Day 30 as described in the SoA (Table 1). Samples will be collected, stored and shipped as detailed in the Laboratory Manual. Fecal samples will be individually collected, weighed and stored. The weight and time of each bowel movement will be recorded. All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage, and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail in the Laboratory Manual. Copper and Mo concentration (ng/g) of each stool sample will be determined by ICP-MS; each sample will be analyzed using a minimum of technical triplicates.

8.8. Genetics

Genetics are not evaluated in this study.

8.9. Biomarkers

Please see Section 8.6 for details of total Cu, ceruloplasmin, ceruloplasmin-bound Cu, and toxic copper as measured by LBC and/or NCC, and Section 8.7 for details of Cu measured in food, drink, urine, and feces.

8.10. Immunogenicity Assessments

Not applicable.

8.11. Health Economics Data and/or Medical Resource Utilization

Health economic and medical resource utilization parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

Not applicable.

9.2. Sample Size Determination

The study sample size is not based on null hypothesis significance testing. A sample size of 13 participants has been selected based on convention for this type of study (Strickland, 1971). To accommodate a 25% dropout rate, approximately 17 participants will be enrolled to achieve 13 evaluable participants.

9.3. Populations for Analyses

The population sets used for analysis sets are defined in Table 6.

Table 6: Populations for Analyses

Population	Description
Screened	All participants who sign the ICF
Enrolled	All participants who sign the ICF, are eligible for the study, and are registered on Day -7
Safety Set	All participants who receive at least 1 dose of ALXN1840
Full Analysis Set	All participants who receive at least 1 dose of ALXN1840
Per Protocol Set	All participants who receive at least 1 dose of ALXN1840 and have both baseline and Day 15 values. Participants with major protocol deviations that are likely to impact the primary efficacy endpoint analysis will be excluded from the Per Protocol Set. Major protocol deviations, and the Per Protocol Set, will be defined, documented, and agreed within Alexion prior to database lock.
Pharmacokinetic/Pharmacodynamic Analysis Set	All participants who have sufficient samples to enable the calculation of PK parameters and provide PK/PD profiles

Abbreviations: ICF = informed consent form; PK = pharmacokinetics

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP). Summary statistics will be computed and displayed by day and period (predose baseline, treatment, steady state, and post-treatment) where applicable. Descriptive statistics for continuous variables will minimally include the number of participants, mean, SD, minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate.

Analyses will be performed using the SAS® software Version 9.4 or higher.

9.4.1. Efficacy Analyses

No efficacy endpoints are included as part of this study, therefore there is no analysis of efficacy.

9.4.1.1. Analyses of Primary Endpoint

The primary objective of this study is to assess the change from baseline in average daily Cu balance after 2 weeks of ALXN1840 treatment at 30 mg/day in healthy participants. Secondarily, the study will also assess whether a net negative Cu balance is achieved following ALXN1840 treatment. The study will also assess Mo balance at ALXN1840 PK steady state.

The primary analysis will be performed using the Full Analysis Set. Change from baseline in average daily Cu balance over Days 4 to 15 will be summarized using descriptive statistics based on data as observed. The 95% confidence limits for the mean change from baseline will be provided.

Copper balance is defined by the difference in Cu input and Cu output. A negative Cu balance will indicate greater Cu output than Cu intake. Copper input is defined as the sum of all Cu input as measured in all food and fluids over the specified period. Copper output will be defined as the sum of all Cu output as measured in urine and feces over the specified collection period. Daily balance values may also be calculated. The study assumes insensible Cu/Mo loss due in sweat does not change significantly with ALXN1840 treatment and is therefore not measured. While menstruation is not anticipated to significantly impact Cu/Mo balance, it may have minor impact on interpretation of the urine data. Dates of menstruation should be collected to help support data interpretation.

Mo mass balance is defined as the difference in Mo input and Mo output. It will be calculated in an analogous manner as Cu balance and includes the additional Mo intake from ALXN1840. Mo mass balance will be calculated at steady state (Day 12 through Day 15) and over the entire treatment period (Day 1 through Day 30).

The average daily Cu and Mo balance, and/or change from baseline in average daily Cu and Mo balance will be calculated using data from the following periods:

- Day -4 through Day -1 representing the pre-dose baseline period (Cu/Mo balance)
- Days 4 through Day 15 representing the 30 mg/day treatment period (Cu balance for primary and secondary endpoints)
- Day 1 through Day 15 ALXN1840 treatment period (Mo mass balance and Cu as exploratory analyses)
- Days 12 through Day 15 representing steady state treatment period (steady state Mo/Cu balance)
- Days 1 through Day 30 representing the entire treatment and post-treatment period (total Mo and Cu balance)

As ALXN1840 is expected to increase Cu removal through fecal excretion, Cu in stool will be critical for determining Cu balance. Because stools can be irregular, assessment of Cu and Mo balance will only include data up to the day of the final bowel movement. For example, if for the Day 1 through Day 15 collection period, the final bowel movement occurs on Day 14, average daily Cu balance for the Day 1 through Day 15 period will only include data averaged from Day 1 through Day 14 (and Day 15 data will be omitted). In the case of the primary endpoints, calculations will be based on data starting on Day 4.

To improve understanding of the effects of ALXN1840 treatment duration, individual periods may be sub-segmented. For example, Day 1 through Day 15 may be divided into Day 1 through Day 5, Day 6 through Day 10, and Day 11 through 15 to assess copper output early following treatment, in the middle of treatment period and at the end of treatment period.

In the case of the 30 mg/day steady state period for Mo balance, fecal data collected on Days 16 and 17 may be used if needed to support assessments for the 30 mg/day Mo steady balance. Use of this fecal data (as needed) is consistent with an approximately 2-day gastrointestinal transit time.

In the case of bowel movement irregularity and to support assessment of Cu output over time, bowel movement Cu and Mo outputs may be averaged over the days between bowel movements (or start of study) to ensure an approximate value for each 24-hour period as needed for calculations. The 24-hour collection period is defined as relative to the first ALXN1840 dose administration.

Additional details will be provided in the SAP.

9.4.1.2. Analyses of Secondary Efficacy Endpoint(s)

Secondary analyses will be performed using the Full Analysis Set. The secondary continuous endpoints (Cu balance, Mo balance, urinary excretion, etc.) will be analyzed using the same methods described for the primary analysis.

9.4.1.3. Analyses of Exploratory Endpoint(s)

Details of the analysis of exploratory endpoints will be provided in the SAP.

9.4.2. Safety Analyses

All safety analyses will be made on the Safety Set.

Safety analyses will include all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics.

No inferential statistical analyses are planned for the safety parameters of this study. The incidence of AEs and SAEs will be summarized by System Organ Class and Preferred Term for each treatment and overall, and by relationship to study intervention. Adverse events will also be summarized by treatment and overall by severity. Serious AEs and AEs resulting in withdrawal from the study will be listed. Participants having multiple AEs within a category (eg, overall, System Organ Class, Preferred Term) will be counted once in that category. For severity tables, a participant's most severe event within a category will be counted.

Changes from baseline in vital sign measurements and laboratory assessments (eg, chemistry, blood cell count with differential, and urinalysis) will be summarized by treatment. Laboratory parameter values will be graded according to the National Cancer Institute CTCAE. Shift tables by treatment will be produced for these laboratory parameters. These tables will summarize the number of participants with each baseline grade relative to the reference ranges and changes to the worst highest grade assessed post-dose during the study.

ECG parameters will be measured at the specified time points as per the SoA (Table 1), including heart rate, PR, RR, QRS, QT, and QTcF intervals. The average of the triplicate ECG

readings at the time points collected will be calculated, and changes from pretreatment baseline values will be assessed by each treatment.

All concomitant medications will be coded and summarized using the World Health Organization (WHO) Drug Dictionary.

9.4.3. PK/PD Analyses

For PK endpoints, analyses will be performed using the PK Analysis Set. Individual plasma total Mo and PUF Mo (as surrogate measures of ALXN1840) concentration-time data will be listed and plotted. The following total Mo (ALXN1840) PK parameters will be derived for individual participants and summarized with descriptive statistics. Analyses of PUF Mo may also be conducted:

- Maximum observed concentration (C_{max}), time to maximum concentration (t_{max}), AUC from time 0 to the time of last measurable concentration (AUC_t), AUC from time 0 to infinity (AUC_∞), apparent terminal-phase elimination rate constant (λ_z), $t_{½}$, clearance bioavailability (CL/F), and apparent volume of distribution (V_d/F).

For exploratory endpoints such as plasma total Cu, ceruloplasmin, ceruloplasmin-bound Cu, and toxic copper as measured by LBC and/or NCC, a concentration-time data will be listed and summarized with descriptive statistics and plotted. The same analyses will be conducted on the absolute and percent changes from baseline of these concentration-time data.

9.5. Interim Analyses

No interim analysis is planned.

9.6. Data Monitoring Committee

There will not be a Data Monitoring Committee, but provision is included for an SRC (Section 9.7).

9.7. Safety Review Committee

An SRC, composed of a minimum of the Investigator and Alexion's medical monitor, will review safety information from the first group (approximately 6-8 participants) through Day 18 including all AEs, safety laboratory data, and vital sign assessment and agree that it is safe to continue enrollment to complete the study. If ceruloplasmin concentrations or AEs findings are suggestive of Cu depletion, the SRC may propose a dose reduction to 15 mg/day for the remainder of the study population

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by UK legislation as a serious breach or as required by IRB/IEC procedures.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator to obtain signed (written or electronic signature) ICF from all study participants prior to any study-related procedures including screening assessments.
- The Investigator or his/her representative will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent or a certified translation if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that signed (written or electronic) informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Signed (written or electronic) consent [or assent] forms must remain in each participant's study file and must be available for verification at any time.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the participants who will be required to give consent for their data to be used as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, www.clinicaltrials.gov or www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the first participant is consented.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the end of study or early discontinuation visit, all data have been collected and entered into electronic data capture (EDC) system, all required documents and study supplies have been collected, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and to provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- In general, primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.

  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.

- Alexion will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the local laboratory or central laboratories as appropriate.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Investigators must document their review of each laboratory safety report and indicate whether out of range results are clinically significant or not clinically significant.
- Women of childbearing potential should only be enrolled after a negative serum pregnancy test result at screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRBs/IECs and should be performed per the time points specified in the SoA (Section 1.3). Screening pregnancy criteria are detailed in Section 5.1.

Table 7: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Clinical Chemistry	Blood urea nitrogen
	Potassium
	Creatinine
	Creatine kinase
	Sodium
	Chloride
	Potassium
	Glucose
	HbA1c
	Bicarbonate
	Aspartate aminotransferase
	Gamma glutamyltransferase
	Alanine aminotransferase
	Alkaline phosphatase
	Urea
	Magnesium
	Total and direct bilirubin
	Total protein
	Albumin
	Calcium
	Phosphate
Hematology	Platelets
	White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
	Mean cell hemoglobin
	Neutrophils
	Monocytes
	Basophils
	Hemoglobin
	Mean corpuscular volume
	Mean cell hemoglobin concentration
	Lymphocytes

	Eosinophils
Coagulation	Prothrombin time - International Normalized Ratio
	Partial Thromboplastin Time
Urinalysis	Bilirubin
	Glucose
	Leukocytes
	Nitrite
	Protein
	Urobilinogen
	Blood
	Ketones
	Microscopy, if required
	pH
	Specific gravity
	Red blood cells
Other Tests	Human immune deficiency virus (HIV)-1 and HIV-2 antibodies, HBsAg, anti-HBC IgG + IgM (if IgG positive), and anti-hepatitis C virus (HCV) with confirmation by HCV ribonucleic acid (RNA)
	Ceruloplasmin (serum) (safety)
	Serum Cu (safety)
	Ceruloplasmin (plasma)
	Ceruloplasmin-bound Cu
	Pooled 24-hour urine Cu and Mo
	Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
	Alcohol breath and urine drug screen (to include at minimum: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, methamphetamine, 3,4-methylenedioxy-methamphetamine, methadone, and tetrahydrocannabinol [cannabinoids])[a]
	Total Cu and total Mo
	PUF Mo and Cu
	LBC and/or NCC
	Follicle-stimulating hormone (FSH) (postmenopausal females only)

Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 6.6.1.5. All events of ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Abbreviations: Cu = copper; LBC = labile bound Cu ; NCC = non-ceruloplasmin bound Cu ; Mo = molybdenum; PUF = plasma ultrafiltrate

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events Not Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

1. Results in death

2. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v 5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the CRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study intervention.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to GDS via Paper Safety Reporting Form
• All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours awareness. • SAEs will be reported using the Safety Reporting Form and submitted to Alexion GDS. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below: – Email: PPD or Fax: PPD • Additional follow-up information, if required or available, should be entered into the CRF and sent to Alexion GDS within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above. • For all SAEs, the Investigator must provide the following: – Appropriate and requested follow-up information in the time frame detailed above – Causality of the SAE(s) – Treatment of/intervention for the SAE(s) – Outcome of the SAE(s) – Medical records and laboratory/diagnostic information • All paper forms and follow-up information submitted to Alexion GDS **must** be accompanied by a cover page signed by the Investigator. • Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD): female participants with a Cu-containing IUD are excluded from study
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner o *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
• **Highly Effective Methods[b] That Are User Dependent**
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o Oral o Injectable o Intravaginal o Transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o Oral o Injectable
• Sexual abstinence o *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c.) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)
Female participants of non-childbearing potential are exempt from contraception requirements. Non-childbearing potential for female patients is defined as any of the following: • Prior to first menses • Postmenopausal, as documented by amenorrhea for at least 1 year prior to the Day 1 visit and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status • Permanent sterilization at least 6 weeks prior to the Day 1 visit: – Hysteroscopic sterilization – Bilateral tubal ligation or bilateral salpingectomy – Hysterectomy – Bilateral oophorectomy

- Collection of pregnancy information
  - If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion Global Drug Safety (GDS) via fax or email (see Section 10.3 for contact information). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow up is required, the Investigator will be requested to provide the information. Further details are provided in Section 8.2.6.

Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the "Pregnancy/Breastfeeding Reporting and Outcome Form") and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile (see Section 10.3 for contact information).

10.5. Appendix 5: Abbreviations

A list of abbreviations and terms are used in this study protocol is provided in Table 8.

Table 8: List of Abbreviations and Definitions of Terms

Abbreviation	Definition
λ_z	apparent terminal-phase elimination rate constant
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_t	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
AUC_∞	area under the plasma concentration versus time curve from zero to infinity
BMI	body mass index
BSA	body surface area
CYP	cytochrome P450
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL/F	clearance bioavailability
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
Cu	Copper
EDC	electronic data capture
EOS	End of Study
ET	Early Termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Drug Safety
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	informed consent form

IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LEA	Long-Evans Agouti (normal Wistar rats)
LBC	labile bound copper
LEC	Long-Evans Cinnamon (Wilson disease model rats)
Mo	molybdenum
MT	metallothionein
NCC	non-ceruloplasmin-bound copper
$NCC_{corrected}$	corrected NCC
NIMP	noninvestigational medicinal product
PK	pharmacokinetic(s)
PUF	plasma ultrafiltrate
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SoC	standard of care
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
$t_{½}$	terminal elimination half-life
t_{max}	time to maximum concentration
TPC	Cu-tetrathiomolybdate-albumin tripartite complex formed after ALXN1840 administration
TTM	tetrathiomolybdate
ULN	upper limit of normal
UWDRS	Unified Wilson Disease Rating Scale
V_d/F	apparent volume of distribution
WD	Wilson disease
WHO	World Health Organization

10.6. Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY		
Document	**Date**	**Overall Rationale for the Amendment**
Original protocol	10 Mar 2020	Not applicable
Amendment 1	07 Apr 2020	To clarify text regarding temporary suspension of dosing if one or more participants fulfils criteria from the adverse reaction rules.

Amendment 1 (07 Apr 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This amendment has been prepared to clarify text regarding temporary suspension of dosing if one or more participants fulfills criteria from the adverse reactions rules.

Change to the Protocol

Section # and Name	**Description of Change**	**Brief Rationale and/or Clarifications**
Section 6.6.1.6 Safety Oversight and Implementation Stopping Rules	The word "may" has been replaced with "will" in the following sentence: • Based on the severity and medical risk to other participants and on request of either the Investigator or Alexion, dosing for all participants ~~may~~ **will** be temporarily suspended until the SRC meets.	The change was made in response to the request by MHRA to clarify that if one or more participants fulfills criteria from the adverse reactions rules, dosing will be temporarily suspended for all participants until the Safety Review Committee meets.

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